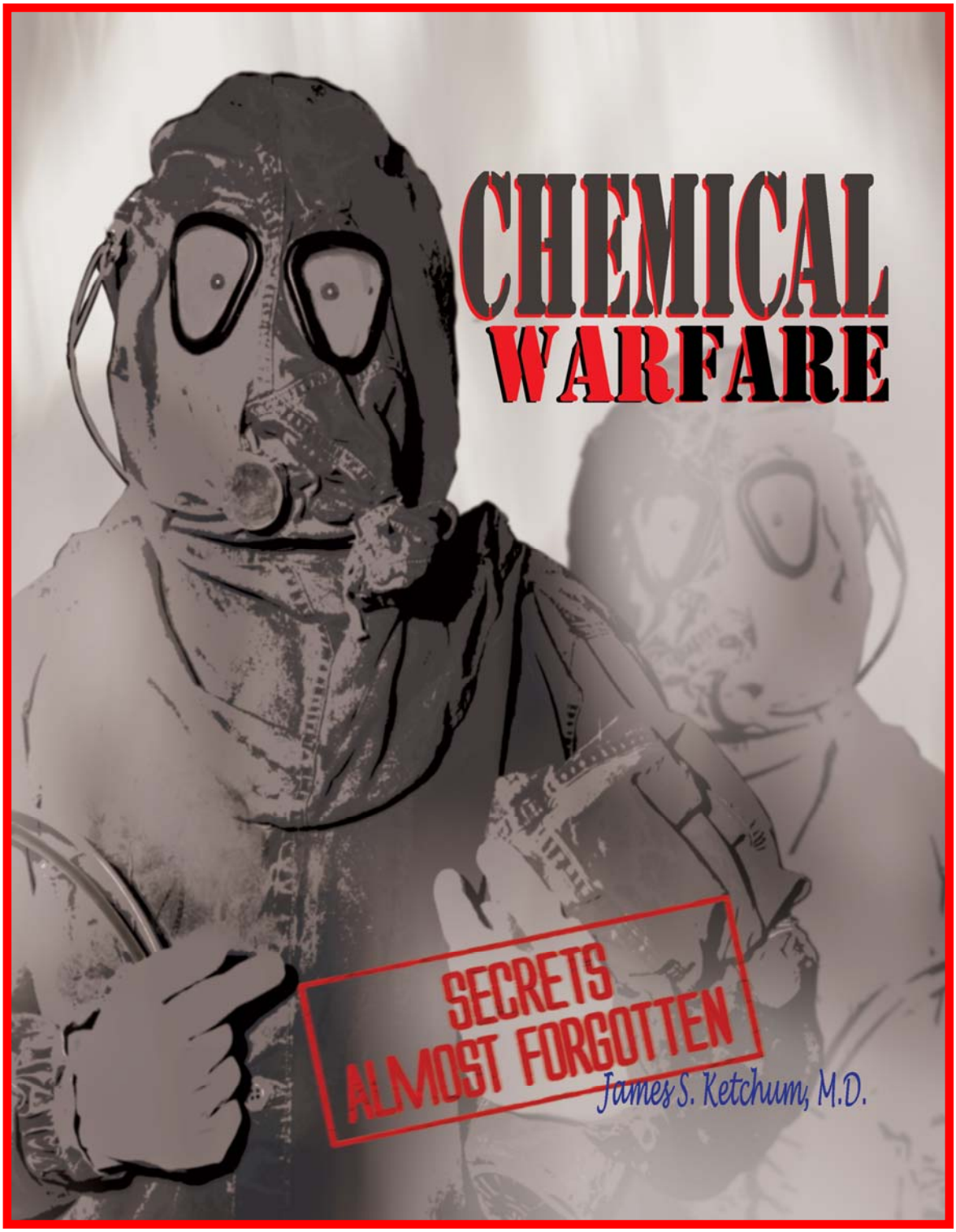
CHEMICAL
WARFARE
SECRETS
ALMOST FORGOTTEN
James S. Ketchum, M.D.

CHEMICAL WARFARE SECRETS ALMOST FORGOTTEN

A Personal Story of

Medical Testing of Army Volunteers with Incapacitating Chemical Agents During the Cold War

(1955-1975)

by
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With a foreword by
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Dedicated to

My loving wife Judy Ann (Schaller) Ketchum
who helped and encouraged me
to undertake and complete
this book

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FOREWORD

My first two interactions with the world of US Government chemical warfare were in the 1950s or maybe the 1960s when I was still a senior research chemist at the Dow Chemical Company in the San Francisco Bay Area. They were totally opposite in the images of secrecy and research process that they presented. I kept no notes, so all is from ancient memory.

The first meeting was with two or three chemists in dark suits and ties who were introduced to me and a half dozen other research chemists as being government researchers in the area of potentially interesting synthetic organic chemicals. We were not told from which laboratory they came and the only clues to their areas of interest were two synthetic reaction sequences which had been drawn on the conference room blackboard. The man with the chalk told us that these two pictures had been worked out successfully, and their question was: could any of us propose a last step which might link them together. The bottom compounds in the two schemes were followed by arrows which pointed to an empty area at the bottom of the blackboard. I asked them why not draw in the structure of the desired product and they said that they were not at liberty to do so.

"Oh, nonsense," I said and got up and went to the blackboard and drew the structure of the target. I drew the isomeric homologue of tetrahydrocannabinol with the terpene double bond down in the terpene 3,4-position and a 1,2-dimethylheptyl chain at the aromatic 3-position. "This is the obvious product you want," I added as I returned to my seat, "So why don't we discuss how this coupling could be achieved."

There was an unmistakable discomfort shared by the gentlemen from Washington. After a bit of discussion I volunteered the statement, "Of course, with three chiral centers, there will be eight distinct optical isomers possible, all of different pharmacology, and some may not resemble marijuana at all in action." The meeting broke up shortly thereafter. A lot of things just couldn't be talked about.

The second meeting occurred at an informal conference with some thirty people present, located at a retreat north of Los Angeles. This was organized by my good friend (and secret trumpet player) Daniel H. Efron, MD, PhD (1913-1972). This get-together was sponsored by the Washington operation he ran, the Pharmacology program at the National Institute of Mental Health. He told me to sit

over there, pointing to an interesting looking man who was a total stranger. We introduced ourselves. I said my name was Sasha Shulgin, and he said his name was Van Sim. "Oh," I asked him, "What is your first name?" "Van is my first name -- I am Van M. Sim."

We quickly discovered that we were both fascinated by psychedelics (they were called psychotomimetic drugs at that time) and that we were both personally experimenting with them. My art was the synthesis of new ones to compare the difference in activity due to structural changes (this at my laboratory at Dow and in my basement lab at home) and his curiosity was met by varying not the compound so much as the setting and the immediate environment around him (this at his laboratory at Edgewood Arsenal). Oh! A government scientist with whom there was nothing in the world that couldn't be talked about.

Thus, this foreword is intended to prepare the reader for a story that has never before been told, the telling of the history, the origins and the development of the physical structure and the variety of people who worked at both the Edgewood Arsenal and its precursor, the Army Chemical Center. This it indeed does, with a flood of photographs and names and candid viewings of the people who worked there during the 11 or so years that Jim Ketchum was a major research person in the medical section. There is a mass of small detail, ranging from unexpected visits and unusual interviews to the conversations taking place during some of the drug experiments with volunteer subjects. This is an intimate portrayal of the structure of the research group, and the slow but inevitable changes in attitudes and research goals that occurred over time.

But to me, this book is much more than an introduction to the Edgewood Arsenal. It is an autobiography of the author himself, from a young man with a developing medical career to an older, articulate analyst of today's world of chemical weapons in general, but particularly the instruments of psychochemical warfare.

It is a pleasure to be able to contribute to this story.

Alexander T. Shulgin, PhD

PROLOGUE

It takes two to speak the truth – one to speak, and another to hear.

Thoreau: ***A Week on the Concord and Merrimac Rivers***

Hot Night in Halifa

It is 4 A.M. – close to the end of another hot night in the desert. American troops are moving into position on the outskirts of the city, preparing to carry out an unprecedented tactical plan. Actionable intelligence, validated by three sources, has established that several hundred Islamic terrorists are in a particular part of the city, some no doubt asleep while others plan attacks with IEDs (improvised explosive devices). A few may be preparing to strap on suicide bombs. Most of the opposition consists of leftover loyalists; some are members of Al Qaeda and a few are foreign extremists, drawn by religious fanaticism and eagerness to die for Islam.

During these dark early morning hours, some of the coalition soldiers are understandably nervous. Their charge is to carry out a plan they have never attempted, except in simulated exercises. Each platoon has gone through drills with gas masks for several days, sometimes also wearing the hated, stifling suits that make it so difficult to function. Uncharacteristically, several dozen vehicles, modified to serve as ambulances, have pulled up behind the ring of coalition troops, tactically placed to make undetected exit from the city impossible. Further away, on improvised pads, crews have modified more than a hundred helicopters and are examining them once again to be sure they have done everything right. They chat and periodically glance at their watches.

Inside each helicopter is a bank of unfamiliar munitions, brought in by armored, remotely operated tanks. They are specially designed smoke generators, each loaded with 100 kilos of sufentanil. According to what medics previously explained to the commanders, this synthetic chemical is so potent that less than half a milligram can quickly produce profoundly incapacitating central nervous system effects. This amount, one of them noted, is about same as the quantity of LSD that they would need to cause a comparable degree of military ineffectiveness. And the mode of action of this drug is quite different from LSD.

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Once in the lungs, this tiny dose – less than a thousandth of the amount of powder in a packet of artificial sweetener – less than the weight of a gnat's wing – will rapidly bring sleep and anesthesia lasting several hours. In larger doses, the drug will produce the same effects but they will come on almost instantly and last longer. No one who inhales sufentanil can stay awake, much less fight. And for added safety, it has been mixed with another synthetic chemical that keeps it from stopping respiration.

The commander and his key subordinates meet in an improvised briefing room. The colonel who is leading the operation reminds the small group that the participants must maintain synchrony in their actions. He tells them again the importance of not using the radio except for essential communications. Chitchat, although tempting, is prohibited.

Analysts have advised him that the delivery systems can take out almost every occupant in the entire target area. The smoke generators are the latest in design. They worked extremely well in all the tests, providing a smooth release and a uniform distribution. The colonel puts his hand on the acetate-covered map, dragging tanned fingers across a crayon-shaded area where most of the terrorists are concentrated.

The junior officers in the room have heard this before, but the final summation somehow jolts them. This will actually happen. It may bring the solution to a big problem. Until now, because they blend into the noncombatant civilian population, coalition troops could distinguish the terrorists only by the rifles and rocket launchers they carry.

One young captain's attention wanders shortly as he thinks of some of his Special Forces personnel. Bitter memories of friends cut down by hooded snipers, cowards who fire from the windows of ordinary homes, continue to haunt them. Even when they see them run inside a building, the need to minimize "collateral casualties" forces the coalition units to hold their fire. Their M-16 rifles and highly accurate shoulder-mounted missiles have to wait until the "unfriendly" target is clearly isolated, lest they bring down a mother and child along with a black-scarfed terrorist.

The meteorologists have reported that the weather is favorable, with a mild breeze, just enough to carry the particles downwind without excessive drifting. If stronger, it would disperse the smoke before it could settle to the ground. If weaker, its spread would be insufficient. By good fortune, a mild inversion condition is present – it will push the air downward. The colonel prays that the calculations are correct and that luck – a needed ingredient – will work in their favor.

One of the junior officers asks whether the amount of material is enough to cover 100 hectares, roughly half of a square mile. He welcomes a firm reassurance. The terrorists could protect themselves if they could mask in a few seconds, but at this early hour, with limited equipment and training, this is a far-fetched possibility.

The colonel runs through the rest of the scenario. Once they locate target personnel, lightweight plastic cuffs should be adequate to secure them. When they get the signal that the area is clear, more than 200 medics will move in quickly. Leave the use of the antidote to the aidmen. They have access to more than 100,000 syringes of naloxone (the standard antagonist for morphine-like drugs). A single injector should be sufficient to revive several captives. Once treated, most of the non-combatant civilians will be able to resume their usual activities. Since symptoms may return when the naloxone wears off, medical surveillance of those affected must continue for several hours.

The amount of panic is hard to predict. Some panic is inevitable, but the battalion medical officer thinks it will be short-lived. Loss of consciousness will soon intervene. A sergeant comments that there won't be much shooting, an observation the colonel confirms with a grim smile, noting that there will be few to shoot – unless the troops move in too quickly.

Prologue

There will be injuries, mostly minor. One company commander speaks for the group – they are tired of what they call "Boy Scout rules of engagement." Like them, he believes the use of their weapons should not require a first move by the enemy.

There is brief discussion of the "political correctness" that seems to govern everything. The colonel points out that PC is a fact of life, even though the enemy will see it as weakness rather than humane intentions. He reminds the men that it took much courage, both in the Pentagon and higher up, to use an incapacitating agent in the face of almost certain disapproval by the world community. Creative parsing of the Chemical Warfare Convention rules must underlie the decision. This operation will make history, he says – and a mile-high pile of nasty headlines. So, everyone must work together and do everything just right.

* * * * *

Thirty minutes later helicopters are in the air and troops are once more testing their state-of-the art gas masks for leaks. When it is time to move in and round up the "bad guys" the soldiers will have to wear their hated protective garments, as well. Each of these steam-bath suits has a small strap-on kit, containing a dozen antidote injectors, along with the usual atropine syrettes for nerve gas – there will be no shortage of medicine.

Smoke now drifts down and spreads, gradually creating a uniform fog. Sufentanil alone might not be visible, but it is part of an aerosol made up of billions of very small drug-impregnated particles. Without additional material to piggyback them, even distribution of the sufentanil molecules would be impossible. It's a fine science. Only in a size range of one to five microns – less than a tenth the diameter of a human nerve cell – will the particles reach the lower lungs, and stay there.

* * * * *

4:30 A.M. The smoke has begun to spread and permeate the partially open buildings. Loud shouting is coming from the town. Men, as well as women and children are screaming and most are running. They think they are about to meet the same fate as the Kurds did under Saddam. Five minutes later, however, they are alive but still don't know it. There is almost no noise on the streets.

The troops advance slowly, prepared for snipers. Surprisingly, there are none. Dozens of bodies are lying in the dirt. Armed Marines systematically enter buildings in accordance with well-choreographed instructions. Inside, young and old lie motionless on the floor. Others seem to be sleeping normally in rumpled beds. When the Marines find weapons, they place them and the sprawled out men beside them on litters. Coalition soldiers carry the victims to nearby vans and ambulances. Tape covers their mouths; non-slip plastic handcuffs hold their hands behind them. Bigger trucks cart off the larger enemy weapons and munitions.

Now the medics are on the scene, busily injecting everyone – women and children first, along with the elderly. They check them all to make sure they are breathing. Chests heave slowly, barely perceptibly in some cases, but all seem to be getting enough oxygen. A few victims are more critically affected. But, there is still time to arouse them with naloxone. Sufentanil has a safety margin – enough to minimize the likelihood of respiratory arrest. No guarantee against fatalities, but they will be far less than in a firefight. All those in critical condition will get medical attention, whether enemy combatant or not.

* * * * *

8 A.M. A hot sun heats the hazy air and illuminates the streets. The operation is essentially over. More than four hundred suspected terrorists, grouped together in secure fenced enclosures, are under heavy guard. No one is mistreated. Non-combatants, now fully awake but confused, are being reassured by Arabic-speaking personnel. They will be okay – no serious aftereffects and no prolonged restraint. But they will have to stay out of the affected area until it is washed down with a neutralizing chemical, already being sprayed from specially equipped trucks.

Prologue

Sufentanil won't penetrate the skin, but specks of it on material, clothing or other items, may lead to ingestion – from fingers that later stray to lips.

Medical personnel tell the drowsy civilians to bathe and wash their clothes. They explain that the sleep-producing chemical will soon be degraded by sun and natural chemical interactions. Danger of secondary contamination will be minimal once the inactivation is completed. Chemical clean-up teams will make sure of this, testing for residual drug before allowing reoccupation of the area. Still dazed, the non-combatants seem to understand.

Meanwhile, taken by surprise, journalists are now busily gathering data, recording images of both the treated and untreated, and barraging all the senior officers they can find with questions. Already they are sending home live footage that will soon be showing up on TV sets all over the world.

* * * * *

Some readers will recoil from the fictional scene described above. It is a dramatic example of "going-it-alone," violating chemical warfare treaties, and bending or breaking international laws. On the other hand, it illustrates the humane employment of what many still consider inhumane weapons. Justification of the unorthodox attack will become clear when the inevitable period of worldwide uproar subsides. Perhaps repugnance toward all chemical weapons will now be more selective. Eventually, life-sparing drugs, by reducing the acknowledged brutality of conventional warfare, may find acceptance.

The scenario is fantasy – some would call it science fiction. But, if it is possible, why should it remain in the realm of the unthinkable? To understand the taboo that surrounds this subject, one must examine how the history of warfare has shaped both national and international policies. Such an examination is a major purpose of this book.

* * * * *

1 COLD WAR: CHEMICAL CALL TO ARMS

War hath no fury
like a noncombatant.

C.E. Montague: Disenchantment

When I tell people that I've written a book about "my life in chemical warfare," they are generally polite but almost inevitably change the subject. Perhaps it is not surprising, therefore, that no one has ever given a full account of what we did at Edgewood Arsenal during the 1960s. It is unsettling, I suppose, to hear a psychiatrist say he worked for a decade studying chemical methods for "subduing" normal people. That is what I did, however, and this book tells the story.

And it's a story that needs telling, one that should have been told sooner. So much of what exists in libraries and on the Internet is incorrect, and so many accounts of what took place are distortions, that a mark of dishonor remains on the escutcheon of our research at Edgewood Arsenal. I ought to know, because I was there and fully immersed in that research.

Perhaps you have heard of BZ, for example, and believe it was a secret concoction, far stronger than LSD, and able to drive people mad. You may not realize that if you ever had major surgery, you probably received a drug just like BZ before receiving anesthesia, to reduce unwanted secretions into your lungs. You probably don't know that more than a dozen similar drugs, all related to BZ, were part of our experimental agenda.

Chapter 1

Many think that the so-called Army volunteers we tested more than forty years ago were not really volunteers. Some claim the subjects were required to take drugs and then undergo interrogation to see if they would give up their secrets. They believe that the chemicals we tested may have left lasting mental or physical disabilities. In short, they assert that Army testing in the 1960s was unethical, incompetent and carried out in violation of basic human rights. These erroneous beliefs could have been dispelled by authentic information long ago, but very little ever appeared in the public media.

So why now? As one of the few who are still alive and able to speak from experience about the details of that decade of testing in the 1960s, I was jolted, as were most citizens, by the events on 11 September 2001. Public fears and misapprehensions about the possible extension of such recklessness to chemical terrorism suddenly began to share the headlines. The real chemical story – the story I had long wanted to tell in detail – suddenly seemed to be an important one. I realized it was a remarkable story that few were still able to tell.

Fear of chemical attack has become an integral part of 21st century life. Such an attack can come at any time and its consequences are difficult to calculate. While weapons experts can provide descriptions of its effects, they speak in terms of possibilities, not probabilities, because the magnitude of the threat is uncertain and the likelihood of its occurrence unknowable.

We wonder if a chemical attack will first be unleashed in a school or a football stadium. Will most of the victims recover as in the sarin incident in Japan? Or will thousands lie dead in the streets, as in the Kurdish villages of Iraq? Will we be able to see the lethal cloud as it approaches or will it be invisible? Will it sear our lungs, paralyze our muscles, eat into our flesh or create terrifying hallucinations? Will death come quickly and painlessly or will we linger in agony? How should we protect ourselves? What are the chances of escape?

Unable to provide definitive answers to most of these questions, chemical warfare specialists continued to repeat what we have already heard: that "a single whiff" of a nerve gas such as sarin, or "a single drop" of a liquid nerve agent such as VX can be fatal. They incorrectly warn us that an enemy can pack enough such poison into a single missile warhead to annihilate thousands of people, perhaps the population of an entire city. They note that even the skin can be penetrated, but then tell us it is even more important to possess an airtight mask.

No wonder the average citizen does not fully understand chemical warfare, when even the best-informed experts do not provide us with straightforward explanations. But perhaps they should not be too harshly criticized. Descriptions of the mechanisms and sequence of nerve gas effects are complex. Efforts to provide the details may produce confusion rather than enlightenment. The deadliness of mortar shells and Kalashnikovs may be familiar, but the complex effects of chemical weapons are not.

The reasons for this lack of clarity are, of course, not difficult to understand. Chemical munitions must achieve their objectives amidst a multitude of variables. Methods of delivery, devices used for dissemination, wind velocity, barometric readings, air temperature, characteristics of the terrain and existing physical barriers will all affect the outcome. In addition, one must take into account the possibility of escape or evasion, as well as the potency and speed of action of the substance itself.

And these considerations, although numerous, make up only a partial list of factors influencing the outcome.

Ordinarily, a chemical attack would be expected to seek as many deaths as possible. But there might be goals other than lethality. Kindling of panic and demoralization may have a higher priority.

Paradoxical as it may seem, one can use chemical weapons to spare lives, rather than extinguish them. The world watched in fascination when the Russians, in November 2002, chose to deploy a relatively non-lethal chemical weapon in a Moscow theater. Inside were a few dozen Chechen rebels, armed with grenades and automatic weapons, holding hostage almost a thousand innocent Russian civilians. The terrorists were prepared to destroy everyone in the building if the Russians did not meet their demands. Fanatical and desperate, they were not afraid to die along with their victims.

Russian military personnel and Chechen terrorists were locked in a stalemate – a three-day standoff. Realizing that the stressed captives could not survive much longer, a Russian commander made a novel, highly unorthodox decision. He ordered a generator, loaded with a still unidentified substance – probably an opiate related to, but far more potent than, morphine – and positioned it where technicians could quietly pump it in as an aerosol from openings in the roof and floor. Within minutes, it rendered the occupants unconscious. Half an hour later, special troops stormed the building, killing the terrorists and freeing the occupants.

Regrettably, the operation was not entirely successful. Over a hundred hostages died along with the terrorists. Psychological shock and general debilitation, a result of insufficient food and water, no doubt substantially increased the number of mortalities. Lacking access to vital medications, some may have succumbed to unstable diabetes, heart conditions or renal disease. By injecting casualties as rapidly as possible with naloxone (the standard antidote for opioid poisoning) Russian medics saved the great majority. Had they started their rescue mission sooner, it is possible that many more would have survived.

However ambiguous the result, this dramatic incident stands out as an example of how a potent chemical agent can be used to preserve life, instead of as a "weapon of mass destruction." Surprisingly, many observers deemed the operation morally indefensible. Still, in the opinion of others, it was a brilliant accomplishment under difficult circumstances.

The procedures followed in this crisis were remarkably similar to scenarios designed forty years earlier by our own Army doctors. Many of the readers of this book were very young, or not yet born, during that tense, uncertain time in history. After the defeat of the Axis powers in 1945, the Cold War, as Churchill named it, was rooted in the growing mutual distrust between America and the Soviet Union.

Although it was not a shooting war, the stakes were every bit as high as in the World War that had only recently ended. Most ominously, each nation had the ability to launch megaton nuclear missiles sufficient in number to annihilate the other. The resulting radioactive fallout would then continue to spread, wiping out populations in almost every corner of the earth. Popular novels and films trafficked in visions of "Armageddon" and "apocalypse". The phrase "mutual assured destruction" became linguistic currency among journalists and commentators.

Some terrified citizens in the 1950s and 1960s became newsworthy subjects for journalists and photographers, when they built and equipped their own bomb shelters, filling them with essentials required for lengthy periods of underground survival. The most nervous and wealthy property owners sometimes paid

contractors huge sums to build structures deep below the surface, cynically designing them to serve comfortably as luxurious apartments.

Nowadays, average citizens are somewhat less obsessed with the nuclear threat. Most world leaders likewise seem less preoccupied with the idea that radioactive weapons of mass destruction still pose an imminent danger, although countries such as Iran and North Korea continue to evoke considerable anxiety. Indeed, some unstable nations have stolen or bought the secrets of nuclear bomb making and even brag about their atomic capabilities, hinting darkly that, if provoked, they would not hesitate to use them.

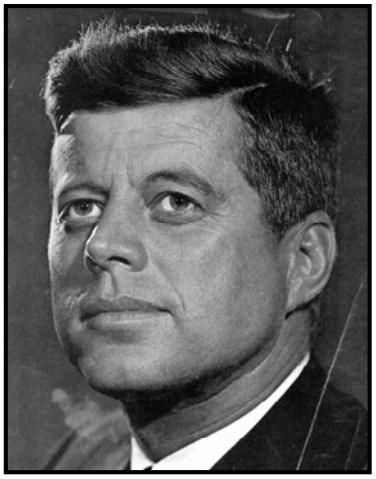
It is interesting to note that even the acronyms for the weapons of mass destruction have changed. We used to be concerned about "NBC" – nuclear, biological and chemical weapons, respectively. Now it is "CBR" – chemical, biological and radiological – devices that provoke the greatest apprehension as we ponder how to plan our defenses. The promotion of "chemical" to the top and the demotion of "nuclear" to the bottom of the list reflect a growing belief – faith may be a more accurate term – that nuclear war is neither highly probable nor easily preventable. A certain degree of fatalism has crept into our national mentality. Many have decided to regard the possibility of nuclear war as too remote to warrant contemplation. The consequences would be too devastating, too unthinkable. If it occurs, it will almost inevitably bring on the final events of our life on earth – hardly worth discussing.

On the other hand, chemical weapons are not particularly difficult to manufacture and armies have actually used them in modern times. Thus, they are now vociferously touted as the most likely threats. Hastily developed detection measures have been deployed in an effort to locate and destroy deadly chemicals before terrorist groups can make use of them. Specially trained dogs now sniff for them in luggage and clothing. An expanding cohort of sophisticated inspectors is learning to hunt for them meticulously, despite mounting costs and annoying inconveniences to travelers. Scientists and engineers are hard at work developing more advanced imaging and analytic equipment capable of visualizing suspicious objects and materials, even when they are concealed within large vehicles and containers.

Modern fear of deadly chemical weapons is engendered by the hideous images of World War I, when countless thousands of courageous troops died helplessly in their trenches, fumes of chlorine, mustard and phosgene sweeping without mercy across their battlements. They clearly knew the nationality of their attackers and could have retaliated in kind, were it not for a woeful lack of comparable weapons. Today, however, the enemy does not align itself with a single nation and no one government can be held responsible for its attacks.

Twentieth century covenants against the use of chemical weapons, such as the Geneva Protocols, now restrain virtually all developed nations. Provisions of the more recent Chemical Warfare Convention (CWC) have further tightened the constraints, outlawing the use of every conceivable chemical weapon. The CWC even bans the use of agents as benign as tear gas (although, ironically, individual nations are not denied the option of using them against dangerous criminals within their own boundaries). And while the CWC prohibitions even extend to drugs and chemicals designed to incapacitate rather than kill, the United States has agreed to abide by them, abandoning the rational argument that prohibition of relatively safe weapons invites more dependence on those that cause more death and suffering.

Major General William Creasy



President John F. Kennedy supported Eisenhower's Blue Sky policy, facilitating incapacitating agent research

Things were much different back in the late 1950s. In striking contrast to today's total ban, the U.S. legislature enthusiastically accepted the novel concept of incapacitating agents. In 1958, Major General William Creasy, Chief of the Chemical Corps, was invited to engage this august branch of government in a lively session. Captivated and at times even amused by vivid images of a cloud of LSD that could disable well-trained troops without causing them physical harm, senators and congressmen voted almost unanimously to endorse Creasy's proposal to triple the Chemical Corps' budget and proceed with studies of this and similar agents in Army volunteers. When asked if he could incapacitate members of Congress in a similar manner, Creasy cavalierly quipped that so far he had not considered this necessary!

President Dwight Eisenhower quickly gave his blessing to this effort. Later, newly elected President Kennedy, almost from the start of his administration, promoted a "Blue Sky" strategy that included incapacitating agents in the growing list of novel military options. Although, as coming chapters will reveal in detail, subsequent efforts to find and deploy humane chemical weapons were not totally successful, this hopeful objective guided secret research for more than a dozen years. Ultimately, even as hope dwindled, the experimental findings remained locked in tight secrecy for at least another decade.

The Edgewood laboratories eventually filed the wealth of data accumulated during these unorthodox studies, leaving them to languish in closely guarded cabinets. Later they moved these documents to even less accessible archives, determined to keep sensitive, classified reports out of the public limelight. Over time, waning interest and fading memories eroded many details of what we had learned, leaving only sketchy summaries and a significant gap in the historical record. This book goes back four decades in an effort to fill that gap.

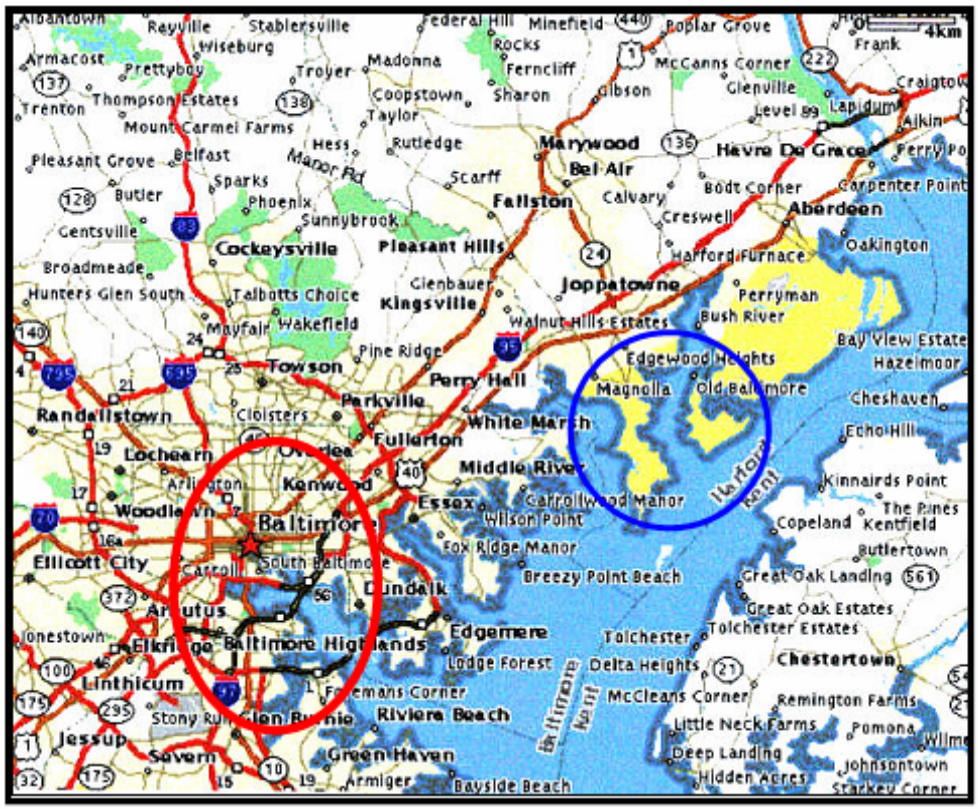
Soon after General Creasy's visionary project began to take shape, I was assigned to Edgewood Arsenal to play a part in its development. Strict secrecy would surround most of our work, lest the Soviets purloin and make use of our diligently acquired information. Stern, sometimes unreasonable rules prevented more than scant reference to our activities from appearing in the media. Because most of the world's anxiety focused on the threat of nuclear war, "talking heads" gave relatively little attention to the arcane medical experiments being conducted at our small chemical installation.

By the time news writers began to report the story in more detail, the program had already begun to wind down. After 1970, the search for a militarily acceptable incapacitating agent had become increasingly out of fashion.

The years passed and the activities that took place in the Edgewood Arsenal medical laboratories during that decade were soon only vaguely remembered by a few of the former researchers. Civilian commentators sometimes spoke of the Edgewood program as a rather unethical, ill advised and generally sub-standard scientific effort that had yielded little of interest to the field of medicine. The erroneous belief that the program was primarily the brainchild of the CIA, already notorious for its ill-conceived attempts in the early 1950s to gain control of human behavior with drugs, added to these unflattering characterizations. Most participating physicians failed to rise to the

defense and refused to grant interviews to investigative reporters, or shifted responsibility to their attorneys. Drawn by the scent of malfeasance, popular authors began to write books incriminating both the CIA and the Edgewood doctors.

The Edgewood Arsenal program and the earlier shady CIA experiments, involving surreptitiously administered LSD and related drugs, became indelibly linked in the public imagination.



Edgewood Arsenal is northeast of Baltimore, near Highway 40

Regrettably, no one other than those who had done the research seemed to have much solid information about the details of our activities at Edgewood. By default, fantasy and rumor took the place of verifiable facts. I watched with distaste as invidious characterizations of our program appeared repeatedly in paperback books and ultimately on oft-visited websites. In 1979, even the prestigious journal Science published incorrect information about BZ, the very potent atropine-like incapacitating agent most often mentioned in books and on Internet websites. It was hard to blame the journal's editor. Few who had been at Edgewood wanted to talk about it, and most of the published information was shamefully superficial.

By the time the original detailed technical reports were declassified (usually at least 12 years after they had first been distributed as restricted documents), most of those who had done the work had quietly moved on. Memories were vague, original data largely inaccessible, and motivation to

publish them virtually non-existent. As the first Regular Army psychiatrist ever assigned to Edgewood Arsenal, I was only one of a small but growing number Army physicians actively involved in the drug testing.

For ten years, I was given the opportunity to play a leadership role in the search for a safe and effective incapacitating agent. The research design was embryonic in 1961, but slowly evolved into a highly structured method for evaluating candidate agents in Army volunteers. I was engaged in measuring the clinical effects of more than a dozen compounds, most of which had arbitrary numbers but no common names, and few of which ever entered the mainstream of medicine.

In the course of testing psychoactive drugs in more than a thousand subjects, we did not limit ourselves to estimating the potential usefulness of incapacitating agents. Along the way, we also re-established interest in a long-neglected antidote that eventually became generally available in emergency rooms. Ironically, very few doctors who use this drug to treat delirium resulting from medication overdose are aware that Army doctors were the first to study it in a controlled experiment and quietly publish their results in mainstream civilian journals.

In the following pages, the reader will find numerous unvarnished accounts of highly trained soldiers trying to cope with the effects of potent psychochemicals – becoming confused and forgetful for hours to days while attentive nurses and psychology technicians carefully measured changes in their ability to function. You will learn the strikingly different ways in which such drugs as BZ, LSD and synthetic marijuana derail thought processes and disorganize behavior. The chapters that follow provide vivid detailed accounts of many bizarre and unexpected incidents, often unearthing forty to fifty year-old photographs and videotape transcriptions from my personal files.

Clinical observations are supplemented by verbatim notes made by medical specialists traveling close beside the volunteers on their chemical trips. They recount the bizarre, sometimes wryly amusing, aberrations in speech and behavior sometimes appearing amidst realistic combat simulations. These descriptions clearly illustrate how small doses of a chemical agent can inexorably prevail, despite the high intelligence and thorough training of the subjects. Adding further to the record are the post-test write-ups by the volunteers themselves, which provide unique insights into the subjective side of incapacitation.

This volume contains frank discussion of the ethical compass that guided our work, particularly with respect to “informed consent.” Some chapters describe, and occasionally take issue with comments appearing in both military and civilian publications, particularly between 1965 and 1982, when public concern about the Army’s testing of drugs in human volunteers dramatically escalated.

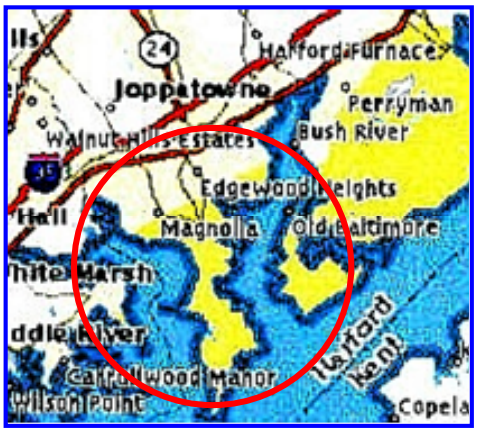
Although my own work at Edgewood was primarily dedicated to the evaluation of potential incapacitating agents, this book includes a discussion of nerve agents – the lethal substances that cause the greatest concern. It closes with a personal assessment of the current threat and a critique both of the facts released to the public, and the limitations of our government’s information policies.

For many years, it was my intent to summarize our psychochemical inquiries in the 1960s – a unique decade of experimentation. Predictably, other activities supervened. But when events in the Middle East reawakened world

concern about chemical warfare, I felt an obligation to carry out this long postponed intention.

What follows is a personal perspective on the clinical study of incapacitating agents investigated in the 1960s. Although in retirement, I felt it important to document the fascinating and informative details of a decade of scientific work might otherwise be lost forever.

Writing what follows required not only vivid recollection of specific events, but close review of previously classified reports, many of them generated while I was still at Edgewood Arsenal. Personal notes, as well as some original data I retained, helped immensely. Most of these exist only in my file cabinets. Interwoven among the names and numbers, are memorable anecdotes, some personal and some that shed light on the dynamics of a military bureaucracy including some political overtones.



Edgewood Arsenal, now part of the larger Aberdeen Proving Grounds, in yellow on the upper right.

Our work took place in a setting where morale was high, curiosity was often rewarded with discovery, and surprisingly strong support was provided by civilian peers, military supervisors and elected officials. Thus, this book often presents an upbeat view of an otherwise somber mission. It frankly recreates the experiences of a psychiatrist who, with much help from others physicians, nurses and technicians, had the unique opportunity to build what eventually became a sophisticated research program.

While focused on experiments, this narrative also depicts the personality of many colleagues. More important, it underlines the patriotism and courage of the many volunteers who trusted us enough to take strange drugs whose effects were not yet fully known. They knew the risks and willingly accepted them. It was the volunteers, more than the researchers, who were the true explorers. They deserve great credit for their starring performance in the offbeat, at times quixotic, drama that took place on a secret stage called Edgewood Arsenal.

For readers, ranging from apolitical scientists, physicians and teachers to ideologues and conspiracy theorists; from historians to incurably inquisitive thinkers; the contents of this book will provide interesting, previously unpublished facts – as well as some new, at times entertaining insights – about an extraordinary decade of now almost forgotten research.

* * * * *

2 INCAPACITATING THE ENEMY: STRANGE FRUIT AND STRAY SMOKE

Ends and Beginnings – there are no such things.
There are only middles.

Robert Frost: ***The Home Stretch***

Chemical warfare has its roots in antiquity. Periodically, armies have used drugs, mostly extracted from poisonous plants, against their opponents. In more recent centuries, chemical laboratories have gone on to produce new and more sophisticated compounds along with more effective devices for their delivery. The American army paid little or no attention to this type of weapon, however, until the 20th century. When German troops used toxic gases in World War I, they found the U.S. and its allies almost totally unprepared.

Although chemical warfare goes back at least 3,000 years, its use has always been sporadic and short-lived. Ingenious attempts to find effective substances and ways to deliver them in the battlefield almost always failed. On

the rare occasions when they proved effective, the parties involved often agreed to ban them in the future. The agreements, however, were never international in scope and opinions differed as to whether or not to outlaw chemical weapons. For every condemnation of their use, there were countervailing arguments in their favor.

The effects of lethal chemical weapons are, of course, abhorrent, even when they account for only a small fraction of the total number of killed and wounded. When toxic chemicals strike, they tend to annihilate specific groups rather than scattered victims. Historically, victory is supposed to go to the courageous and most skilled, but chemicals make courage and training irrelevant, leaving no heroes. Eerily, most deaths resulting from lethal chemical agents leave corpses without wounds. The victims of gas attacks rarely go down in legend.

For these reasons and no doubt others, it has generally been the most despotic and underdeveloped nations that have had the least compunction about their use. In more "advanced" countries, certain "noble traditions" of warfare seem to have created a natural aversion to anonymous killing by poison, the use of which is usually associated with cowardice and treachery. Accordingly, it has generally proven useless to argue as some military experts did (especially after WW I) that war was not "playing marbles" and if chemical weapons could achieve victory more swiftly and with less loss of life, they should be used. (In WW II, a similar line of reasoning ultimately prevailed. President Truman unleashed the atomic bomb for that very purpose – to conclude a war and avert useless deaths on the battlefield.)

Attempts to ban chemical warfare always fell short of success. Even though the United States signed the 1925 Geneva Protocol, the Senate would not ratify it.

After World War I, some military analysts pointed out that we should have taken the threat of chemical attack more seriously. Had we provided gas masks and training to our troops, tens of thousands of dead soldiers could have remained alive. Many thousands more (unless exposed to blister agents) "could have lived out their lives free of painful disabilities. In a 1932 letter to Secretary of State Henry L. Stinson, US Army Chief of Staff General Douglas MacArthur argued that staying abreast of technical advances in the field required continuing research and testing. As with nuclear weapons, many asserted that a retaliatory chemical capability was necessary to make aggressors think twice before using such weapons.

Recognizing our earlier naiveté, the War Department established the Chemical Corps in 1922, centered at Edgewood Arsenal in Maryland. Over the next forty years, the U.S. escaped a repetition of the chemical atrocities of the First World War. Ironically, it was mostly Hitler's personal phobia of chemical retaliation that saved us from the thousands of tons of nerve agents already synthesized and stockpiled by the Nazis.

In the 1950s, heightened awareness of the threat led to renewed U.S. efforts to build a sturdy chemical defense, including improved methods of training, detection, protection, decontamination and treatment, along with contingency stockpiling of the very nerve agents we almost faced in WW II. Although we subsequently armed ourselves with similar weapons, we made it clear that we would never use them first. Franklin Roosevelt, in particular, emphatically stated that chemical weapons were despicable. Accordingly, the policy of no "first use" became an axiom of military planning.

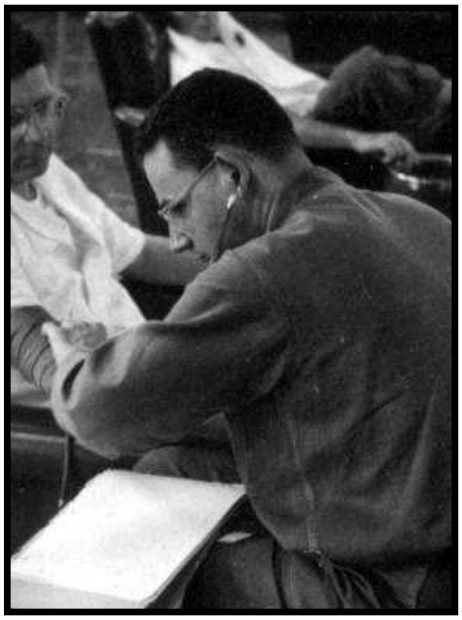
Jeffery Smart has described the 1960s as the "decade of turmoil" in the

Chemical Corps. During this period, the U.S. made serious efforts to develop a new class of weapons: the "incapacitants" – otherwise referred to as "non-lethal agents." And it is here that this book picks up the story.

Incapacitating Agents

What is an incapacitating agent? Simply defined, it is any physical or chemical agent that can render target personnel unable to carry out their duties for minutes to days, with low probability of death or persistent injury and a very high likelihood of complete recovery. Although physical agents such as deafening noise, blinding light, microwaves, electric shock and ensnaring devices may all be considered to be incapacitating weapons, this book is about chemical agents.

While the term "incapacitating agent" seems to have first appeared in the 20th century, the concept is extremely old. Not only have armies used chemical weapons against both enemy troops and civilians, but criminals have also employed chemical agents to simplify robberies or to buy extra time necessary to carry out complex illegal activities.



Sp-5 Ephraim Goodman scoured the libraries for historical and clinical material related to atropine.

Historical incidents illustrate various attempts to use drugs in a military setting. Some of the substances used bear a striking similarity to modern chemical weapons and provide useful illustrations of their potential military effects. As we initiated our own research at Edgewood Arsenal in 1961, we concentrated on incapacitants, focusing on anticholinergic (atropine-like) drugs. A review of the existing literature seemed like a good place to start. We asked Ephraim Goodman, a psychologist in our clinical laboratory, to search for historical records of the behavioral effects of high doses of atropine and similar agents. He scoured the stacks in several libraries and after several weeks submitted a draft report that exhaustively summarized both military and non-military uses of atropine to produce either intoxication or death.

Physicians have, of course, used atropine for many centuries as treatment for a variety of conditions. Therapeutic doses generally range from 0.5 to 2.0 mg. At doses above 10 mg, atropine causes profound mental changes. Following massive overdose (above 100 mg), the outcome can be lethal.

Goodman visited the Library of Congress and other archives in his persistent search. He waded through 100 years of The Journal of the American Medical Association, as well as The Boston Medical and Surgical Journal (continued as The New England Journal of Medicine), Lancet and The British Medical Journal.

His fluency in German also allowed him to review other specialized sources in detail, including Fuehrer-Wielands Sammlung von Vergiftungsfällen (continued as Archiv für Toxicologie) from 1930 to 1962 and Deutsche Zeitschrift für die Gesamte Gerichtliche Medizin from 1922 through 1939. An examination of standard medical literature indices from 1880 to the present reveals additional major reports in other sources. Never published, Goodman's draft manuscript nevertheless remains a treasure trove of incapacitating agent history, extracted from more than 300 articles both for medicinal and non-medicinal purposes. The latter include robbery, seduction, Satanism, tribal justice by ordeal, location of precious objects and stolen articles, individual thrill-seeking and practical joking. With more positive intent, these plants were revered by some primitive religions and were sometimes used to

initiate youths into adulthood.

Accidental overdoses were especially common. Of 576 cases of atropine intoxication, almost half were due to oral ingestion of plant material, particularly by children below the age of five. Opthalmological, liquid medicinal, parenteral and percutaneous overdoses made up the remainder. Significant differences in the source of the drug occurred among age groups, however. Individuals above the age of 61, for example, were inclined to encounter overdosage from eye drops or medicinal plasters.

Although not as common nowadays, in the period from 1950-55, 10% of live admissions of children under five years of age to Scottish hospitals were for intoxication resulting from ingestion of atropine-containing plants. Among pediatric admissions to a South African Hospital during the same period, fully two-thirds were victims of solanaceous alkaloids. Surprisingly, physicians frequently failed to recognize that atropine was the basis for the clinical features they observed. Often, they wrongly attributed the signs and symptoms to syphilitic paresis, post-partum psychosis, dementia praecox (schizophrenia), acute manic-depressive psychosis (bipolar disorder), or any of a variety of infectious or traumatic conditions.

The signs and symptoms of atropine intoxication have been wryly summarized by H. P. Morton (1939), in the form of five easy to remember similes: "Hot as a hare, Blind as a bat, Dry as a bone, Red as a beet and Mad as a hen." In more professional language, atropine intoxication (as observed by Forrer and Miller during their atropine coma treatments in the late 1940s) consists of two sequences: the first neurological, the second, behavioral.

The neurological sequence, according to these clinicians, is as follows:

> 1) Progressive muscular incoordination 2) Decreased pain sensitivity 3) Hyperreflexia with development of a Babinski sign (upward motion of the big toe following stimulation of the sole of the foot).

The behavioral sequence is as follows:

> 1) Clouding of the sensorium 2) Disorientation 3) Loss of time-space relationships 4) Distortion of perception with illusions and hallucinations 5) Confusion 6) Coma. (The last of these usually appears only following large overdoses.)

Historians have described the consequences of mass intoxication as early as in the last half-century BC, when Antony's army was exposed to belladonna by an enemy force and experienced both delirium and deaths, according to Plutarch and case reports. A summary of some of his findings follows.

> "They chanced upon an herb that was mortal, first taking away all sense and understanding. He that had eaten of it remembered nothing in the world, and employed himself only in moving great stones from one place to another, which he did with as much earnestness and industry as if it had been a business of the greatest consequence. Through all the camp there was nothing to be seen but men grubbing upon the ground at stones, which they carried from place to place."

As a result of the widespread global distribution of solanaceous plants (atropine containing members of the potato family), a variety of cultures have employed them. Similar poisoning occurred among Colonial troops in Virginia in 1676. The affected soldiers needed confinement for eleven days (a surprisingly long

period). On 14 September 1813, while on the march, a company of French Infantry unknowingly consumed atropine-containing berries. Poisoning of monks in a monastery around the same time disrupted their well-learned and habitual rituals. A group of sailors, intoxicated while on board ship in April 1792, was fortunately able to call for help by firing cannons and running up signal flags, allowing some to survive.

The following excerpt describes the delirious condition in the case of eight East Indian troops poisoned in 1895:

"Most of them were unable to answer when spoken to, and those who could, had forgotten their own names. Some lay on the ground in a dazed condition; others sat up constantly making fidgety movements with their fingers, picking up small particles of sand or pebbles from the ground or appearing to be searching for something they had lost, and occasionally looking up with a half-vacant, half-wild expression."

Similarly, the French soldiers who poisoned themselves in 1813 by naïvely consuming wild berries containing solanaceous alkaloids also soon became delirious. M. Gaultier, the attending military physician, described the victims as:

"...in continual agitation. Their knees sank under the weight of the body, inclining them forwards, and carrying their trembling hands towards the earth, endeavoring to collect little stones and bits of wood, which they always let fall or threw away to recommence the same pursuit."

Goodman comments that this grubbing on the ground was typical behavior in belladonna-intoxicated children, as well as adults. (In later chapters, BZ-intoxicated volunteers will be seen to exhibit very similar behaviors.)

Age, health and environmental factors appear to play a significant role in the susceptibility to, and potential lethality of atropine toxicity. The very young and the old as well as those with debilitating conditions such as tuberculosis or hypoglycemia, are especially vulnerable. The presence of a hot, dry environment increases the danger of death through hyperthermia. Belladonna drugs inhibit the ability to perspire, the cause of most of the deaths in hot climates. In cases of extreme overdose, cardiac failure is probably the determining factor.

It is difficult to estimate the lethal dose in man due to the many confounding factors that may be present, as well as the selective reporting of deaths following either unusually high or low dosage (both of which probably have more medical "news value"). One authority has declared a "surely fatal dose" to be about 1200 mg. Most pharmacology texts, on the other hand, tend to give estimates at least ten times lower.

Based on pooled data, Goodman calculated that 450 mg is the average lethal dose (LD_{50}), about forty-five times the dose that produces delirium. One report in the literature documents a case of recovery from an oral dose of 1,000 mg of atropine. Also, at least one individual has survived 500 mg (from 100 to 150 times the delirium-producing dose) of the related but more potent drug scopolamine

The military mass intoxications mentioned above were mostly accidental. But in his review, Goodman also includes a history of the deliberate military use of atropine and atropine-like substances, i.e., hyoscyamine (atropine) and hyoscine (scopolamine), both obtainable from plant sources. In one instance:

"An officer in Hannibal's Army, about 200 BC, used atropa mandragora (mandrake) as a chemical ambush. According to the officer, "Maharbal, sent by the Carthaginians against the rebellious Africans, knowing that the tribe was passionately fond of wine, mixed a large quantity of wine with mandragora which in potency is something between a poison and a soporific. Then, after an insignificant skirmish, he deliberately withdrew. At dead of night, leaving in the camp some of his baggage and all the drugged wine, he feigned flight. When the barbarians captured the camp and in frenzy of delight greedily drank the drugged wine, Maharbal returned, and either took them prisoners or slaughtered them while they lay stretched out as if dead."

In the struggle for power between Pompey and Caesar (in approximately 50 BC) troops in Africa were deliberately poisoned by placing substances in their drinking water. Subsequently "their vision became hazy, as in a fog, and an invincible sleep overtook them. Then followed vomiting and jerking of the whole body." L. Lewin (1929), an expert on psychoactive plants, believes that their difficulties in visual accommodation, muscular excitation and desire for sleep clearly point to intoxication by solanaceae. The widely distributed Hyoscyamus falezlez and Hyoscyamus muticus are indigenous to North Africa and may have been the plant material used to drug the troops.

The next documented example of the use of solanaceae for military purposes apparently did not occur until nearly eleven hundred years later:

"In the reign of Duncan 1034-1040 AD., the eighty-fourth King of Scotland, Swain, or Sweno, King of Norway, landed his army in Fife. The Scots retreated to Perth after a battle near Culross. Duncan sent messengers to Sweno to negotiate surrender and during the discussions supplied the Norwegians with provisions. As expected, this was looked upon as a sign of weakness. The Scottish forces under Bancho entered Sweno's camp while the invaders were intoxicated with wine dosed with 'sleepy nightshade." (G. Buchanan, 1831).

Historical evidence of the oral use of the solanaceae for military purposes next exhibits another gap, of over eight hundred years.

"In 1881 a peaceful railway surveying expedition under Lieutenant-Colonel Paul Flatters of France was proceeding to the Sudan from Algeria, through the territory of the Touareg. These Berbers who, unlike other North Africans, veil the men and not the women are a raider people who did not completely surrender to French authorities until 1943. The Touareg call themselves "The Blue Men" and "The People of the Veil"; the other inhabitants, however, call them 'The Abandoned of God.'" Flatters ignored a warning letter and marched into an ambush on 16 February 1881, losing approximately half of his force, or all of the personnel in the area where the ambush took place. On the next day, the five French and fifty-one indigenous survivors started to march to a French outpost. This party was trailed by a force of approximately two hundred Touareg.

* * * * * *

"On 8 March 1881, their supplies having been observed to be low, they were approached by three men who claimed to be members of another tribe. These men offered to sell the party provisions. On the next day, three bundles of dried dates were thrown into the camp, and varying quantities were consumed. The French members of the party apparently ate more than the indigenous soldiers.

"Shortly thereafter signs and symptoms of solanaceous intoxication were manifested. Five of the fifty-six men disappeared in the confusion of the first few minutes. Thirty-one of the remainder were so sick that they were unable to look after themselves. In the evening, some attempted to crawl away into the desert. The Frenchmen had been tied down by the senior indigenous soldier to prevent injury. There was some improvement by morning." According to R. Leder (1934), "And so they set off, half mad, bent double under excruciating pain, their legs crumbling away under them, their voices shrill, their words unintelligible.

"On the second day after the poisoning they reached an oasis, where a force of Touareg awaited them. By this time, however, the survivors were able to function as an effective fighting force, and thus the attack was repulsed. Two of the French, said to be under the influence of the drug, rose and marched forward to death.

"After more difficulties, the party evaded the Touareg and found water. They resorted to cannibalism to sustain life. On 29 March 1881, twelve Algerian soldiers reported to a French outpost. The poison has been identified as Hyoscyamus falezlez."

Other examples cited by Goodman include the poisoning of 200 French soldiers by Chinese reformers in Hanoi on 27 June 1908, all of whom recovered. One of the intoxicated soldiers saw ants on his bed, a second fled to a tree to escape from a hallucinated tiger and a third took aim at birds in the sky. Another incident was the abortive attempt by Soviet agents in 1959 to poison the staff of Radio Free Europe in Munich by putting atropine in saltshakers in the cafeteria. A double agent foiled this effort.

An example of an early attempt to disseminate belladonna alkaloids as an "aerosol" occurred on 29 July 1672, when troops of the Bishop of Muenster assaulted the city of Gröningen. It proved fruitless. The fumes dissipated in the open air, and the heat of combustion destroyed the active principles of the vegetable poisons contained within the shells. Despite the ineffectiveness of this weapon, the French and Germans soon negotiated a treaty at Strasburg on 27 August 1675, outlawing the use of poisoned shells.

Claude McClure, MD Trained as a neurosurgeon and biochemist, Major McClure became Chief of the Biomedical Laboratories in 1974.

Goodman submitted his paper for official review prior to publication in 1962 with our enthusiastic encouragement. Dishearteningly, our department chief, Major Claude McClure, declined to sign the necessary approval, even though the manuscript contained no classified information. His comment was that it was too long and detailed to be acceptable as a journal article.

The draft thereafter languished in our files until 1997, when we took the liberty of extracting portions of it for inclusion in a chapter on "Incapacitating Agents," subsequently published in the first edition of the Textbook of Military Medicine. Goodman himself was lost to our "tracking station" soon after he completed his compulsory two years of military service. Despite several attempts, we could not find him, hoping to persuade him to complete and publish the manuscript. This

is regrettable: it is a masterful scholarly work that students of pharmacological history should be able to access.

Meanwhile, in modern times, a partly successful use of incapacitating agents was the previously mentioned Russian rescue in 2002 of almost a thousand civilians held hostage in a Moscow theater. Although many died, it seemed clear that unless the terrorists achieved their demands they were prepared to bring about the death of everyone, including themselves. This action broke the taboo against deliberate use by a government of an "incapacitating agent" against humans, but it seems probable that the taboo will be reinstated and continue to remain in full force for the foreseeable future.

* * * * *

3 HELLO, EDGEWOOD ARSENAL!

How often things occur by mere chance which we dared not even hope for.
Terence: *Phormio, V. I*.

My Christmas surprise in 1955, as I approached graduation from Cornell University Medical College, was a persuasive Army recruiter.

"You can be among the first to join our newest program for young about-to-be doctors," he said. "The Army will make you a 2nd Lieutenant, with full pay and benefits without your having to do anything but finish your last year as a medical student."

The "all-purpose room" of our tiny 5th floor no-heat apartment (1954)

It sounded terrific. I had spent eight years scratching out the cost of my education with the help of scholarships, college loans, and part-time work as a sperm-donor, file clerk, common laborer, camp counselor, typist and night technician at a downtown blood bank. I worked straight through summers and almost every vacation break.

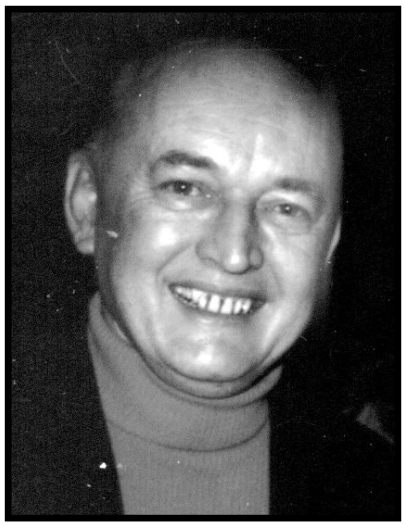
For most of my four years in medical school, I lived like an artist in a garret on East 66th Street, in a fifth floor walk-up tenement, with no heat. The price was right: My roommate and I each paid $9.75 a month for rent, and we were located close enough to walk to Cornell on 69th Street. We had a total of 300 square feet of floor space, a 9 x 12 foot living room and the bathtub was in the kitchen, but somehow it seemed okay. Come to think of it, we were each paying less than four cents a month per square foot of New York floor space. And tuition at one of the best medical schools in the country was only $900 a year in those days (it might be $50,000 by now).

Chapter 3

I didn't even realize we were poor until the Army recruiter held out his offer of $340 a month. It was too much to resist. No longer would breakfast consist of an old pickle jar half-filled with black coffee, loaded with lots of sugar and topped off with half a pint of heavy cream – a thousand calorie meal that cost only about a quarter and produced nothing worse than a mild degree of nausea, and perhaps an extra bit of lining for my coronaries.

The next week I traveled to Governor's Island and filled out the necessary forms. I swore that I would be a loyal and faithful officer in the Medical Service Corps[1] and took the ferry back to Manhattan basking in my newfound affluence.

An internship at Letterman Hospital in San Francisco came next. In July, I crossed the country in my recently acquired beat-up 1948 convertible Studebaker and arrived in San Francisco feeling like a courageous pioneer. I delivered 50 babies, performed two appendectomies, and spent my free time cruising the Officers' Club for female companionship, which was readily available. I could hardly foresee that in four years, my life would change dramatically and I would become a real pioneer, exploring the vast, secret world of chemical warfare at an obscure Army installation called Edgewood Arsenal.



Colonel Roy Clausen, M.D. Chief of Psychiatry at Walter Reed Army Hospital during my residency (1958).

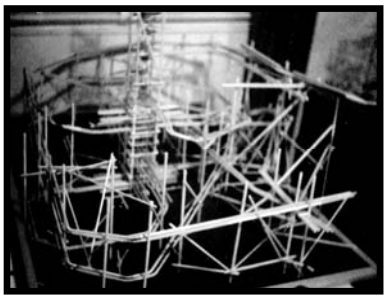
Following internship, I spent six months at Fort Sam Houston, Texas, learning to be a proper Regular Army Officer; followed thereafter by a hoped-for transfer to Walter Reed Army Hospital in Washington, D.C. There, I learned the basics of psychiatry. I discovered I had less faith in Freud than in the biology of schizophrenia.

"Many of Freud's writings are still in the original German," commented a fellow resident at a department dinner party.

"Yes, and thankfully most of them are still untranslated," I quipped.

"What a character!" my department chief guffawed. We got along famously after that – he was a notorious iconoclast himself.

I disciplined myself, in those days, getting up at 4:30 A.M. to study books on cybernetics, and insisting on boring my fellow residents with a computer model I had made from bendable soda straws, tinker toy parts, paper clips and marbles. Success and failure were equally stimulating and nothing seemed to faze me for long. I was young, carefree and passionate. Our department chief allegedly commented to one of my mentors, with a tone of resignation, that I had done very well at anything I actually liked. He had evidently decided to accept my incurable lack of conformity.



Gravity-operated "binary adder circuit" made of soda straws, straight pins, tinker toy parts and marbles (1959)

Dr. David Mackenzie Rioch, a stern-faced, fundamentally benign man with dark bushy eyebrows, seemingly sensed that I might have been cast from a different mold. He was a relentlessly dedicated scientist who supervised my efforts at outpatient therapy for an hour each week. As civilian Chief of the Neuropsychiatry Division of the nearby Walter Reed Army Institute of Research (WRAIR), Rioch had a prestigious and well-earned international reputation.

At first, I would arrive for my hour of supervision carrying voluminous therapy notes, relying on them for details during our sessions. Eventually, Dr. Rioch told me, with a tinge of exasperation: "I don't like all those notes." I had always thought it was cool to write down

[1] Prior to receiving an M.D. degree, one is not yet in the Medical Corps, but in the Medical Service Corps.

everything that patients told me. (This remained a lifelong habit.) In this case, however, I felt it best to defer to Dr. Rioch's wishes; thereafter I presented only what I could remember, a change which he acknowledged with approval.

Rioch's illustrious career had started at Harvard in neuroanatomy, after which his interests moved progressively from the structure of the brain to the anatomy of the mind. His span of knowledge was truly awesome.

My apartment on Georgia Avenue during residency – 3 blocks from Walter Reed Army Hospital (1959)

In the second year of residency I was allowed a three-month elective in his department where I learned, among other things, the fine art of drilling tiny holes in the skulls of cats and precisely inserting electrode wires deep inside the brain. This experience gave me an idea. I decided to try to teach cats to make their wishes known by communicating with their brain waves.

On Thanksgiving Day I skipped turkey dinner and, alone in the lab, completed my first successful feline implantation. I was flush with pride but my furry patient was not as fortunate. Although he gave nice brain tracings, and continued to meow effectively when hungry, he never seemed able to learn the niceties of EEG communication. Instead, he ultimately succumbed to the delayed consequences of a wound infection. The veterinarian who was supposed to monitor him while I was away on leave had failed to watch him closely enough.

I was pretty sad about this. When he became sick, I took him home to my bachelor apartment for two weeks and fed him milk with an eyedropper, as he lay curled up on a blanket in the bathtub. Penicillin cured the local abscess, but my kitty never regained full neurological function.

Resilient in temperament, I decided I had done my best and began a different project. I compiled a lengthy review article entitled "Electrosleep, Electronarcosis and Electroanesthesia." It won lavish praise from my supervisor, Dr. Robert Galambos. Dr. Rioch liked it as well, but pointed out that the reference material came from confidential Soviet sources and it would be a breach of protocol to publish it.

That was the second crash landing by a fledging research bird attempting initial flight. I affected unconcern about my lack of success. That may be one reason Dr. Rioch called me over to his office a year later.

"Jim, there's a situation at a place called Edgewood Arsenal, about an hour and a half north of here."

"Really?" I said, all ears to situations.

"Edgewood has a highly classified program on incapacitating chemical agents getting started up there and they don't have anyone trained in psychiatry. The investigators gave some PCP to five civilian volunteers and one of them ended up in the hospital for six weeks with a paranoid psychosis." That didn't sound too encouraging. I was pretty sure I knew what was coming next.

"Would you be interested in an assignment there when you finish up your residency in December?" he inquired. His Scottish brogue flowed through my inner being like a hypnotic potion. How could I resist? Accordingly, I became a reborn fledgling, this time as a psychopharmacologist.

I wanted to see what I was getting into so I arranged an exploratory visit. The map led me to an unimpressive looking installation five miles off the main highway running from Baltimore to Philadelphia. I showed the guard at the entry gate my official travel orders, and he directed me to Building 355, an unpretentious two-story whitewashed concrete structure.

Colonel Douglas Lindsey, MD (1918-1999). Trained as a surgeon, he commanded the Edgewood Arsenal Medical Laboratories from 1959 to1962.

Signing the visitor sheet, I entered the office of the Chief of the Medical Research Laboratories, Colonel Douglas Lindsey. He was a slim, wiry man in his early forties, and emanated an aura of relaxed authority. Unlike other senior officers, he was dressed unpretentiously in Army fatigues. The other officers dressed normally, with colorful service ribbons on their blouses and shiny rank insignias on their shoulders. Doug Lindsey's uniform had evidently been cut from a different bolt of cloth.

"Captain Ketchum, I presume," were his first words. "You must be the psychiatrist we've all been waiting for." He led me across the parking lot to some wooden barracks, where World War II Chemical Corps soldiers had once resided. It wasn't very impressive looking – several cantonment style claptrap wooden buildings joined together by one long narrow hallway, its floor paneling partially covered by a worn rubber strip creased with narrow non-slip grooves. "And this is Dr. Kazuo Kimura," added Lindsey. "He will be your initial primary supervisor." A tall massively constructed man, Asian in visage, Kimura offered me a firm but not intimidating handshake. "Welcome to Edgewood Arsenal," he said.

1961 – Dr. Kazuo Kimura – Trained as a pediatrician, he was the Acting Chief of the Clinical Investigation Branch

"Very nice to meet you," I replied, making an effort to conform to the rules of normal etiquette. "I'll leave you with your new boss, then," said Lindsey and off he went, diminutive frame erect, with a stride that signaled "other important things to do."

"You've come on a good day," said Dr. Kimura. "We're running another test with a drug called EA 2277." I suddenly realized I was about to enter a new world full of secret names and numbers.

The ward, large enough to accommodate 20 bunks for enlisted troops, contained only half a dozen widely separated hospital-style beds. A young soldier sat on the edge of one of them, restlessly fumbling with his pillow. He was trying to stuff it back into the pillowcase from which he had just removed it. He couldn't make it fit, so he turned his attention to the sheets. Then, suddenly, he became interested in the buttons on a technician's shirt.

"He's a bit out of it right now," said Kaz. "So I don't think I can introduce you. He wouldn't understand who you are, why you are, or where you are."

"So I see," I commented, watching the soldier's performance with great fascination.

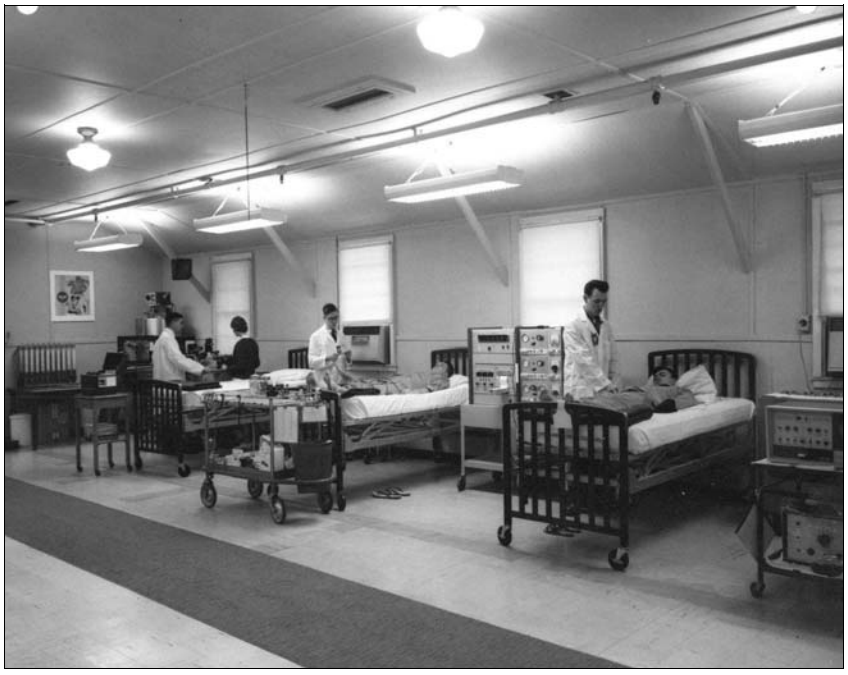
"Ain't that a piece of shit," the volunteer said unexpectedly, addressing no one in particular, in a slurred but surprisingly loud voice. Then he laughed abruptly. "I knew the fucking IG was coming. That a horse over there?" Abruptly, he went back to "un-making" his bed.

In rapid succession, I met two of the psychologists, including the previously mentioned Ephraim Goodman. Goodman seemed to feel a need to stand at attention

next to the young physician who was busily making notes about the volunteer's strange behavior.

"Bill Gordon's our only Navy doctor," Kaz explained, noticing that I had my eyes on the blue trousers under Bill's white coat. "He's been handling the EA 2277 testing we started a couple of months ago. If you decide to come, you'll be arriving just in time for him to start his residency." "Oh," I said. "Well, it actually looks quite interesting. I'm really looking forward to coming." I said it sincerely because there was no doubt in my mind that working in this strange atmosphere was just the sort of thing that would satisfy my appetite for novelty.

After returning to Washington, I assured Dave Rioch I would be happy to work at Edgewood. In due course, as my residency drew to a close, transfer orders arrived and I was soon on the road with my wife and our 5-day old infant son.



Until 1961, all volunteer testing took place on this ward in the "annex." Psychology technicians assisted the physicians. By 1962, registered nurses were hired and an adjacent ward housed volunteers undergoing testing with incapacitating agents such as BZ and LSD. Later, padded areas provided much better physical safety.

Edgewood Arsenal (at that time known as the Army Chemical Center) was located at the tip of a peninsula about 25 miles northeast of Baltimore. Its widely separated buildings looked peaceful beneath a fresh snowfall.

A wide airstrip ran north to south along the midline. At its edges, inlets of the Chesapeake Bay Post created watery boundaries. From our new quarters in Grant Court, a dirt road ran through the woods to Skippers Point, where picnics and boating were popular during the summer months. On the north side of the main road, was a nine-hole golf course. In the warmer months, grassy areas surrounded the airstrip and deer nonchalantly grazed there in the twilight hours.

The Medical Research Laboratories (Building 355) were located about a mile south of our Grant Court apartment, and the larger Chemical Research and Development Laboratories (Building 320) were a mile and a half further down the same road.

Only about 1,000 military personnel and 5,000 civilian employees were working on the Post (many fewer than the 17,000 personnel assigned there in its more active years). Most of the civilian workforce lived in the neighboring towns of Edgewood and Bel Air, rendering the Post a quiet, almost rustic scene after quitting time.

The Medical Research Laboratory was generously staffed with well-educated scientists. In 1955, 32 were college-educated officers, 12 among them being physicians from some of the country's best medical schools. Three officers had PhD's and one had earned both PhD and MD degrees. Among the 117 civilian researchers, 55 held Master of Science degrees or higher.

In 1961, the Kennedy administration gave a generous financial boost to medical research, further increasing the number of professionals. In terms of formal education, the staffing of the Edgewood Medical Research Laboratory was certainly far from shabby. I felt privileged to become part of its research team.

With surprising dispatch, after my arrival in 1961, I received a temporary Top Secret security clearance and very soon thereafter, a permanent one. Evidently, my past record was reassuringly devoid of red flags. Although almost all the research in progress at Edgewood Arsenal was classified – from Confidential up to Secret – physical security appeared surprisingly minimal. Two single guard entry gates and a simple perimeter of chain link fencing and barbed wire defended the grounds against intruders. The other research buildings usually had solitary security guards who casually checked ID's and the required signatures on entry and exit. The age of metal detectors and bomb-sniffing dogs had not yet peeped over the horizon.

Quarters for junior officers (below the rank of Major) were located in this row of houses or in Grant Court, visible in rear (1963).

The "Annex," where physicians had offices and conducted volunteer studies, also had very little visible security. One could often enter it freely through unlocked doors. I remember coming in at night and feeling a spooky "Twilight Zone" sensation, when walking alone through its deserted halls.

During World War II, the annex had housed Chemical Corps soldiers; later it was refurbished for use by researchers. Of course, there were locked cabinets and that sort of thing, but in general the atmosphere was informal and the safeguarding of documents rather casual.

It was dark when our family arrived at Edgewood. Our assigned apartment in Grant Court, reserved for junior officers, was cold and contained only a few temporary furnishings. Our baby son had a cough and fever. Remembering that Kaz Kimura had been a pediatrician before he accepted a research job at the Medical Labs, I called him right away and he graciously prescribed appropriate medicine.

Soon, my adventures in the Clinical Investigation Division began. I spent the first few days learning the names and responsibilities of staff members and observing tests with EA 2277. Before long, however, I became impatient to get off the bench and onto the playing field.

Specialist-5 Ephraim Goodman, the brilliant psych tech I had met on my initial visit, was pleased that I had arrived. He led me through the established routines for administering chemical agents, entering written observations in charts and evaluating the mental status and degree of incapacitation of the drugged volunteers.

Goodman had a master's degree in psychology and was a limitless source of information about almost every aspect of the experiments. He should have been an officer, but was afflicted with an excess of modesty, as well as the compulsive personality of a perpetual scholar. He had no desire to be in charge, preferring to

retain the status of a loyal assistant. We therefore got along famously since I had an inordinate need for autonomy and liked decision-making.

Bill Gordon, however, became progressively miffed, believing I was trying to muscle in on the operation too soon. I had discovered, for example, a whole department devoted to film documentation, located in the Chemical Research and Development Laboratory – nerve center of the Edgewood conglomerate. Soon, with the backing of Colonel Lindsey, I was boldly arranging for the Graphic Arts department to make a short movie of a volunteer under the influence of an incapacitating agent. I assumed the role of examining physician in the film, and had the camera crew take moving pictures of the young man as he bumbled through simple tasks. He became unable to assemble a rifle and dropped the ruler as he tried to measure two points on a military map. He recoiled from the vision-testing apparatus as though it were a hostile aggressor, and then started sipping beer from an invisible can, savoring the taste of its non-existent contents. He had already taken off his upper garments (for no apparent reason) and was quietly singing a little tune.

Van M. Sim, M.D. (1922-1990) Trained as an internist, he was Chief of Clinical Research from 1955-1961 and Chief Scientist of the Medical Research Laboratories thereafter.

It made good footage, but it pissed off Bill Gordon who was annoyed to find himself shunted off to the wings in the role of spectator, while I commanded center stage. Some of the psychologists were also becoming restive as I began to change the type and frequency of the performance testing they had put in place before my arrival.

Sensing the discontent of the staff members, who at first had seemed so glad to see me arrive, I decided to do the psychiatric thing – visit the boss and confide my growing discomfort and sense of rejection.

Kaz was in his office in the main building, leaning back in the adjustable chair that barely accommodated his voluminous frame. He was smiling as I came in, a sort of Asian smile that reminded me of the Zen masters I had read about during my residency.

"What's up, Jim?" he began, lifting his gaze from whatever he was doing.

"I like the work, Kaz, but I get the feeling that I am creating some resentment among certain members of the staff." I paused, and assumed a mildly hurt demeanor.

"Well Jim, it's not that no one appreciates your work," he said in a fatherly manner. "But when you come charging into your new job like a bull in a China shop, it's bound to ruffle a few feathers." His metaphors were slightly mixed but his meaning was clear.

In return, I reluctantly acknowledged the accuracy of his observation. "I'm doing my best," I said. "But I don't seem to be getting much love."

"For all you know, you are loved very much." He smiled again, seemingly amused by my way of expressing myself. "It's not what you're doing; it's your manner of doing it."

"I see." It was not the first time I was destined to be confused with Napoleon. "Okay, I'll try to be a little more sensitive."

"That's the way," said Kaz. "Don't get discouraged. Things will work out. But take it easy, go a little slower. You'll be running the show soon enough."

I took his advice and things improved. I became a bit more tactful, and even apologized to Bill Gordon for being self-absorbed and intrusive. I told him I realized he had been "the Man" for quite a while before I came on the scene. I confessed that I tended to be overeager at times and was capable of stepping on toes without intending to. Bill seemed surprised by my candor. He quickly forgave me and we had no further problems.

Thing were actually going smoothly by the time he left in June. I was now deeply involved in giving mind-altering drugs and watching their amazing effects. More than once I walked into the ward area in the middle of the night to see how the volunteers were doing after they had absorbed a fairly large dose of EA 2277 (later to be renamed CS 4030, then TK and ultimately its permanent moniker: BZ). It was quite a long acting drug, whose effects did not peak until 8 hours. Then, strange and unpredictable behavior emerged, increased, decreased, and finally faded away a day or two later.

One night I came in at 2 A.M. Two volunteers, under the influence of a generous dose of BZ, were sitting at a table in the area set aside for meals. Sitting close by, two of the night shift technicians were vigilantly monitoring them, ready to deal with any troublesome behavior.

The two volunteers seemed not to notice me. I watched with interest as one of them suddenly shouted into an aluminum water pitcher; calling out to someone he evidently thought had fallen into a well. Abruptly distracted by my questions, he then attempted to take a bite out of a non-existent chicken. "This thing is rubber," he said. He sounded like a politician, jaded from attending too many fundraisers.

Out in the hallway, Van Sim suddenly ambled by, wearing his underwear. "Oh no," I thought. "I hope he hasn't been getting into the BZ again." Van had acquired a long-standing reputation for fearlessness, insisting on trying every chemical agent himself before giving it to volunteers. For such (perhaps ill-advised) heroism, he had received a certificate for outstanding civilian service, based on his bravery and dedication.

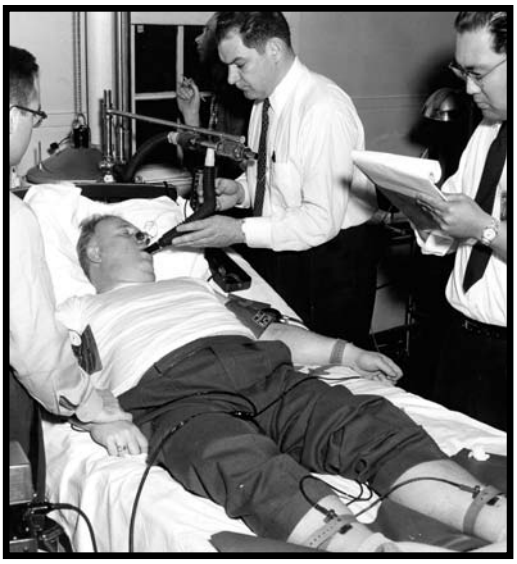
"Hi, Jim," he said in the deep voice that always seemed to be originating from somewhere in his bowels. "What are you doing here?"

"I sometimes come in late at night to check on the guys," I said. "They get pretty interesting around midnight. What are you doing?"

He had what looked like the glass faceplate of an old-fashioned watch taped to his wrist. "I'm trying to see if LSD has any effects through the skin," he replied somewhat distractedly. "I've got it in some ethylene glycol under this watch glass."

"So far it hasn't had any particular effect," he added. I was still dubious. For one thing, I was uneasy about people testing themselves and had said as much soon after I began running my own experiments. I also knew that Van had taken LSD by mouth a number of times (for one reason or another) and once or twice by injection. He had also ingested a dose or two of "red oil," the super-concentrated potion of marijuana extract that had enjoyed a few moments of notoriety when it was first produced. Red oil had conjured up images of a safe and possibly somewhat pleasant incapacitating agent in the minds of some commanders. On reconsideration, however, they had decided it was too lacking in potency (and perhaps too socially unacceptable) for military purposes, and shelved it.

Van continued to mumble further about his theories of how LSD exerted its effects. His mumbling did not seem much different from the way he sometimes mumbled during the day and his explanation did sound reasonable. I decided he was probably okay after he explained further that he had gone to sleep in his office at the end of the ward in his underwear, and had just gotten up to use the latrine. After all, as one volunteer later commented after an LSD trip, "It's nothing to get worried about. We're all probably jacked out of shape a little bit anyway."



Dr. Van M. Sim as a volunteer, taking sarin nerve gas from Dr. Bernard McNamara, Chief of the Toxicology Division – courage was one of Van's greatest virtues.

Edgewood turned out to be as enjoyable a place to work as I had hoped. It even felt good to be among the slightly "jacked out of shape" people of the world, whether they were staff or volunteers. I made sure, however, that no volunteer who was seriously "jacked out" went on a drug test with BZ, LSD or anything that might dislodge his personal stability "jack." I was not in favor of pushing anyone even close to the edge of a psychiatric cliff, and carefully interviewed every volunteer before allowing him to become a psychoactive drug subject.

COL Lindsey soon became an empathic friend and my most dependable "on location" ally. He had a colorful personality and a sort of "Go, Army" attitude. Trained as a surgeon, he seemed to be afraid of no man (or woman), including generals. Many legends had sprung up around him. One was that he despised wearing new looking uniforms. When obliged to replace his worn out military cap with a fresh one, for example, he defiantly ran a new cap up a flagpole for 30 days to give it a properly weathered look.

As a lecturer, he displayed a carefree attitude toward lethal chemical agents; even when everyone in class knew that a small drop was more than enough to cause death. While addressing a spellbound audience of young officers, he would sometimes partially immerse one finger in a small beaker of pure VX for a few seconds. Without interrupting his lecture, he would then amble to a nearby sink and casually wash the deadly chemical from his finger. The teaching point was that VX could not enter the skin instantaneously, and that accidental exposure of a small area would not be harmful as long as the site were promptly and thoroughly decontaminated.

Lindsey engendered other legends. Once, when a doctor asked some volunteers to enter a chamber filled with CS tear gas, Lindsey went right along with them and refused to come out. He found that if he could manage to tolerate the first twenty minutes or so, he would became adapted to the irritant effects and could function normally. This profoundly impressed both volunteers and staff. Ordinarily, even highly motivated soldiers would not submit to more than a few minutes – sometimes only seconds – of exposure to the painful effects of CS on eyes and respiratory passages.

However, when a young female officer called to inform him that she was in her apartment, intending to shoot herself, Lindsey's confident attitude carried him a bit too far. Ignoring the recommended protocol for such situations, he raced over to her quarters, charged up the stairs and peremptorily shouted for her to put down her pistol "or else." Unfortunately, this approach proved ineffective. A few seconds later, a single shot rang out, making clear the sincerity of her intent.

All of this was past history by the time I arrived at Edgewood. Lindsey had recovered from this brief lapse of judgment and returned to his usual idiosyncratic and irreverent ways. He wrote official memoranda in a format that was decidedly not in the Style Guide for Military Authors. But, for all his quirks, the lab personnel greatly loved and respected both his eccentric style and his startling creativity.

His off-the-wall sense of humor emerged unexpectedly one day when I dropped by his office to say "Hi."

"Ever hear of the Journal of Irreproducible Results?" he asked me.

"Actually, no," I replied.

"It's put out every few months by a renegade group of iconoclasts in Israel," he explained. "Serves as a good counterbalance to some of the puffed-up stuff that scientists occasionally bully editors into publishing. I have an idea for an article to write on the subject, if you'd like to help me."

"Sure," I said.

"I was thumbing through an old urological journal and one of the authors referred to the Coudé catheter, paying tribute to Dr. Coudé for inventing it."

"That was gracious," I said.

"The Coudé catheter wasn't actually named after anyone. It means, 'curved' in French. This got me laughing, and then I thought to myself 'if a so-called scholar thinks it was named after a doctor, who knows what other eponyms came about that way.' "

"That's a great idea," I said. "We could point out the important contribution of Siegfried Gestalt, who obviously started Gestalt psychology. And how about Max Factor for Factor analysis?"

"Those are good ones," he laughed. "And don't forget about 'Olë Bjorkan," inventor of the beer-can opener." By this time, we were both in stitches.

Within a couple of days, we had drafted an article, filled with reverential recognition of important achievements by under-appreciated non-existent innovators, so rarely acknowledged in the medical literature. It was great fun to see our satire appear in the *J. Irreprod. Results* a few months later.

Carl Stearn: Lean, cool, calm and dependable administrator

"My first peer-reviewed article," I commented when he showed me the reprint. "Of course someone should give credit to Dr. Peer for developing that ingenious review procedure."

The workdays were becoming more and more predictable. I would come to the clinical testing facility at 0800 (unless I had been up half the night documenting some volunteer's bewildering antics) and Carl Stearn would already be at his desk.

A lean, unflappable civilian administrator for the Department, Carl always dressed in a white shirt with dark tie and pants. I don't recall if he was from

Texas, but he had the kind of smooth drawl that made him seem like he would be perfect as a sidekick in a John Wayne movie.

"Hi, Doc" he greeted me each morning. I liked the way it sounded.

I hated administrative chores, and was not too happy when Doug Lindsey told me he wanted me to be the rating officer for the other physicians in my branch. True, I was a captain, but they were captains too and all I had on them was date-of-rank. Unfortunately, this was often the key consideration in determining the military pecking order. I anguished for several days about it, since I liked to be liked, and was hesitant to write anything critical about my fellow doctors. Heightening my discomfort, I was first supposed to counsel each of them face-to-face in a private session.

Malcolm Bowers was no problem, of course. He was an athletic "golden boy" who had been a star quarterback in college, and was already fully trained as an internist. At Edgewood, he had become fascinated with the weird nighttime dreams reported by some subjects after they received a small dose of a nerve agent. I admired this alert observation and was not surprised when he went on later to become a psychiatrist, a professor at Yale, and a world-renowned expert on chemical changes in the brains of schizophrenic patients.

I had a problem, however, rating an anesthesiologist who had been selected to examine John Glenn, following his historic orbital voyage in a space capsule. After this honorific assignment, I guess he felt no need to continue being particularly energetic back at Edgewood Arsenal. Like many draftee physicians, he probably would never have chosen to be at Edgewood Arsenal in the first place. Nevertheless, for some of the doctors, Edgewood probably seemed like a good place to take refuge from the rigors of ordinary Army doctoring, which might involve having to work in a combat environment.

"Andrew," I said as we sat down for the counseling session. You're certainly a competent physician, but I must point out some negatives that I plan to include in your otherwise very acceptable efficiency rating." He glared at me as I tried to remain dégagé and impassive. Fortunately, I had brought a list, not wanting to rely on memory, and proceeded to reel off what I considered his shortcomings. He listened in skeptical silence, and I was greatly relieved when he looked grim but decided not to offer rebuttal. We departed in opposite directions and I exhaled gratefully as I headed for lunch.

Thankfully, I was not usually responsible for rating the enlisted-grade personnel. That was the job of Master Sergeant Ignace Ditchkus, highest-ranking of the non-officers. "Ditch" was slightly grey at the age of 40-something (a seemingly advanced age) but he was energetic and reliable. His assistant was Specialist-5 Rudy Rivera, who made sure the volunteers appeared on time for pre-test physicals, lab work and interviews prior to participation in tests.

Speaking of Sergeant Ditchkus, I cannot resist telling a story about his skill as a diagnostician, for which I owe him a sheepish debt of gratitude. One morning, I had awakened to find that a horrible, unbearably itchy blister had suddenly appeared between two of my toes. As the days passed, it grew larger and began to exude fluid. Suddenly, I became gravely concerned.

Time magazine had recently reported some cases of cutaneous anthrax appearing on the European continent. Sandals, made in India and cut from leather cured in cow dung, were the source. Consulting my textbooks, I found a description of anthrax skin lesions that seemed very much like the one between my distal digits. (Of course, I had never seen a case of anthrax, and my

pathologist friend Ken Carter later chided me that not a single case of anthrax had been discovered in the United States that entire year.) Remembering that I had indeed recently purchased a pair of imported leather sandals at the PX, and worn them at the swimming pool, I promptly dubbed myself a canny diagnostician. I had managed to connect the dots!

Delighted by the certainty that I had anthrax, I presented my theory to the Post Infirmary doctor. I even brought along the sandals, hoping he would have them tested for the presence of anthrax spores. He seemed to accept my reasoning and prescribed a course of penicillin. After I had taken it for ten days, there seemed to be no improvement – in fact, my itchy blister was getting worse.

Early one morning, when there was no other medical expert around with whom to discuss the problem, I finally confided my fears to Ditch. The wise sergeant suggested rather offhandedly that I get some Desenex ointment at the PX and use it for about a week. Sure enough, the blister healed completely! Without saying as much (no doubt drawing on his vast clinical experience in Army shower rooms and barracks), Master Sergeant Ignace Ditchkus had cannily recognized the problem as athlete's foot.

I went back to the dispensary and apologized to the doctor. I ruefully acknowledged my relative ignorance about athlete's foot and told him that thankfully my sergeant knew what it was and had guided me to the appropriate treatment. The doctor said he was glad it had worked out. As I was leaving his office, he added, "By the way, your sandals are over there on the top shelf." I thought I detected a slightly derisive tone in his voice, and the hint of an ironic smile briefly crossing his face.

The sandals were still in the brown paper bag I had brought to the dispensary. It gradually dawned on me that no one had attempted to culture them. The dispensary doctor had consciously been humoring an obviously under-trained, possibly delusional psychiatrist! Worse, there was no way to make a graceful exit.

And so it went at Edgewood – a constant oscillation between seriousness of purpose and absurdity.

* * * * *

4 HUMAN GUINEA PIGS – NOT!

If anything is sacred, the human body is sacred.

Walt Whitman *Leaves of Grass*
"I Sing the Body Electric"

Why would anyone volunteer to take an unnamed chemical, even in the interests of medical science and national defense? The intuitive answer might be that nothing short of extortion could induce a rational adult to take such a risk. Surely, only extraordinary and substantial inducements could lure a normal soldier into honoring such a request.

Surprisingly, we never needed to browbeat, threaten or hint at repercussions for someone's unwillingness to participate in a drug test. Invariably, would-be volunteers inundated us with applications, year after year. An abundance of troops were obviously more than willing to jump through all the hoops required in order to make the list of accepted candidates. In fact, the ratio of the number of applicants to the number accepted increased progressively throughout the 1960s.

If these were "guinea pigs" or (as some writers have referred to them), "unwitting guinea pigs," one would have to assume that American soldiers in those days lacked basic intelligence. They must have been suffering from personality disorders, or been harboring devious reasons for wanting to take chemicals whose names they might never know, from doctors who could not tell them every detail of the effects to expect. Certainly, they could be perceived as lacking in common sense to take a drug that might deprive them of their mental

faculties for up to several days. Undoubtedly, they would want assurances from some independent government agency, such as the Food and Drug Administration, that any chemical they agreed to take was perfectly safe.

How, then, could one explain the fact that between 1955 and 1975, approximately 7,000 healthy enlisted men freely chose to come to Edgewood Arsenal? Each had already met all the Army's requirements for service, been through the rigors of basic training, and proven his ability to follow the rules of Army life. Yet they came, and all left Edgewood without suffering detectable brain damage or any other serious injury. Furthermore, many of them even requested a second assignment to Edgewood the following year, when the recruiters returned as scheduled to their Army areas.

In 1961, I gave a test dose of the sleeping medication Seconal to a 35-year old career sergeant. He proudly informed me beforehand that this was his sixth visit and he would no doubt be back again next year. I had to tell him that this was unlikely – it would be unfair to all the other soldiers who wanted to be part of the program.

Unwitting guinea pigs? Naïve young men taken in by Army propaganda? Mentally marginal soldiers who could not make good decisions? Ignorant individuals who didn't know what they were getting into because of tight secrecy? In my view, none of the above!

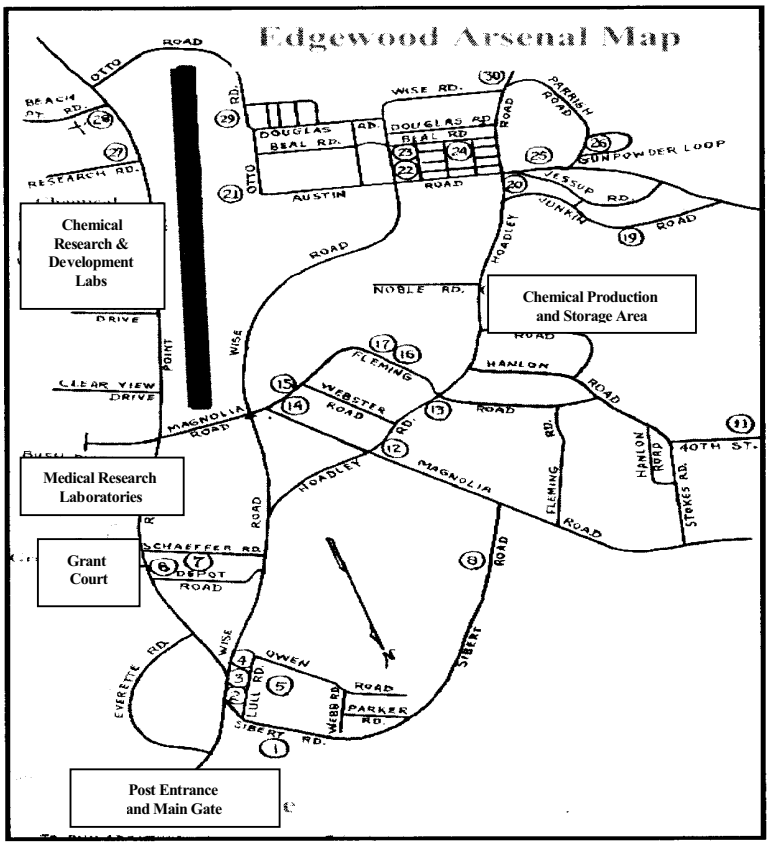
The men accepted into our program were above average in education and intelligence. Their average AFQT (Armed Forces Qualification Test) score, administered prior to induction, was equivalent to an IQ well over 110, placing most of them in the top third of the general population. With few exceptions, all had graduated from high school and many had completed a year or more of college. All were in the normal range with respect to personality and mental health. None had a record of bad conduct, either before or after they signed up. Their motives for volunteering were quite straightforward. These were not fanatical patriots. They were just soldiers who saw Edgewood Arsenal as an attractive assignment, where they would not have to undergo unreasonably dangerous or stressful procedures. They understood that they could freely say "no" if they had doubts about any test.

Grapevines exist in every organization, but few are more extensive than those in the military services. Providing reliable information and advice to buddies is a corollary of the Code of Conduct. Soldiers who spend two months in a testing facility surely bring back stories of their adventures – about the gas masks they tested, the discomfort of a tear gas chamber, or the strange trip produced by a drug called "LSD" or "BZ" that had them doing crazy things for hours or days.

Instructions were given prior to departure not to discuss the details of any tests they had participated in. In reality, this was a pro forma admonition. Exhorting people to maintain secrecy perversely guarantees that many will share their secrets. Although senior officers at the Edgewood Lab insisted that volunteers not divulge their experiences, it is doubtful that any of them truly believed that the men could resist telling stories to their buddies when they returned to the home installations.

Although most of us recognized that the Army grapevine, like the Internet today, was basically unmanageable, we were obliged to withhold the code names and structures of classified chemical agents. Contrary to what some writers have asserted, however, our doctors described and truthfully answered questions

regarding the general nature of a drug's effects and the purpose of the experiment before asking for a signature on a consent form. (Actually, in the course of their two-month assignment, many overheard the names of their drugs and could learn from a bunk companion what the effects were like.)



Schematic map of Edgewood Arsenal, showing location of labs and living quarters

Nevertheless, years after extensive testing with drugs such as BZ and LSD had ceased, investigative reporters continued to apply the pejorative "guinea pig" cliché to Edgewood volunteers. If one accepts this designation as correct, perhaps all who decide to sign up for military service, without being told all the details of the dangers they might encounter, should also be considered "guinea pigs." I suppose it all depends on one's "weltenschaung." Nevertheless, no matter what one may think about allowing young soldiers to volunteer as test subjects in chemical experiments, the men themselves seemed to regard it as an attractive prospect, year after year. For more than two decades, volunteers came and kept coming, rarely expressing regret about their decision.

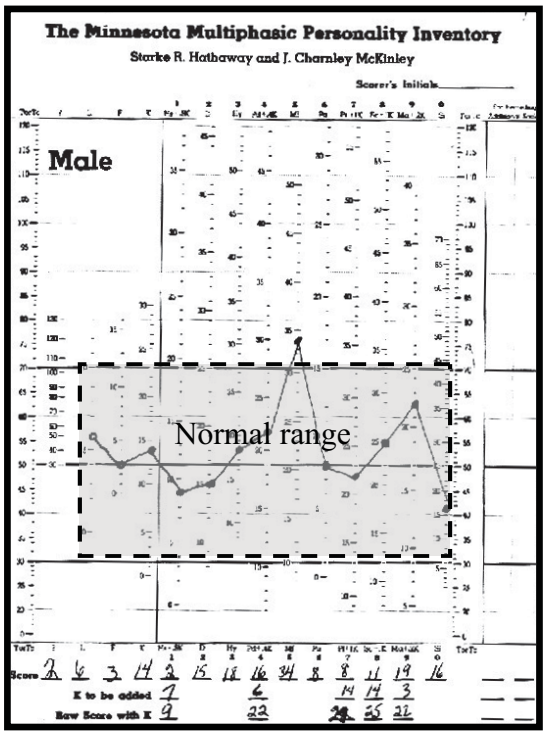
In 1955, as the program was just starting, the need for volunteers was modest. At first, Edgewood Arsenal requested only twenty men, but then the number increased to 30 and by 1963 the requirement had risen to 50 every two months. Eventually a cohort of 60-80 arrived, requiring the prior review of as many as 300-500 applicants. Surely, this should convince most observers that a great many soldiers wanted to come to Edgewood.

Yes, there were inducements. They included a light duty schedule, $1.50 per day (the standard pay for temporary duty assignments), comfortable air conditioned barracks, a 3-day pass each weekend (unless on a test), a comprehensive medical examination not ordinarily available at their home installation, and a letter of commendation at the end of the two month assignment. As the IG noted in a later review of the program, these were actually quite substantial inducements for the average low-ranking soldier. Furthermore, there was no penalty for changing one's mind. Even after arriving, volunteers could decline any test they wished, or even opt out of their assignment altogether, in which case they would return to their previous assignments without prejudice. Quite a good deal!

Inducements, incidentally, are part of almost every experimental program, in or out of the Army. Newspaper ads recruiting volunteers for similar civilian experiments usually promise a monetary reward. Sometimes compensation comes as a health benefit – free therapy with a new drug along with free

examinations and careful follow-up by a skilled physician. Occasionally, it may be a lottery-type proposition, whereby the only reward for one's services might be the chance to win a flat screen TV, a portable computer or a free vacation in Tahiti. The final decision always rests with the individual. In our program, it was no different.

It was not easy to become an accepted candidate. Each man was required to fill out a lengthy personal history form, detailing his education, prior disciplinary problems, past or present medical problems, allergies or physical limitations, predilections for street drugs or alcohol, future occupational and career goals, and reasons for volunteering. Those who said they fervently believed it was their "patriotic duty" to take drugs "in the interests of National Defense," or "to see what a secret drug feels like," were generally rejected. We were more likely to accept those who said they wanted a chance to visit friends or relatives on the East Coast, or a change of pace from boring jobs as desk clerks or motor pool mechanics.



Example of an MMPI profile

At each Post, following a presentation by the briefing team, those still interested stayed in their seats and filled out the numerous pages of the personal history form. Then they spent up to an hour and a half completing the Minnesota Multiphasic Personality Inventory (MMPI), a widely used instrument for detecting psychiatric problems or profiling personality characteristics.

First developed by Hathaway and McKinley in 1947, the MMPI is an interesting test. Each question is a statement which the applicant checks "true" or "false" as it applies to himself. The originators chose its 550 items from a much larger pool, intuitively derived from clinical experience. Initially, they administered their inventory to individuals who had already been psychiatrically diagnosed. Then they selected items that distinguished each diagnostic category. These became the basis for the final 550-item standardized form, still widely used by psychologists after almost 60 years.

Items most consistently answered true (or false) by each diagnostic subgroup are useful indicators of that diagnosis. For example, patients with paranoid symptoms usually check "true" when asked if they think other people often talk behind their backs, while non-paranoid patients usually do not. Eventually 13 "scales" were established – for example, the Ma Scale (manic tendencies), D Scale (depressive tendencies) and Pd scale (psychopathic tendencies.)

Three validity scales were also included: L (lying), F (falsification, through inattentiveness to the test, deliberate attempt to mislead, or disturbances in thinking) and K (a scale reflecting the degree to which an individual tries to "put his best foot forward" or present himself in the best light without actually lying). Depending on the circumstances, some who take the MMPI actually try to score high on one or more of these scales. Those who want to "fake good" (for example, be viewed as psychologically well adjusted in order to be selected as a volunteer) will have a high "L" score and probably a high "K" score as well. Those who want to "fake bad" or who cannot comprehend the questions or give

improbable or inconsistent answers will score high on the "F" scale. High scores on any of the three validity scales can be grounds for non-selection.

In summary, there was no coercion. If anything, local commanders sometimes discouraged or even refused to let valued members of their units go to Edgewood. Would-be volunteers were often among the best men they had. Nevertheless, every year each of the six Army areas in the Continental United States provided more than enough eager candidates. Admittedly, when not undergoing testing with a chemical agent, a volunteer's life was probably much less arduous at Edgewood Arsenal than it had been back at his Post. He could visit nearby cities such as Baltimore and Philadelphia on weekends, and had plenty of free time on his hands when not busy with barracks duties.

Each volunteer was interviewed on arrival and again prior to departure.

The selection process was initiated by a local announcement that a team from Edgewood Arsenal was coming to describe their research program. Higher authorities ordered commanders to set aside sufficient time at the Post auditorium for would-be volunteers to complete applications, but only if they wished. From 500-1,000 curious soldiers usually showed up. An Edgewood physician would be there to tell the story of our program and show a movie of the facility and testing procedures. After that, those who were interested completed the required forms.

Upon arrival at Edgewood Arsenal, each volunteer went thorough a battery of medical and psychiatric examinations. They were then placed in categories. Some were allowed to test psychoactive drugs at the higher dosage levels. Others would be eligible only for low doses. The remainder would receive no drugs at all but could test protective clothing or equipment.

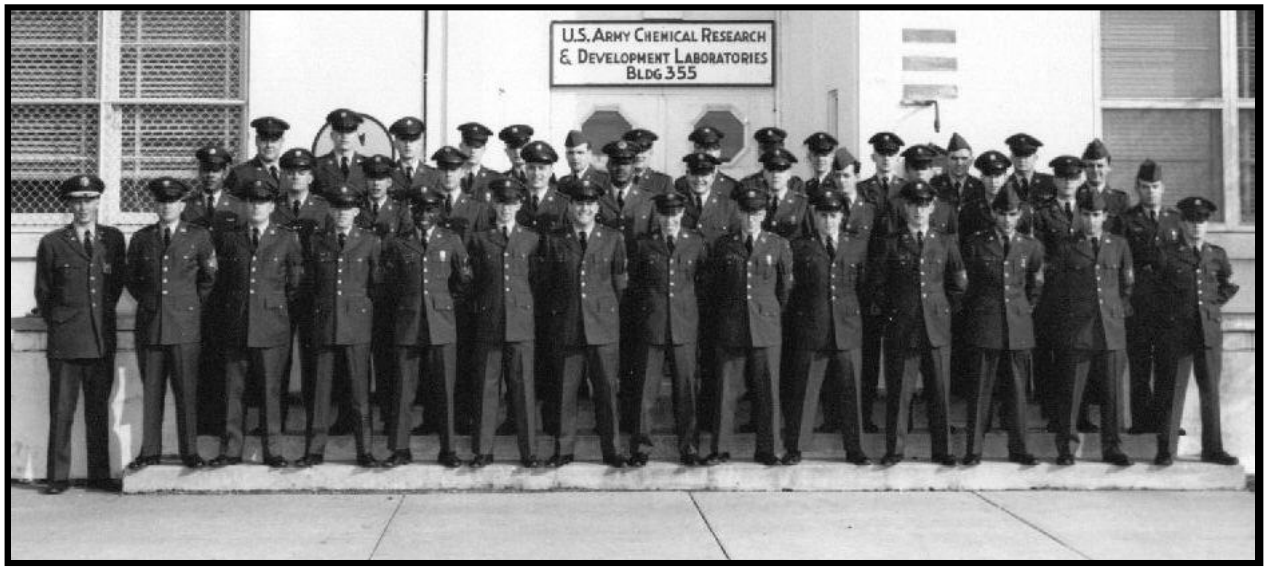
Our screening process, although hardly as rigorous, was remarkably like that used to select astronauts. The difference was that at Edgewood, we were seeking soldiers ready to go into "inner" rather than outer space.

A second informed consent, beyond the initial general consent given at the time of arrival, preceded any commitment to a particular procedure. A third consent form was required if we planned to document drug effects on film or on videotape.


The medical staff provided a repeat of lab tests and physical exam for each volunteer prior to their return to Post of origin.

Volunteers were frequently willing to participate in a second or even a third study, usually involving different chemical agents. We always required at least one drug-free week between tests – usually more. This gave us time to watch for possible after effects. Finally, at the end of his two-month assignment, each volunteer received a repeat physical exam and comprehensive battery of lab tests to assure his full recovery.

As mentioned, some 7,000 enlisted men participated in the Edgewood Arsenal chemical agent testing program, most of them from 1961-1970. None, to my



Volunteers on steps of the Medical Research Laboratory building, dressed in their best at the end of their two month assignment.

knowledge, returned home with a significant injury or illness attributable to chemical exposure. Nevertheless, years later, a few former volunteers did claim that the testing had caused them to suffer from some malady. Follow-up LSD studies at the Walter Reed Army Institute of Research (WRAIR) in 1978 were unable to support these claims. A detailed statistical review of morbidity and lethality rates in subjects given BZ conducted by the National Academy of Sciences (NAS) in 1981 also failed to reveal any detectable ill effects. Following any unusual procedure, medical or otherwise, it is almost inevitable that someone will eventually challenge its safety. As with cell phones and breast implants, claimants may attribute unexplainable physical or mental infirmaties to some previous (often long ago) event. This is predictable, even when there is no scientific evidence supporting a causative connection. A major problem, when trying to ascertain the long-term effects of a particular single experience, is that many "intervening variables" (e.g., use of drugs or alcohol, trauma, illness) muddy the waters; absolute certainty is therefore unattainable.

It still interests (but more often irritates) me to read news articles referring to the Edgewood volunteers as "guinea pigs" or, especially, "unwitting guinea pigs." As I have commented during media interviews, real "guinea pigs" do not volunteer freely or sign consent forms. Nevertheless, many persist in the use of this shop-worn cliché. I would say just the opposite – that our volunteers performed a patriotic service, and almost invariably felt good about it!

Perhaps we should always expect that some dissenting group will challenge scientific findings that do not support their beliefs. It also seems natural that some individuals will attribute monetarily compensable damages to unlikely causes – there is certainly no shortage of lawyers and juries ready to agree with them!

* * * * *

5 AN INTERESTING DRUG TO START WITH

I think it is much better that . . .
every man paddle his own canoe.
Frederick Marryat: ***Settlers in Canada VIII***

Before getting into the "heavy duty" chemical agents such as BZ and LSD, it might be useful to discuss a more familiar drug. In 1961, although tests with BZ were already in progress, we also took some time to look into the incapacitating properties of tetrahydrocannabinol (THC), the active ingredient of marijuana.

Edgewood studies in the late 1950s had already demonstrated that delta-9 tetrahydrocannabinol, the active principle of Cannabis indica (a "weed" that grows in the wild – and sometimes in underground hydroponic farms), was not sufficiently potent to become a chemical weapon. Those studies involved the use

of "red oil," a concentration of a synthetic relative made by chemical extraction and purification. Red oil engendered a powerful high, but not within the dose range thought necessary for any practical military purpose. The Chemical Corps called it EA 1476.

Historically, attempts to use THC as a weapon dates back 2,500 years or more, when the Chaldeans allegedly burned massive amounts of its plant of origin in an effort to render an attacking force incompetent. Supposedly, they burned enough hemp to generate a huge cloud of the stuff, but the success of this approach is uncertain – the smoke might easily have affected both attackers and defenders. (Modern observers of the drug scene might speculate that this could even be a way of averting war altogether.)

Chemical Corps interest in cannabinoids came alive when an analog of THC, code named EA 2233, emerged from the laboratories of Arthur D. Little under the supervision of chemist Harry Pars. Before proceeding to a summary of the experiments we carried out with EA 2233 in late 1961, a brief detour "back to the future" is appropriate.

Harry Pars, as I remember him, was a tall, dark-haired, well-dressed and well-spoken man. He was a frequent visitor to Edgewood during the early 1960s, persuasively presenting progress reports about his latest work with marijuana-related synthetic drugs at planning committee meetings. All of this was classified, of course, but in August 1966, Harry evidently received clearance to publish a paper in The Journal of the American Chemical Society. He titled it (in part) "… physiologically active nitrogen analogs of tetrahydrocannabinol."

This article did not escape the vigilance of investigative reporters from the San Francisco Chronicle. A swarm of reporters soon surrounded Harry, curious to know more about a footnote acknowledging that some of his work had been "carried out for the U.S. Army Edgewood (Md.) arsenal [sic] in collaboration with the Sterling-Winthrop Research Institute, Rensselaer, NY, under contract No. DA18-108-AMC-103(A)"

Media brouhaha soon developed around the notion that the military might conceivably be making common cause with the counter-culturists, who for years had extolled the smoke-able "flowering tops" of Cannabis as instruments of peace. The irony that a "straight" military laboratory was investigating "Synthetic Pot" as a potential instrument of chemical warfare was too rich for the fourth estate to ignore. Here was a forbidden mind-altering substance, whose use had for decades been under futile attack by anti-drug government agencies as well as all "right-thinking" citizens – and here was the US Army, apparently contemplating its use on the battlefield!

Poor Harry! In response to what must have been a withering barrage of questions from reporters, he at first conceded that the Arthur D. Little firm regularly accepted substantial government contracts involving secret work. He then made the disastrous admission that he might occasionally fend off a questioner to protect a secret project. "If I had a contract with anybody – well, our clients are held in confidence unless they themselves want to disclose," Dr. Pars said. "I think that's an Arthur D. Little policy."

As the hounding continued, Harry at first claimed that the A.D. Little contracts were essentially limited to supplying about six pounds of a potent synthetic relative of THC to the National Institutes of Mental Health for $75,000. Dr. Bob Petersen, speaking for NIMH, immediately expressed "shock and surprise" that anyone might suppose that such a compound could have any military applications.

Another NIMH scientist went out on a limb, saying that it was "incredible" that marijuana in any natural or synthetic form could serve as a chemical warfare agent. THC itself, he said, deteriorates rapidly and is too bulky and expensive for such use. LSD is cheaper, more stable, and packs a bigger punch in a smaller dose. He added that one could readily introduce an easily carried quantity of LSD into the food or water supply of a major city, enough to alter radically the sense perceptions of its population for 12 to 24 hours.

These extravagant disclaimers, coming from an official NIMH spokesperson, are so inaccurate that it is hard to know where to start setting them straight. To begin with, THC does not ordinarily deteriorate rapidly, as shown in a careful study of shelf life of marijuana potency published in the Proceedings of the New York Academy of Sciences more than thirty years ago. If protected from moisture and heat, Cannabis buds usually deteriorate only about 5-10% per year and much less if kept refrigerated. In purified form, THC would weigh far less than the buds and would require only a few dozen milligrams to produce substantial impairment of performance. This, of course, represents a low degree of potency compared to LSD, which requires only 1 or 2 tenths of a milligram (100-200 mcg) to be effective. LSD itself, however, far more than THC, is highly unstable in the presence of heat, ultraviolet light or chlorination. Certainly, it is not cheaper than THC. Six pounds of LSD (the amount of THC sold to NIMH for $75,000) would cost orders of magnitude more.

As Augustus Stanley Owsley, the folk hero chemist who provided the San Francisco Bay area with its purest supply of "acid" in the 1960s could testify, the street value of six pounds of LSD might have been roughly $75,000,000 if distributed as 300-microgram "dots" on blotters. (Today, doses sold on the street average closer to 50 mcg, which no doubt explains the increasing rarity of severe reactions requiring medical attention.) Although the cost of synthesis in an A.D. Little lab would be much less per gram than in Owsley's cottage industry, it would still have been exorbitant. In the early 1950s, when the CIA naively tried to order ten kilograms of LSD, Sandoz, the holder of the patent, politely informed the CIA that its total production to date had been only about ten grams.

The assertion that one could affect a city with "an easily portable" quantity of LSD dumped into its water supply is outrageously inaccurate. Powerful as it is, tons of LSD would be required to create an effective concentration in the huge volume of a major city's reservoir. In the presence of sunlight and chlorination, it is doubtful that residual LSD would have any perceptible effect by the time it reached consumer faucets. The amount of chlorine in a glass of ordinary tap water is sufficient to rapidly deactivate a full dose of LSD.

The reporters next served up a damning rebuttal to Dr. Harry Pars' hedging reply that he only sold synthetic pot to NIMH scientists (who, in turn, obviously wanted to wash their hands as quickly as possible of any awareness of military interest in the compound). Reporters pointed to an acknowledgement included in Harry's published report. "You stated in your article," one of them noted, "that you were 'indebted to Dr. A.T. Shulgin, at that time with the Dow Chemical Company, for drawing our attention to the synthesis of these nitrogen analogs, and to Dr. S.W. Hofmann of the research laboratories, U.S. army Edgewood arsenal (sic), for his encouragement of this work.' What's the story?"

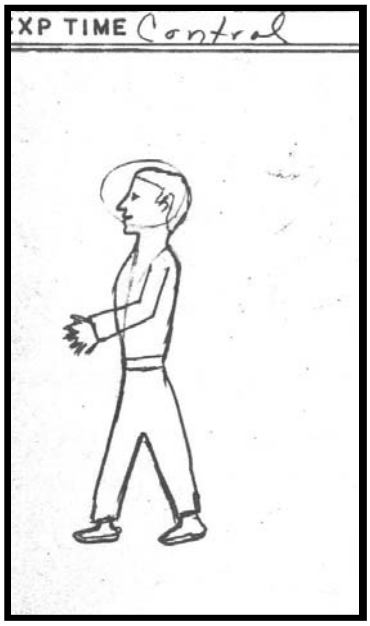
"Confronted with this evidence," continues the March 1, 1969 San Francisco Chronicle article, "Dr. Pars denied he had made an earlier denial. 'Why would I deny something that's on the public records? " he asked.

"But then he added 'It is not my business to be telling you what the

Department of Defense is or is not doing…I'm certainly not going to go out of my way to disclose things about Department of Defense work.'" R.I.P., Harry Pars!

This story speaks volumes about the adversarial stance of the media in the late 1960s, especially regarding chemical warfare research. Apparently, no one wanted his or her work tainted with even the hint of military relevance. The fervent disavowal by the NIMH spokesperson is especially ludicrous, loaded as it is with demonstrably untrue assertions about LSD and apparently intended to imply that NIMH was innocent of any connection with Army weapons research. To quote Sir Walter Scott, "Oh what a tangled web we weave, when at first we practice to deceive." This might be a fitting commentary on the foolish dialogues between press and scientists during that era. Truth often seems to be the first casualty of political correctness.

The mention of Pars' indebtedness to Dr. A.T. Shulgin takes us in still another fascinating direction. Alexander ("Sasha") Shulgin, whose work we will discuss later in this book, was (and remains) the psychochemical genius who first described the subjective effects of dozens of mind-altering drugs, including MDMA ("Ecstasy"). Before I came to know him personally, he too was outspokenly opposed to the Army's meddling with soldier's minds by giving them synthetic psychoactive chemicals. In the last decade, however, he and I have found common intellectual ground and developed a congenial friendship.



Draw-a-Man Test – Control

Meanwhile, back at the lab, volunteer experiments in 1961 were ramping up and beginning to operate at full tilt. When Harry Pars supplied us with a synthetic analog of THC for clinical testing, it came as a mixture of eight stereoisomers. (Stereoisomers are different spatial conformations of the same molecule.) It was not yet feasible to separate the eight isomers for our first studies and consequently, we could not yet explore the relative potency of each of them individually.

Nevertheless, to test the range of psycho-activity in relation to dosage, we undertook a study of the mixture (referred to as EA 2233), starting with oral doses of 10 mcg/kg and progressing to a maximum of 60 mcg/kg. We tested two subjects at each of the six dose levels.

From a potency standpoint, the results were less than exciting. At low doses, performance scores did decline slightly and some subjects reported mild symptoms suggestive of marijuana effects. However, a substantial alteration in both cognitive performance and mood occurred only in one of the two individuals who received the highest dose (60 mcg/kg). This volunteer clearly showed a drop in performance scores, and developed clear-cut signs and symptoms of a marijuana high.

Although he had never been a marijuana user, it was interesting that he experienced much more intense effects than his partner did. We videotaped the following interview seven hours after he received the compound:

Q: How are you?
A: Pretty good, I guess.
Q: Pretty good?
A: Well, not so good maybe.
Q: You've got a big grin on your face.
A: Yeah. I don't know what I'm grinning about either.

Draw-a-Man Test – 06:35 hrs.

Draw-a-Man Test – 28:35 hrs.

Q: Do things seem funny or is that just something you can't help?

A: I don't – I don't know. I just – I just feel like laughing.

Q: Everything seems funny.

A: It seems like one thing about everything seems funny. And it's got – well, something that sticks out in my mind.

Q: How do you mean?

A: I don't know. We drew pictures a little while ago. My buddy drew one ([Laughing] and I drew one later on. [Laughing uncontrollably). That's not even funny!

Q: Yeah?

A: I made a green hat with a feather in it, and I don't know why.

Q: You made a green hat?

A: Yeah. A green felt Swiss hat on a cowboy.

Q: How could you make a green one with a black pencil?

A: I don't know. I just think it was green. It seemed like it should be green.

Q: Did it look green when you drew it?

A: Yeah.

Q: It did?

A: Yeah. I don't know why.

Q: Were there any other colors?

A: No. Just a green felt hat. I don't know why. It just stuck out.

Q: About what time is it now?

A: About – the early afternoon. About 2:30 or so.

Q: You don't have any trouble keeping track of the time?

A: I don't know. I – I hear people talking every once in a while about what time it is. I can pick up bits from that, that sounds like they seem later each time.

Q: Does the time seem to pass slower or faster or any different than usual?

A: No. No different than usual. Just – just that I mostly lose track of it. I don't know if it's early or late.

Q: Do you find yourself doing any daydreaming?

A: Yeah. I'm daydreaming of all kind of things.

Q: What kind of things?

A: Oh, everything. That light there looked like an ocean at one time.

Q: The light looked like an ocean?

A: Yeah. Like a wave or like being on an ocean liner looking off in the – across the sea as the sun was setting.

Q: Could you see all that?

A: Yeah.

Q: Was that pretty to look at?

A: Yeah. It was pretty.

Q: What other things can you imagine?

A: Well, I kept imagining about those pictures we drew, and little things like that. I don't know why. I just seem – I don't know – everything seems like it's so far away. I – it's like running in water up to your chin or something.

Q: Oh, it is? What's that like?

A: My arms feel real – like I couldn't raise them or, if I had to defend myself or anything – just, you know – everything seems comical.

Q: Do your arms and legs feel like they're bigger or smaller or any different?

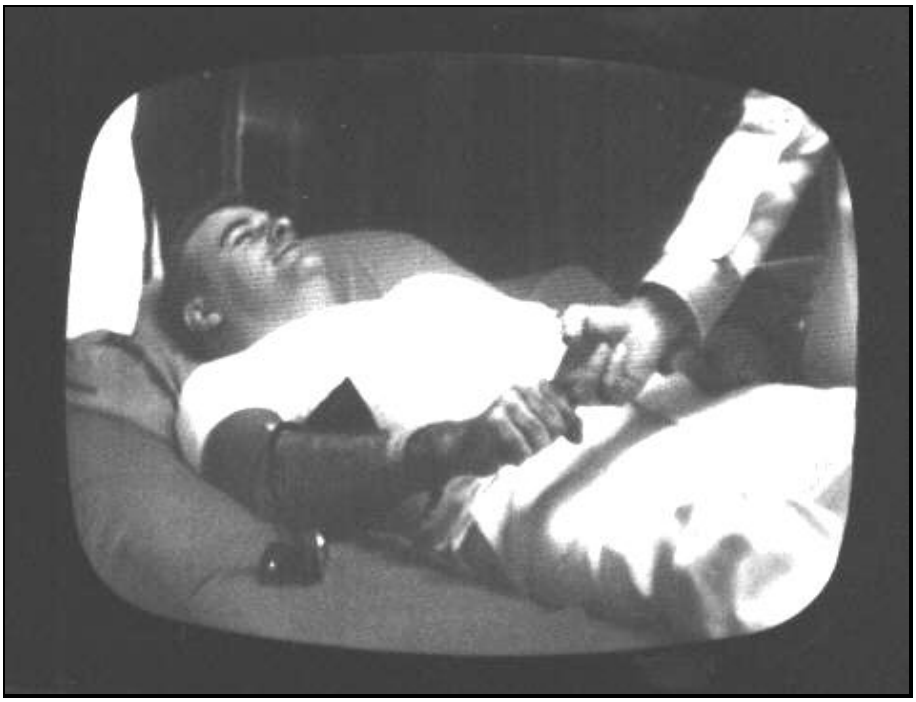
A: That's just like – like they're numb – like a – like trying to move real fast in water. Can't very well –

Q: Is this a nice feeling?

A: It gives you a … contented feeling like some [inaudible] of – peace and quiet.

Q: Suppose you had to get up and go to work now. How would you do?

A: I don't think I'd even care.



Volunteer subjects feels fine and finds everything amusing while the doctor tests the strength of his grip as part of neurological exam

Q: Yeah? Well, suppose you, you know, you – well, like the place were on fire?

A: I don't think it would be – it would seem funny.

Q: It would seem funny? Do you think you'd have the sense to get up and run out or do you think you'd just enjoy it?

A: I don't know. Fire doesn't seem to present any danger to me right now.

Q: Nothing seems to have any – can you think of anything now which would seem hazardous or worry you or are you just in a –

A: No. No. Everything just seems funny in the Army. Seems like everything somebody says, it sounds a little bit funny.

Q: Can you tell me what you mean – funny? Like what?

A: I don't know. Like somebody telling jokes. Something like that.

Q: Is it that kind of funny?

A: Yes. No but, you know – I don't know what kind it is. It's a humorous sound just –

Q: Is it like when you're in a good mood and you can laugh at anything?

A: Right.

Q: You don't feel – this is not like feeling worried? Just like some types of people laugh when they feel worried or tense, nervous. It's not that kind?

A: No. It's like being out with a bunch of people and everybody's laughing. They're just –

Q: Having a ball?

A: Yeah. And everything just seems funny.

Q: Would you do this again? Take this test again?

A: Yeah. Yeah. It wouldn't bother me at all.

The subject, of course, did not know the name of the drug he had received, which makes his responses even more interesting. This puts in doubt what some skeptics have maintained: that the marijuana "high" is as much the product of suggestion as it is a true pharmacological effect. Although no effects were "suggested," this volunteer's experience was characterized by pleasant relaxation, an unflappable sense that everything was amusing, visual imagery – including colorful illusions and fantasy – and a belief that he would not be able to function due to his lack of concern about anything. These are among the classic symptoms of marijuana intoxication. At intervals during the experiment, subjects were required to "Draw-a-Man," a commonly used projective test, indicating distortions of self-image as well as the physical and mental capacity to create a coherent representation of the human body. This volunteer did not lack a sense of humor as revealed in several of his "Draw-a-Man" responses. (The elapsed experimental time is written in at the top of each figure.)

Draw-a-Man test at 35:00 hrs.

Nurses made notes at frequent intervals about each subject. The entries in his case read as follows:

0-2 Hours: Feels fine. No symptoms noted.

2-6 Hours: Eyes bloodshot. Tired and somewhat dizzy on standing. Reaction time prolonged. Mouth dry. Speech and behavior normal. At 4 hours begins to find everything laughable. Appears euphoric. Definite changes in perception.

6-15 hours: Appears "drugged." Talks in a sleepy manner. Laughs at small incidents. Time seems altered. Believes he would not perform if at work. Having "weird dreams." Continues to laugh at trivia. At 10 hours, is sleepy and has some gaps in memory for previous few hours. Feels "all washed out" as if he had "had the flu." At 12 hours given 15 milligrams of Dexedrine orally. At 14 hours, more alert and performance is improved.

15-40 hours: Light-headed on standing. Occasional lapses of memory. Slept well. Ate breakfast. Complains of "stomach" pain before and after eating. This and all other symptoms subsided and no abnormalities were noted after 30 hours.

Compared to the 2-4 hour duration of the subjective effects of natural marijuana, the effects of a mixture of the eight isomers of this synthetic derivative lasted much longer – up to 30 hours. We gave some Dexedrine to the above subject to see if it would reduce or shorten his symptoms. Not surprisingly, his alertness improved but all the other effects persisted unchanged.

About four years later, the individual isomers of EA 2233 became available in purified form and Dr. Fred Sidell initiated another series of trials. At very low intravenous doses of isomers 2 and 4, blood pressure dropped enough to cause concern and Number Facility performance did not change significantly. Rather than take further risks, the lab suspended all testing of EA 2233 isomers. Conceivably, if large declines in blood pressure (particularly on standing) had not occurred, additional testing of isomers 2 and 4 might have proven fruitful.

The intravenous route is far more effective with THC compounds than the oral route. As Dr. Leo Hollister reported more than a decade after Edgewood trials with THC ended, the main psychoactive part of natural marijuana (delta-9 THC) is several times more effective by the intravenous route than when smoked. In turn, when it is smoked, it is considerably more effective as by the oral route. If these differences apply to the more potent synthetic isomers, incapacitating symptoms might appear after very low doses. One or more of the

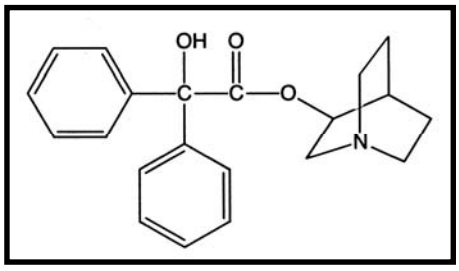
isomers might even be as incapacitating as some of the synthetic BZ-like drugs.

Thus, it may be that through an abundance of caution, the Edgewood laboratory veered away from a possibility that newspaper reporters had scornfully rejected: that a popular "pacifying" street drug might actually have real potential as a weapon of "chemical warfare!"

* * * * *

6 BZ: TINY BASEBALL GAMES AND DC-3s ON A PADDED FLOOR

"You can observe a lot just by watching"
Yogi Berra



Chemical structure of BZ

According to a children's book, the Princes of Serendip had a habit of looking for one thing and stumbling on something better by accident. In 1952, Hoffman-La Roche Inc. chemists created a possible ulcer drug called RO2-3308 – not bad for ulcers, but better at causing hallucinations. Within a decade, Chemical Corps workers were loading this remarkable substance into experimental munitions. They gave it a shorter name: "BZ" (no doubt shorthand for "benzilate," a subset of the glycolate chemical family). Credit Hoffman-La Roche Inc. with "serendipity."

After testing BZ extensively in animals, the Medical Research Laboratories gave very small doses to volunteers and obtained only minimal effects. As doses approached half a milligram (i.e., 5 or 6 micrograms per kilogram of body weight), however, hallucinations started to appear. It was potent and it worked!

Not only did it work, but its effects lasted a long time. At just above half a

milligram (i.e., 7 or 8 mcg/kg per kilogram of body weight), volunteers consistently became stupefied. After 4-6 hours, they were usually "out like a light." By 12 hours, they were moving around again, but were totally disoriented and unable to do much of anything.

Forty-eight hours later, they were usually approaching normal on their performance tasks. A day or two after that, they were fully recovered – some even said they felt invigorated! We realized this could be an effective incapacitating agent – maybe the Soviets already had it in their arsenal. Chemical Corps commanders thought it important to stay ahead of them.

Systematic testing of BZ began in July 1960. By March 1963, we were ready to submit a summary of 22 different BZ studies, each designed to explore a particular aspect of its pharmacology. More than 300 enlisted men had helped to develop the details of BZ's remarkable profile.

It took almost three years, and an estimated 100,000 hours of professional effort by physicians, nurses, technicians and volunteers to learn all the things we wanted to know about BZ. There were many questions to answer. What dose must one give to produce incapacitation? For that matter, how should we define incapacitation? How fast did effects develop at various doses, and how long did they take to clear? Was BZ equally effective whether taken by mouth, by vein, by muscle, through the air or on the skin? What was the lowest dose that could cause mild but significant effects – the "minimal effective dose?"

Those were just a few of the questions. There were many more. What would happen if we gave twice the incapacitating dose? Did everyone react the same to a given dose, or were some either extremely sensitive or extremely resistant? To what extent did various doses affect heart rate, blood pressure, respirations, body temperature and pupil size? What were the effects on vision, hearing, strength and neurological functions? If you give the same dose of BZ twice to the same individual (after a suitable interval) would the results be the same? What if you give it several days in a row – would the effects be additive?

One extremely important consideration was whether BZ effects could be reversed. If we did find an antidote, how safe would it be? Would it be practical for a medical technician to use it in the field? Could a soldier treat himself if necessary? Would he then be able assemble a rifle, put on a gas mask, navigate obstacles, read a map, and communicate coherently by radio or telephone?

Finally, what would happen if we gave BZ to a group of soldiers? Could they continue to cooperate with each other or would they each go into their own private world and be useless – even detrimental – to the performance of unaffected men around them? Would some of them become obstreperous, or even dangerous, while incapacitated? There seemed no end to the questions one might ask.

Other considerations were particularly important to military commanders. For example, how high a dose could the average person survive if no treatment were available? How much would weather conditions – particularly heat – affect the likelihood of a fatal outcome? Just how much BZ would a chemical officer in the field need to disseminate to achieve desired effects throughout a given area, and how much variation in dosage would each type of munition produce?

What would be the most efficient way to deliver a drug like BZ? If employing an aerosol, what particle size would be most effective? Would BZ really be a practical agent for use in combat and if so, under what circumstances? What kinds of unpredictable behavior might one have to anticipate?

Our work was definitely cut out for us. It took us considerable time to decide how best to conduct the various performance tests. We needed to consider frequency of measurement, ease of administration, effects of practice and relationships between performance in the lab and performance in a military situation.

As a psychiatrist, I was naturally most interested in observing the effects of BZ on thoughts, feelings and behavior. From what I had seen during my visit to Edgewood in late 1960, when Kaz Kimura and Bill Gordon were doing the testing, there seemed little doubt that I had witnessed volunteers in a state of delirium.

I had previously seen delirium only a few times – in alcoholics suffering from DT's and in occasional cases of drug overdose. I vividly recalled a senior officer who had swallowed a large handful of sleeping pills and was admitted to Letterman Army Hospital. When I first saw him, he was on the pediatric ward, sitting in an extra large crib with extra high railings all around the sides creating, in effect, a man-sized cage. He was out of danger, but also very much out of touch with reality. Grossly disoriented, he sat mumbling and picking at various objects in the bed. It was impossible to interview him so, to counteract the sleeping pills, I decided to order a hefty dose of amphetamines. This not-so-bright idea turned him into a non-stop radio commentator on every disconnected subject crossing his mind.

So, even though I had limited experience with delirium, it was clear to me that volunteers under the influence of BZ fell into that general diagnostic category. The term "delirium" derives from the Latin verb, "to rave." It certainly seemed to be an apt term. Once they regained the ability to speak somewhat coherently – after several hours of stupor – constant raving would be a good description of their incessant speech. I often sat with them for several hours, trying to get the gist of what they were saying, trying to learn whether they could answer questions meaningfully and trying to ascertain what sort of imaginary things they were seeing.

I had never previously had the chance to observe a delirious person for an extended period, and found the unending kaleidoscopes of speech and behavior fascinating. As a consequence, in my 1963 report I was able to summarize what I had learned from hundreds of hours spent with dozens of delirious subjects. I had watched them descend into disorientation and physical helplessness, become progressively unreachable, as though transported into a world that was for the most part palpable and visible to them alone, and then gradually return to reality.

The world of delirium is not the psychedelic world created by drugs like LSD, throbbing with overwhelming insights, stunning alterations in shapes and colors, and breath-taking shifts in the nature of time itself. Rather, it consists of familiar, sometimes panoramic, visions of football fields, "trains, planes and automobiles," and intimate hallucinations of family members or fellow troopers from their home installations. It includes realistic but fleeting encounters with "lions, tigers and bears," progressively diminishing in size to rats, mice and insects as intoxication slowly subsides.

I watched volunteers carry on conversations with various invisible people for as long as 2-3 days. Then, fatigue would finally set in and they would fall into a deep restorative sleep. When they woke up 10 or 12 hours later, they were much more aware of their circumstances. Within another day, they were back to their socially appropriate and intellectually competent selves.

That is the executive summary.

In the complete 1963 report, I gathered all the features I had observed and placed them in conventional psychiatric categories. Medical specialists seem to enjoy using pedantic language that underlines their erudition, and I must admit I was not immune to this affectation.

Although too long to reproduce in full, I have extracted excerpts from my summary report, hoping they will clarify what BZ is as well as what it is not. The following description is lengthy, but the term "BZ" has been loosely bandied about so often in discussions of chemical warfare (frequently in a sensationalistic manner, and usually quite inaccurately), that a full description seems necessary to correct some erroneous impressions.

THE CENTRAL NERVOUS SYSTEM EFFECTS OF BZ

General Effects

"Following the administration of an incapacitating dose of BZ, a typical sequence of events occurs. The onset is more or less insidious, with the first symptoms becoming noticeable at about one hour. Early central nervous system manifestations include heightened deep tendon reflexes, ataxia, incoordination, slurring of speech, dizziness and headache. Nausea, usually without vomiting, is frequent. Subjective weakness, without appreciable loss of strength, occurs primarily in the legs.

"During the first phase (1-4 hours), discomfort and apprehension are present. Extreme restlessness occurs, sometimes with involuntary clonic spasms of the extremities and birdlike flapping of the arms. Errors of speech and scattered moments of confusion may be noted.

"After a crescendo of restlessness and ataxia, a second phase (at 4-12 hours) begins.

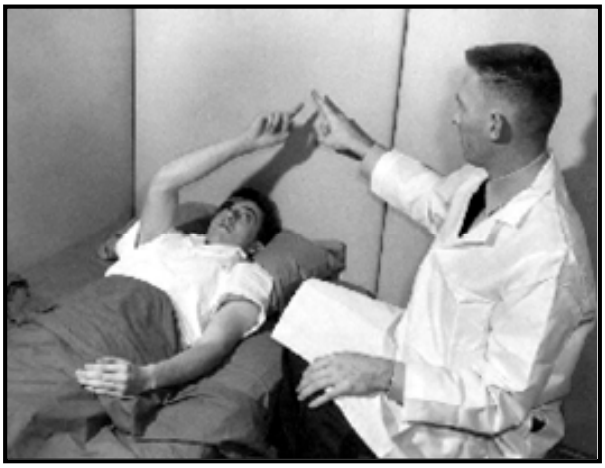
"During this second phase, sedation, stupor and even semi-coma develop. The individual sleeps, or appears to sleep, and responds only to direct and sometimes only to strong, stimulation. Spontaneous groping or crawling may alternate with lying quietly. The subject mutters incoherently from time to time. Sometimes he shows "obstinate progression" as he stubbornly tries to crawl in a straight line over, past and through all obstacles. As this primitive behavior (reminiscent of the "running response" in decorticate animals) subsides, the subject enters a third phase, beginning at about 12 hours, during which more spectacular symptoms develop.

Sedation typically follows restlessness after the administration of BZ

"As speech returns over the next few hours, it is in clipped, flat accents, containing rapid bursts of commonly associated words and phrases, particularly those that are colloquial and habitual. Logical continuity is lacking and most sentences are meaningless or absurd. Hallucinations seem to dominate the field of awareness, and real objects and persons are generally ignored or ludicrously misinterpreted. Touch seems to become the most important sensory system, and the hands are ceaselessly active, exploring clothing, bedding, walls, floor and crevices of the environment. Smoking and drinking of phantom cigarettes and beverages are very common.

"As delirium subsides, food and drink previously ignored or refused

may be accepted in small amounts, although appetite and thirst are generally decreased. The subject begins to respond to short instructions and may be quite tractable, but at times is negativistic and refuses to cooperate. If he feels annoyed, he may strike out at the source of his annoyance. Attention span is very short and distractibility is correspondingly heightened. Drawings and handwriting show marked deterioration.



At scheduled intervals during BZ testing, the physician conducts a brief neurological examination of each subject.

"While incapable of sustained intellectual effort, the subject may persist in an activity in spite of failure, ceaselessly prying at cracks in the wall, for example, in an endeavor to escape from an enclosed area. Sometimes he may succeed in conveying some wish, such as a desire to use the latrine, and then be too confused to execute his intention. At other times, he may react violently to hallucinated events and engage in pantomime combat with phantom assailants or in ludicrous play with imaginary companions.

"As recovery proceeds, the subject gradually begins to converse in a more rational and coherent fashion, but his grasp of the situation is still impaired and he often makes paranoid misinterpretations. He may feel, for example, that someone is out to kill him or that his food is poisoned. He may wonder why he is under such scrutiny and why he is being 'reated like a little kid.'

"While recovering, the BZ-intoxicated subject tends to deny that he is impaired and tries to make excuses for errors or failures during testing or questioning. The casual examiner may be fooled into thinking that little or no impairment is present. During this period, the overall demeanor and manner of acting is sometimes reminiscent of paranoid schizophrenia.

"If the reaction lasts more than a day, a period of deep sleep generally precedes full recovery. Return of appetite, interest in recreation and a normal display of enthusiasm and spontaneity in conversation are reliable indications that the delirium is over... "

"…One intriguing finding is the frequent report by subjects, both during and after recovery from the drug experience, of the illusion of red coloration of the skin, both their own and that of undrugged personnel who are with them. One or two individuals have thought their hands were bleeding when washing them under the tap. Whether this is an optical phenomenon related in some way to engorgement of retinal blood vessels or is central in origin is not known…."

"…With small doses of BZ, excitation is sometimes not seen at all, or is very mild and transient. Instead, sedation is the predominant effect. It is not uncommon for subjects receiving doses between 2.0 and 5.0 mcg/kg at 10:00 hours experimental time (expressed in hrs:min rather than "1000) to sleep through the afternoon, most of the evening, and then through the night, recovering normal alertness by the following morning. This is not attributable simply to boredom, since at very low doses and with other types of agents, daytime sleeping is either absent or limited to short naps…"

"...Frequently, time "stands still" for the incapacitated subject, from

sometime on the first day until nearly complete recovery, two or three days later. When he "comes to," he may think it is still the day on which he received the drug, sometimes in the face of external evidence to the contrary. For example, one man commented on the third day of the test: "You know, if I didn't know it was Friday, I'd swear it was Sunday" (which it was). When asked to explain, he commented that the Post was nearly deserted, "like it would be on Sunday." …"

"...With regard to persons in his vicinity, recognition may be accurate for individuals whom he has met prior to testing, such as the doctor or nurse; other people may erroneously be greeted as old friends from his outfit, or even relatives. At times, he may react to large objects possessing a vertical shape as if they were people. One subject tried to provoke a fight with a simulated gun mount; another said "Excuse me, Sir" to the water fountain when he accidentally brushed against it. In more extreme states of confusion, he may even initiate conversations with hallucinated individuals. He conducts these one-sided conversations in such a natural, unstudied manner that acting is out of the question…."

"…Occasionally, he will take vigorous action to deal with imagined emergencies. Subjects may call frantically for medical assistance to treat an illusionary woman who has supposedly just been run over by a car, or shout up at the air-conditioning vent for someone to "throw down a shotgun and some shells" so he can protect himself from the mob he imagines coming toward his room. One subject scrambled halfway over a seven-foot-high partition, fleeing from "a guy with a gun" and the nurse caught him by the heels just before he vanished head first down the other side…"

"...Organized, complex panoramic hallucinations are most common between 24-48 hours after exposure to doses at or above the incapacitating dose. These may be benign or even entertaining – one subject described with great enthusiasm a Lilliputian baseball game being played on the floor in front of him. Later, particularly during the night, the visions may be gigantic and terrifying.

"Still later, in place of elephants and giant snakes, he sees rats, squirrels or spiders and gradually these diminish to become bugs or ants, which he labors to brush from his clothing and bedding. Finally, they disappear or are correctly perceived as pieces of lint, dust, loose threads, raised markings on the floor, nail heads, paint drippings or whatever would have been clearly recognized as inanimate a few hours before…"

"…Another curious disturbance of memory function is perseveration – the tendency to repeat the same response inappropriately. This may take a unique form: the subject initially cannot answer a question and seems unable even to remember what the question was, but when the examiner asks a new question, he replies by correctly answering the first! Simultaneously, he seems not to have heard the second question, nor to realize he has responded inappropriately…"

"...After recovery, amnesia is greatest for the period of greatest incapacitation, with fair recall of the onset stage. Amnesia for early phases of recovery is not total at the time of emergence from delirium, but for a while develops further. As time goes by, they fade quickly, in much the same way as dreams recollected in the morning are forgotten by noon. Many subjects demonstrated that if questioned early, they could recall many of the paranoid misperceptions of the previous day, and in retrospect

recognize them as distortions. Later, they did not remember this.

"In general, however, very little is permanently remembered for more than a few hours after recovery, which no doubt accounts for the commonly held medical belief that delirium is characterized by subsequent amnesia... "

Registered nurses are able to provide effective reassurance to confused subjects

"...Speech is slurred, the voice develops a monotonous nasal sound, and its volume wanes to an almost inaudible level. This period of incoherent mumbling is sometimes referred to in older medical literature as "mussitant delirium" (mumbling delirium).

"Handwriting is impaired in quality and is usually reduced in size, sometimes to the point of micrographia. When asked to write on a blackboard, a subject's ordinary natural tendency to compensate automatically for the examiner's increased viewing distance by increasing the size of the letters, does not occur. Once again, the loss of ability to maintain a sense of "context" seems to be a major problem…"

"… [The] peculiar concatenations and distortions of language elements are almost impossible to imitate – they seem to result from an extreme loosening of the entire verbal associative system. As such, they may create a humorous effect, since the shift is so rapid and unpredictable that at times their remarks have the flavor of creativity and wit. (The things that subjects say and do, in fact, are often very funny and it is sometimes difficult to keep from laughing at their antics, professional standards of decorum notwithstanding.)

"During severe delirium, attempts to clarify the intended communication by asking the subject to repeat or explain something are usually futile. It does no good to say "What do you mean by that?" because the subject does not know what he said, does not really grasp the question and may not realize what he is saying when he answers…"

"...Unlike schizophrenic psychosis, familiar to the clinician, delirium at its height shows no thematic consistency, no trend and no obsessional preoccupation with a single related set of delusional ideas, systematically connected in a persecutory or grandiose system. Instead there is a marked loosening of associations approaching randomness, muttered phrases, outbursts of profanity, scattered references and allusions to other times and places, brief periods of intense examination of trivial objects, facial expressions of perplexity or wonderment, chuckling amusement or tender concern, repetitious fingering of bedclothes or pajamas, sudden requests for information or personal articles (which are promptly forgotten) and so forth ad infinitum. When addressed, the response is often courteous and noncommittal, such as "Fine, Sir" in answer to the inquiry "How do you feel?"… "

"...Such individuals seem unable to appreciate the reality of their deficits, and will offer ridiculous alibis and wildly implausible explanations for their failure to perform adequately in the areas affected by their intoxication. Stalling and temporizing maneuvers are common, such as asking the examiner to repeat the question, or asking for clarification of the instruction when in fact they have completely forgotten it, inquiring naively "You mean me?" or "Did you want me to do that right now?"… "

> "…Paradoxically, one of the most reliable indications of recovery is the return of awareness by the subject that he is not as proficient as he should be. Subjects who receive an incapacitating dose usually regain this awareness by the third or fourth day. By this time, their objective performance on addition and word recognition tests has generally risen to 80 or 90 percent of their baseline level, and the principal symptoms are some residual lassitude and blurring of vision…"

Additional points, not included in the 1963 report:

Although apparently awake, intoxicated subjects were in many ways neurologically asleep, as demonstrated by characteristic EEG slow waves. Neurologists sometimes refer to this paradoxical condition as the "pseudowakeful state." In many respects, it resembles the mental activity of normal dreaming, but without the usual suppression of physical activity. With regard to the crawling behavior often seen during early delirium, a colorful Italian term to describe this appears in the older literature: "progresso ostinato" (obstinate progression). Another old term, "carfologia" (or "carphology"), refers to repetitive plucking at clothing, bedding, or imaginary objects in space. The term "wool-gathering" was long ago introduced to describe this kind of fingering of the empty air.

A vivid example of interpreting people as objects was provided by one subject, who tried to take a bite out of my white coat, thinking it was a loaf of bread. He twisted my arm and wrestled with it briefly, as though it were a crooked pipe that needed straightening. Likewise, the nurses were often explored as if they were interesting but inanimate stimuli. They soon became adept at tactfully withdrawing from such innocent groping.

A highly intelligent tri-state chess champion provided a striking illustration of the persistence of over-learned skills. We decided to measure his ability while intoxicated with BZ. During the pre-test baseline phase, he played several games with one of our chess-playing psychology technicians. In every case, he won after just a few moves.

After an incapacitating dose of BZ, he played hourly against the same technician. For three hours, he won with ease, but took progressively longer to reach checkmate. In the fourth hour, he made several foolish moves but still managed to win. In the fifth, he became so irritated at losing both his queen and a rook that he knocked his king down in disgust. Refusing to play further, he declared heatedly that "in no way" was he "going to lose like a duffer!"

Around midnight, I visited him in his room. He had emerged from stupor and was sitting in the middle of the padded floor, intently studying an upside down magazine. I offered a game of chess. He eagerly accepted. Although helplessly disoriented and delirious in every other respect, he managed to keep his attention on the game, making mostly legal moves, but occasionally a bizarre or inappropriate one. Although a very mediocre chess player, I beat him decisively!

Instead of being upset, as he had been earlier when incapacitation was just developing, he cordially remarked "good game" and pleasantly offered to play again! Totally absent was any recognition of his poor performance, as well as the previous signs of frustration and irritation. His competitive drive had lost its emotional heat. I concluded that, from thousands of games of chess, his familiarity and interest in the game had enabled him to play almost by rote, despite frequent lapses. The next day, I beat him after a long struggle and the day after that he

overwhelmed my amateurish attempts with dispatch.

Paranoid withdrawal from conversation was common while subjects were emerging from delirium. Although again able to communicate and solve simple problems, they often harbored anxiety-producing ideas and were still subject to frightening illusions. It was especially important at such times to have a skilled nurse or other reassuring staff member close by who could often mitigate their fears through explanation and calm reassurance. Such reassurance did not always succeed in preventing misperceptions, but at least it promoted a more benign interpretation of confusing events.

This may be a good place to correct some common misconceptions about the effects of BZ and related belladonnoids. Those unfamiliar with the delirious state have often referred to BZ as "hallucinogenic" or "psychotomimetic." It is undeniably "hallucinogenic," but the term is hopelessly contaminated by its inexact use in reference to drugs like LSD and psilocybin. Such drugs produce striking illusions, but subjects generally know they are unreal.

BZ is undeniably "psychotomimetic," but only in the broad sense that it causes a true loss of contact with reality. It also lacks most of the distinguishing features of the natural psychoses. Schizophrenia, for example, rarely produces visual hallucinations. BZ, on the other hand, seldom produces well-organized delusions (as may occur with LSD). BZ does not produce persistent social withdrawal, as seen in chronic schizophrenia, nor does it create the annoying overfriendliness of the manic phase of bipolar disorder.

In fact, nothing about BZ's mental effects is unique. The signs and symptoms are identical in almost every respect to those seen following toxic overdoses of a variety of common drugs, such as antihistamines, tricyclic antidepressants, bromides, and barbiturates. Delirium can also occur after head injuries, post-operatively following heart surgery, or during advanced kidney or liver failure. None of these are easily distinguished from the delirium produced by BZ.

Delirium tremens (the "D.T.s") resulting from alcohol withdrawal is slightly different in that it is usually preceded by "the shakes," convulsions and occasionally by "alcoholic hallucinosis" – characterized by accusatory auditory hallucinations. As observed 60 years ago by Maurice Victor, an expert on alcohol problems, delirium tremens usually does not appear until day 3 or 4 following abrupt withdrawal from alcohol. The patient is generally malnourished and grossly deficient in vitamin B_1 (thiamine) as the result of a diet consisting of little but alcohol. This deficiency further compromises mental function.

"Delirium and Allied States," a classic 1935 monograph by Curran and Wolff, lists over 100 possible causes of delirium. Their detailed clinical descriptions of these confusional states would apply equally well to BZ intoxication.

One of the most egregious errors made by writers referring to BZ in lay publications (and even some prestigious scientific journals) is to characterize it as some kind of secret "super-potent hallucinogen," developed by the Army for purposes of riot control, or as a horrible chemical weapon. Such inaccurate descriptions put an unfair Dr. Strangelovian stamp on Army chemical research. Once again, BZ is not a diabolical potion, hidden in some science fiction pharmacy full of mind-bending substances. Boring as it may sound, BZ is just another deliriant.

It is, however, a potent and long lasting deliriant. As will be illustrated in a later chapter, half a milligram can render a soldier incapable of functioning in a simulated military environment for two to four days. The half of a milligram required

could sit comfortably on the head of a dressmaker's pin – roughly equivalent to a barely visible grain of sand.

LSD, in comparison, produces incapacitation at less than the BZ incapacitating dose, although the mode of action is quite different. Although writers frequently claim that BZ is much more potent than LSD, they are misinformed. Once again, hearsay overtakes fact.

The consistency of BZ's pharmacological effects, rather than potency alone, led to its adoption as an official "standardized" incapacitating agent, the first and only one so "honored" in more than a decade of research. Since it was never officially used as a weapon by the United States (although some claim otherwise) its standardization was more symbolic than a harbinger of actual deployment.

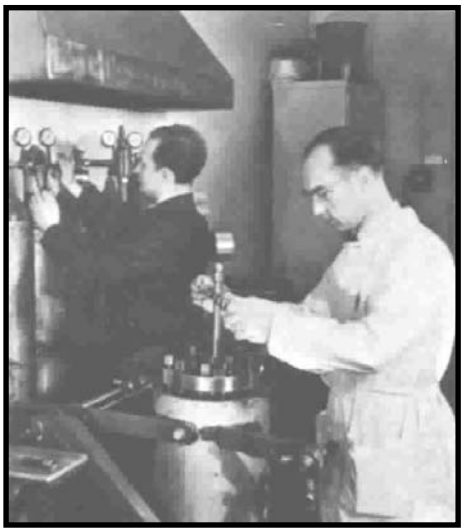
* * * * *

7 LSD: THE OTHER ACID TEST

1943

The bottle of "acid" is covered with dust.
But air-tight and steady it stands,
Awaiting the smile on a Swiss chemist's face
And the touch of a Swiss chemist's hand.

(With apologies to Eugene Field's "Little Boy Blue")



Albert Hofmann – Discoverer of LSD

"By 1615 (two hours after LSD administration) all three subjects manifested behavior which was in marked contrast to that observed in the pre-drug state. Carter, who had been cooperative and communicative during the initial period after LSD ingestion, had retreated into an almost completely mute state. This was not, however, considered to be a stupor, but rather appeared to be the result of his suspiciousness, which often assumed paranoid proportions. He appeared to be quite restless, constantly pacing the floor and checking the doors. When questioned, he would not respond but merely smirked and looked away."

I was at the kitchen table, eating Puffed Wheat and reading Paul Fiddleman's notes. They were pretty good. I alternated bites of cereal and paragraphs of his single-spaced typing on legal sized paper. I wished he could have used 8 ½ x 11. They'd fit better in the charts without folding. But Paul had his little ways of being different. We could always Xerox his pages down to conventional size.

It was still dark outside and I was the only one up. I liked this time of day. It made me feel that I had a jump on the world. By the time most of the staff was awake, working on their first cup of coffee, my three cups would have kicked in and I would be full

of new ideas for the next experiment. I wanted to get more realism into the performance measures – things that we could do inside the ward area or perhaps on the grass just outside.

> "Carter often sat at the table, staring at the other subjects but making no attempt to join in activities or conversations. For a while, he kept trying to leave the test area, but would return when asked to. This behavior continued for almost five hours, although as time progressed he became more and more verbal."

Paul liked verbal. It gave him a chance to ask questions and interpret answers, something he had learned well during his PhD training as a clinical psychologist. He was a new arrival and I was glad he was getting his feet wet. He hadn't seen how LSD affected normal people before, but he got to observe three distinctly different versions of it yesterday.

Increasingly, daylight was creating a yellow fringe around and under the window shades. I pulled on the ring hanging from one of them and let it go; it rapidly rolled up to reveal the tight cluster of trees not far behind our ground floor apartment. Although it was November, its leaves were still red and gold.

I glanced at the clock over the kitchen sink. One more piece of toast and it would be time to switch from bathrobe blue to Army green. Still a few minutes left, however, to read the first volunteer's story. It was quite accurate, corresponding closely to what I too had observed.

> "Carter became quite hostile at times, attempting to test the personnel and "trap" them. He would ask for something like aspirin and then refuse to take it, asking, "What is this?" He was minimally cooperative during testing periods; often I'd have to ask him several times to do something. For a time he kept to his cubicle, emerging only to pace the floor and check the doors, or to sit for a short time at the table. It was during this time that he showed some posturing, although not to a marked degree. He gave one the impression that he felt he had "solved" the meaning of the various procedures and was quite amused at the feeble attempts to trick and "test" him.
>
> "Carter appeared to interpret all situations as pre-planned and set up merely to trap him. For example, he would pick up pieces of a picture puzzle, which had been knocked down earlier in the experiment and flip them on the table, giving the impression that he "knew" we were dropping extra pieces on the floor to bother him, but that he was not going to be fooled this way."

Quite a vivid description! I paused to put on green trousers, socks and not-shiny-enough black shoes, holding the socks to the window to make sure they were indeed black, not blue. In dim light, it was hard to tell the difference – a couple of times Carl had noticed that I had on one of each and had teased me about it.

"What is it with you Doc?" he had commented. "Last week you came in without your nametag. You're thinking too much."

Okay, so I was absentminded. I had to laugh too. Who knows? Maybe I could be a professor some day. I sat down again, poured one more cup of coffee and continued reading.

> "Gradually he became more and more communicative, yet it was impossible to elicit any information as to his subjective impressions. He would prefer to continually ask questions as to the purpose of the experiment, the time (which he and Lewis became very concerned with, asking during one period every 30 seconds or so) or where the other people

taking part in the experiment were (e.g., "Is everyone here who was here at the beginning?").

"After a while he became quite concerned as to when he would be over the effects. He started to perseverate about this, wondering whether he would know that he was finished with the "test," or whether we would tell him. Approximately five hours after LSD administration, he seemed to have cleared up a great deal and was able to discuss his experiences.

"At this time he became quite verbal and seemed to be trying to work through some experiences by reporting them. He described how he had thoughts and feelings which he was afraid to discuss and yet at the same time felt that the machines and the personnel were noting what he was thinking and in fact were causing his reaction.

He reported sexual feelings, which frightened him, particularly toward the nurses who were taking his pulse. He was afraid that he might do something to them, or say something that would get him into trouble. He also believed he was a prisoner of war and that the medical personnel were questioning him about things and making him talk and say what they wanted him to say."

The nurses, who had recently joined the staff, were very professional and, in my opinion, more motherly than sexy. I suppose a Freudian analyst might have enjoyed speculating about unconscious Oedipal drives. Well, to heck with Freud! It was true that LSD stimulated the libido in quite a few of the volunteers, but it rarely produced any serious guilt feelings or unacceptable acting out. Maybe talking to Paul about it all had even been therapeutic. Paul probably reassured him that he was okay, that this drug tended to bring out sexual fantasies and they were nothing to fear or be ashamed of.

I buttoned my shirt and added my food-flecked black clip-on tie, grabbed my scruffy green officer's cap and was out the door. I still had Paul's notes in my hand, planning to finish them in the car or when I got to the parking lot. Reading while driving was a bad idea, even though I would probably not pass any other cars on the short drive along Wise Road. I decided to finish reading the report on Carter before turning the ignition key.

"During this time he was obviously concerned about self-control, afraid of what he might do. He had suspicions about the other participants in the experiment, feeling that they were not affected by the agent and that they were in on the "plot."

"He was sure that the whole procedure was being recorded and that all the people who had been present initially still remained, although in altered form. For example, he reported feeling that some of the male personnel had the voices of female nurses, and in fact were female nurses in disguise. The television cameras were supposedly not only recording his very thoughts but were influencing him. He would never face the camera and smile.

"In general, Carter's reaction was clearly paranoid in nature, characterized by a great deal of suspicion concerning the procedures and personnel. He tended to project unacceptable thoughts and impulses onto some malevolent force, namely the "machines" (TV and recording devices) and/or the personnel."

Impressive! Paul had always been both observant and analytic. He was easier to work with than were some of the other psychologists. They were more into experimental than clinical psychology and were often skeptical about some of my quickly planned studies. Lengthy discussions about experimental design usually turned into futile arguments.

As I entered the parking lot, I could see that the lights in the front office were on. Ever dependable Carl was almost always there ahead of me. I decided to put Paul's notes in my briefcase and read them later

"Looking pretty good, Doc." Carl did a quick inspection of both me and my uniform as I entered and closed the ridiculously flimsy wooden doors behind me. They surely would be a sturdy barrier to prying eyes and Russian spies! Maybe we'd get lucky someday and get a new building. I had heard that Materiel Command would soon commission an architect to start working on the blueprints.

A new building, however, was still just a pipedream. It would probably take another five years (actually it turned out to be seven years) to get through all the necessary budgeting, funding and actual construction. The Army was usually in no hurry to upgrade its facilities, even though this was supposedly a high-powered secret lab. Just to get one padded room took months of lobbying up the chain of command (and especially behind the scenes).

"BZ again today, Doc. Rudy's bringing the two volunteers over from the barracks around seven-thirty." He'd never seen the point of saying "0730 hours."

"That's good." I ambled along the long rubber-floored breezeway to the next wing and down the hall to my office. I still had time to read some more of Paul Fiddleman's summary.

> Lewis, while also appearing quite disturbed during the peak of the drug effects, showed little or no paranoid thinking. Rather, he was more withdrawn and at times openly antagonistic and negativistic. Often he would refuse to complete the experimental tasks without considerable prodding. Typically, he would just go through the motions and then retire to his cubicle to lie down. This negativism appeared rather early. While the other two subjects were still working at their tasks, Lewis refused to do so.
>
> He was more verbal then Carter and in fact covered up very little. He spoke continuously about his feelings of confusion ("Sometimes I'm here and I know it's over, and then I go out again") and how he would "fade in and out." He verbalized feelings of anger toward the nurses and other observers, one of whom he called a "Kraut." He made angry asides to another individual who was fixing the recording devices
>
> Two things in particular concerned him. One was the apparent size of things. He felt he was huge and the door was very small, but as he approached it, the reverse occurred. He was concerned that the objects on the table (saltshaker, pencils, cigarettes, etc.) were excessively large. He thought about escaping and made numerous attempts to sneak out. In fact, he and Morgan spent some time discussing a specific escape plan.

I was beginning to appreciate Paul's style as well as his observational skills. As a soldier, he might appear short of perfection, but at least he was usually well groomed. He had no doubt picked up a bit of pudginess since his days as quarterback at Brooklyn College. "Of course we never won a game," he would explain. "Brooklyn College is not exactly a football powerhouse. Sometimes we even had problems finding eleven students willing to be trampled on by the teams from Columbia or NYU. On most plays, I got rid of the ball as fast as possible, and I never tried to scramble." I continued reading:

> Lewis thought he saw horses outside and decided that he and Carter could "scatter," get on the horses and ride away. He stayed in his room for long periods planning this escape. Visual imagery varied in tone, causing him to be either pleased or disturbed. Mostly he gave only vague descriptions of its content, other than a "beach" where he felt all alone.

> The feeling of isolation was intense and he reported wanting to be with people. He also reported somatic changes and for a while wasn't sure if he had urinated or perhaps was actually in the act of urinating. A great deal of body image distortion was present. His arms and legs grew, shrunk or felt numb and sometimes he felt he had lost control of various bodily functions.
>
> Time distortion was quite upsetting for an hour or so. He would constantly ask about the time and seemed quite concerned at the way it dragged. He was, however, more outgoing than Carter and much less suspicious, but expressed more direct hostility, negativism and confusion. Quite withdrawn and ruminative at times, he would suddenly "come to life" and enter into the ongoing discussion. During one interchange, he revealed he had once made a suicide attempt, which he had not mentioned during the pre-drug interview. His description of such experiences lacked much emotion.
>
> At 1900 (almost seven hours after administration) he was still confused. He thought he heard girls' voices and wondered who they were; simultaneously he became more negativistic, flatly refusing to submit to blood pressure tests. He explained that he felt he was being "pumped up" and might very well burst ("either the machine would go up or I would.").

Good teaching points there, I thought. Paul was describing a more familiar LSD response: a subject who shifted frequently from silence and withdrawal to uninhibited conversation during which he revealed things he might normally have withheld. Rather than project malevolence on the environment, his concerns involved distortions of size, time and his own body. He did not readily accept the idea of being a victim and made active plans to escape. He resisted being controlled by displaying annoyance and refusing to take tests. Characteristically, his "escape plans" remained ideas that were never carried out. His recovery took longer than most and periods of negativism came and went, reflecting the "wave-like" character of LSD's effects on mood and clarity of perception.

I read on. The third volunteer seemingly had a positive reaction to the oral dose of 1.5 mcg/kg they had each received:

> "Morgan, in contrast to the other two subjects, had a rather benign experience. He acted intoxicated at times and seemed quite euphoric. The drug's effects did not last very long and four hours after administration he seemed quite clear. He described being quite amused at the antics of the other two subjects and at times egged them on, even encouraging their delusions. His mood was consistently one of mild hypomania and he found most of the procedures quite entertaining.
>
> "Morgan reported visual effects consisting of light and color changes and some distortion of objects, but he was not particularly concerned about them. He was by far the most outgoing throughout the experiment and sought other individuals to talk to. Sometimes he felt intoxicated and silly but this didn't bother him either. Outside of a short period of time when he shared some of Lewis's escape plans, he seemed to be intact throughout the test.
>
> "Overall it appeared that both Carter and Lewis were pretty grossly impaired by the agent and would not have been able to carry out any task directed activity. Carter did not trust anyone and was suspicious of any activity. Lewis was confused and reacted with negativistic behavior. He was able to develop an "escape plan" but lacked the initiative to carry it out. When asked where he would go if he escaped, he was unable to say, outside of referring vaguely to going to the NCO club to get a beer. He felt that once he got out of the test area, he would somehow miraculously be immediately rendered free of drug effects.

> "There was some group interaction in which he participated but this was of a random nature. It is doubtful as to whether any goal-directed group activity would have been possible. Lewis didn't trust Carter, who didn't trust anyone. Morgan, the most intact of the three, served as a sort of bridge between the other two, yet it is doubtful whether he could have manipulated the situation so that meaningful group activity could be initiated and maintained.
>
> "It is curious that neither Lewis nor Carter could assess the impairment of the other and each felt the other was not experiencing any drug effect. Morgan, on the other hand, was quite amused at the antics of the other two. He appeared to be the only one able to function effectively and even he would have had difficulty, since random thoughts and false perceptions often interfered with task completion."

Nice job, Paul!

These three volunteers represented only a fraction of the varieties of experience we observed in our volunteers. Other publications provide additional examples. In their highly scholarly book, *Psychedelic Drugs Reconsidered,* Lester Grinspoon and James Bakalar provide many other examples of individual personal experiences. Highly literate or artistic individuals often describe elaborate spiritual visions or "magical mystery tours" (as in the Beatles song, perhaps inspired by such trips).

Raising the Colors!

By 1962, we had completed an oral LSD dose-response series while simultaneously moving forward with the evaluation of BZ. The Post engineers had built a fully padded ward for us, with six individual padded cubicles. We also had been given an additional nurse, and the closed circuit TV system was now capable of monitoring tests from several vantage points.

A group of four volunteers, all of whom had previously been through an experience with a full incapacitating dose of BZ, were quite willing to be subjects in a second test involving a drug that we told them would be of relatively short duration. As usual, we withheld the fact that it was LSD, but predicted they would have unusual sensations, changes in perception, and emotional effects that could vary considerably from person to person. They would all probably have difficulty scoring well on the NF and SC cognitive tests for a few hours but, in all likelihood, would recover fully by the end of the afternoon. Then, if no one objected, we would sit down together and record a post-test discussion for the cameras.

I knew all four men fairly well from interviews before, during and after the administration of BZ two weeks earlier. They also knew each other quite well, not only from the BZ test, but also from sharing the same barracks, where considerable bonding takes place in the course of a two-month assignment.

I interviewed them individually once again and later briefed them as a group, a day before the scheduled LSD study. Only then did we ask them to sign separate informed consents, one for the test itself and one for the videotape recording. Apparently undaunted by the rigors of their previous tests with BZ, they seemed eager to discover the effects of a different chemical agent.

It was an exceptional day. Although it was never our intent to produce any psychiatric benefits, it was striking that one soldier had a surprisingly therapeutic experience. Each man was in his own separate cubicle, with a technician sitting close by. At scheduled times, a nurse would enter each cubicle to converse, take

vital signs and measure the subject's competence on the NF and SC tests.

Unlike the other three, the fourth volunteer became quite withdrawn and uncommunicative. When most of the effects had subsided, we gathered for the promised discussion. It was only 10 hours since we had administered the drug. The effects had barely worn off, and recollections were still vivid. Three of the volunteers were still reeling from the brilliance and beauty of the colors they had observed – they raved about them. They also described several other aspects of their LSD experiences, many of them typical but some of them unusual.

I was fascinated by the ability of unsophisticated subjects, none having more than high school diplomas, to describe their thoughts and emotions, as well as what some might refer to as "ineffable" perceptual alterations. They communicated ungrammatically but with unvarnished simplicity. Many more highly educated and articulate individuals might do no better in conveying the distortions of time and space, the powerful emotional effects (which often seemed to consist of a longing for interpersonal closeness – with sexual overtones) and difficulties with reality testing.

They helped each other with regard to true versus imagined events. In the upcoming transcript, the reader will see that G's preoccupation with the Ace of Hearts seems to relate symbolically to love and affection, although he never presents it that way. H's longing to hang onto the beauty of the fantasy world suggests a concrete feeling of loss when the ordinary world came back into focus.

The following was taken verbatim from the videotape, slightly abridged due to its length (45 minutes).

I [**K**] am in (**BLACK TEXT**). [**C**]arr (**GREEN TEXT**) is the natural leader. Secure within himself, he, more than the others, encourages [**G**]ates (**BLUE TEXT**) to talk about feelings he is reluctant to describe. [**G**]ates is shy, much less self-possessed, and sees himself as unable to share positive sensations, especially the brilliant colors that [**H**]arwig, [**S**]tover and [**C**]arr all rave about. [**H**]arwig (**PURPLE TEXT**), who is about to be married in two weeks, looks up to [**C**]arr and tends to chime in with him. Both he and [**S**]tover (**RED TEXT**) come across as "country boys," less articulate than [**C**]arr, but similarly good-natured and relaxed. [**S**]tover, like [**C**]arr, gradually becomes a "co-therapist" and tries to help [**G**]ates share his negative experience with the group. He is the peacemaker who points out that everyone has problems and [**G**] should not feel different or rejected.

The group discussion consists mostly of a comparison of ups and downs during the LSD "trip" (with positive emphasis on its strange magic as well as the negative sense of loss as the effects wane). It also resembles a group therapy session, focused on [G]ates. Eventually, [G]ates manages to reveal feelings of shame and consequent paranoia during the test. Without saying as much, he confides unacceptable erotic feelings, seemingly directed toward the nurses, which tormented him and left him feeling isolated and alienated. When [G]ates finds the others to be surprisingly empathic and accepting, he realizes that his self-pity caused him to miss the "fun" parts of the LSD experiences. He brightens up and wants to try the drug again and see "the colors." The transformation is striking.

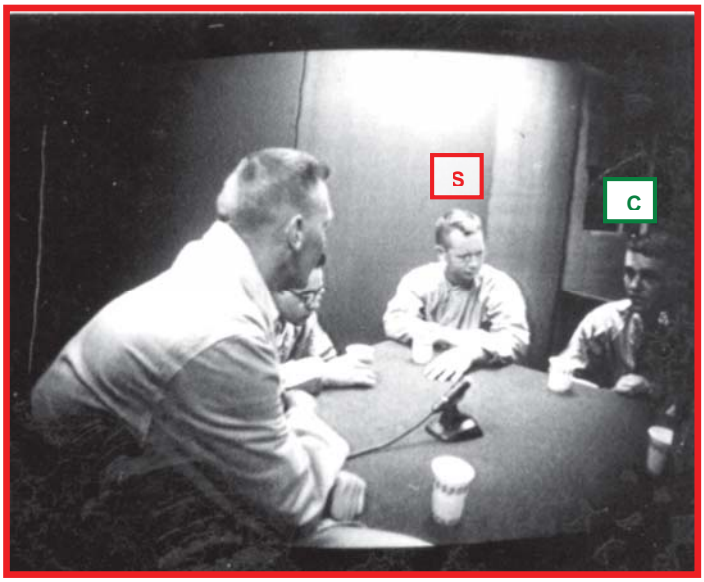
K: I'll tell you how we did this. Once before we had a group of four guys and we just made it an open discussion, without any special questions. That worked out pretty good, so why don't we try it again that way. Just anyone who wants to start some…

S: [Pointing to G] You talk about it. O.K.? You watched everything… G was talking about the colors. This was something that I enjoyed in a way. [Laughing] You can lay down and close your eyes and it's a wonderful world of fantasy. It's all in color, and it's colors that you've never seen before and...

C: "Color by Med Volunteers!"

[All laugh]

S: Yeah. And it's really beautiful. I, myself, I just went off into a dream; or I couldn't say actually a dream, but it was so nice I just didn't want to come back. [H playing with something under the table – bent over looking at it] And when I would start coming around, I found out that I, I didn't even know where I was, and it had to go through me quite a few times before I even knew where I was or what I was doing here, or anything else.



K: That's why you didn't want to talk or do anything? You were …

S: That's right. Like in the film we just seen. I might have been sitting here, [laughing] but I was way off on Cloud 9.

C: Yeah. That was me.

S: Now, there's things that happened that I remember, but I still was way off on Cloud 9.

C: When you [S] was talking about the colors – I didn't get like he did. The interview we just saw in there, you know, relaxed or anything. [C is very expressive with his hands.] Then we went ahead and had a vital sign, and I was laying there and I remember laying my head on the pillow and I closed my eyes and, like you said, seeing all kinds of beautiful colors. And I opened my eyes and on the wall, right by where my bed is, there's something's been spilt there at some time or other, and it just looked a real pretty shade of green, you might say. And all kinds of colors. Like he said, I was just out there floating. It was great! You know I could feel like what I was – I could tell that there was the, whatever I took was doing it to me, but yet I didn't mind it, you know. And like the way I felt, physically, is – you've seen how on the Fourth of July these things that go up in the air and burst open like that [demonstrates]? That's just how I felt inside. It kept – like when you're cold and get goose bumps all over you, you know, that sensation. That's what I kept getting over and over again. [H playing with juice cup] It was like a warm glow. And it, it felt good to me. [Laughing] I enjoyed it.

G: I was in the same room you were.

S: We, I want to ask you this. You didn't … [Indicating G]

G Don't ask me anything. [Shaking head "No"]

S: Did you close your eyes and imagine, or go off in any kind of dreams or anything?

G: I had my own dream. [Speaking in low voice as if to himself]

C: [To G] How'd you feel inside?

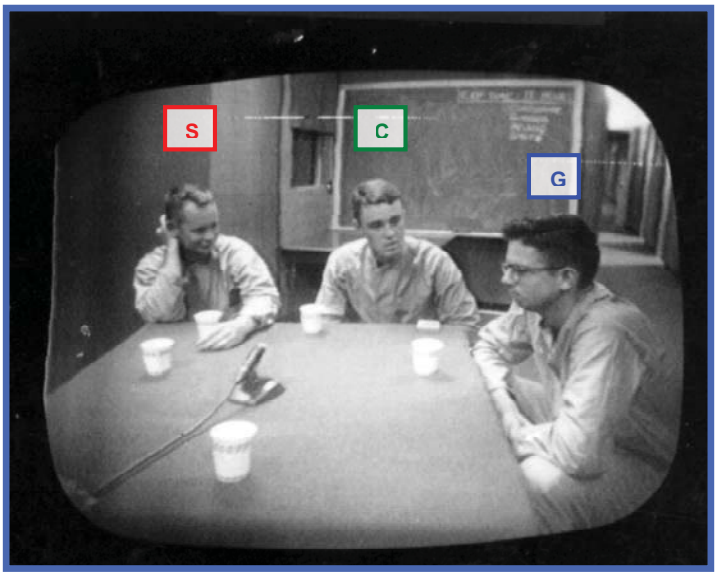
H: Everything was funny. The least little movement. It was cutting through my sides. Boy! [rubs side] it hurt!

C: Yeah. It puts you way out. I can imagine – I mean it really gets me inside, you know. I mean, I wanted – I know, between H and I – well, he's getting married in just a few days and I just got engaged, and it really got me – and him, too. I mean, just far as tearing you up inside. You feel like you want to be wanted, you know.

H: Yeah. It comes back down out of that cloud. It was bad.

C: You feel like everything's away from you. You feel like you're being tromped on, you know. Really put down.

H: Well, when you're up on that cloud it's wonderful, but coming back off of it, back down, you know, to normal. It's bad.



S: Going into it's nice.

H: All these here doors came backing off the walls, didn't they?

C: Yeah.

H: You know they all came back and then the wall came all together and the world came to.

C: You know I come out of that at the same time cause you were down here and I was in my room and …

H: I heard 'em say 'they're starting to come out, you'd better get 'em in their rooms'."

G: I can't explain that.

C: Well, give it a try.

G: I felt – it just felt to me that this drug, or whatever it is you gave us, just brought out everything that was inside. Just brought everything inside to the outside. [Nervously moving fingers on tabletop]

C: Yeah. That's what I said. It appeals to the emotions.

G: Right. Puts everything on the outside inside.

S: I think the drug that we had before would have a whole lot more psychological effects. And really tear you up more that way. This is more…

C: This is – you mean the one you and I had? [BZ]

S: Yeah. That's right.

C: Yeah. Oh well, yeah.

S: This is more of a quick knockout punch [Snaps fingers] like that. And you're just knocked out.

G: I couldn't stop myself though.

C: Well, yeah. Well, what do you expect?

G: I tried.

C: Nobody said you didn't try.

G: Crap. [Looks over shoulder at camera]

C: That's what the test was run for – to see what would happen.

G: I know it. They found out. [Playing with juice cup again]

C: Well, that's no big thing.

S: G, I think you're letting some of your emotions get involved here.

C: Yeah. Yeah. Your self—self persecution here.

G: That's what I am. That's the whole trouble. It's just the way it came out.

C: What?

G: To me – that's the way it came out.

H: Oh. You're mixed up anyway.

C: What? What came out?

G: [To H] I know I'm mixed up.

S: Now – now don't go saying he's mixed up. You never say that about anybody. Everybody's mixed up to a certain extent.

C: Yeah. Everybody's jacked out of shape.

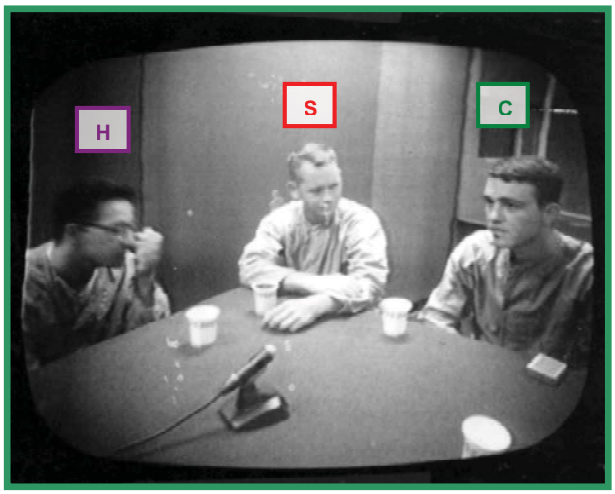
[H laughs at this]

G: Only some do a little bit longer.

C: But you're worrying about yourself too much. And it's not yourself, it's the test they're concerned with. You, personally, really don't have anything to do with it. They're trying to solve the effect of the average human being, and that's just a number of people, to find out what the average is. Just like the control test you took.

G: That's right.

C: So you shouldn't feel personally about the thing. So why don't you want to talk about it? Heck, I did a lot of things on the last test I was on that I wasn't very proud of, but it was nothing to be ashamed of.



G: That's what I'm afraid of. I'm awake on this test. I know what I did. The last test I can't remember. [BZ]

S: If you've ever – Sir [to Ketchum] If you've ever watched Walt Disney's opening in color television. You know where that…

K: Kaleidoscope?

H: Hm-hmm.

S: Kinda like on "Peter Pan", you know. Where they come out – where the girl comes out. You know the fantasy dream part and all that there?

C: Tinkerbelle. Yeah.

S: Well, that's what it was kind of like.

H: It was more prettier…

S: I could say that would be about the closest thing that'd be in reality to.

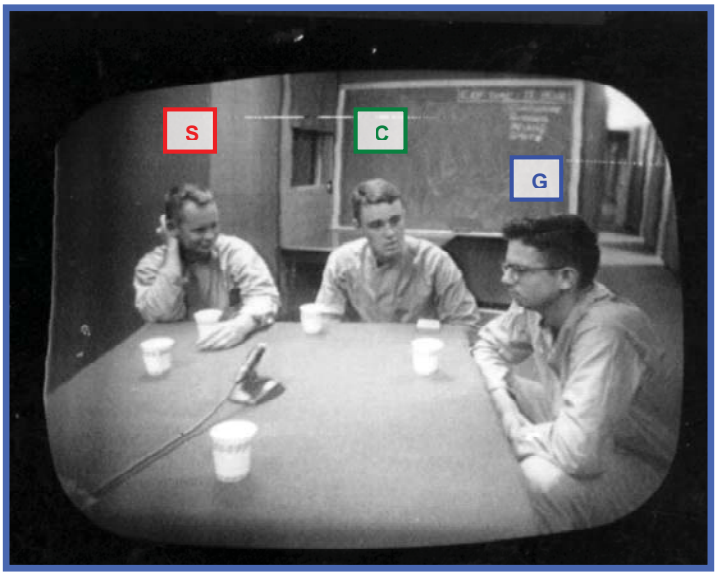
C: I felt, you know, warm all over, and it wasn't an uncomfortable warm. It was just a glowing warm. My skin felt dry and smooth, but it just felt for as – you know, constant for a long time then pretty soon it would die off, and then it would just come back in bursts [snaps fingers] and then it felt like the drug was wearing off, or going through my system more even.

K: What would have been the effect on you in a combat situation?

C: I don't know. I think H and I would have just laid in the foxhole and laughed like hell. That's about the extent of it.

H: I think that's about all we could have done…You sure couldn't put no females out there on the battlefield.

C: Yes. That's where it would get me.



[Light laughter]

C: Seriously. It would have. [Laughs] I would have been running around the battlefield looking for them.

[S banging on bottom of cup with fingernail]

G: Something you might not think – these cards here. I had them in my room playing with them. This Ace of Hearts here. Every time it'd come up right there. I'd floor that sucker. I'd shuffle the cards, and where's the Ace of Hearts? I don't know where it is now, but right there it was. Every time. I couldn't get rid of it. Just…I thought about eating it awhile.

[Laughter]

H: He did the last deck like that. [Referring to the previous test they were on in which Gates tried to eat some of the cards.]

G: That got on my nerves though. I'd put that Ace of Hearts down there; I'd shuffle through the cards just like so. [Shuffles cards] Ace of Hearts sitting right there.

H: That's the two of clubs.

S: Did it have any colors to you at all…

C: Yeah. Didn't you get any of this imagination effect?

H: Everything was wonderful. You know. There was nothing wrong. You couldn't be going any better. But coming back out of it, that was the bad part.

S: Probably coming back you might say is just like about coming back from the dead.

H: That was just about the worst for me.

C: Well, coming back was so bad, you see, it was so wonderful out there – you'd just come back and start realizing what was happening.

H: You just kept wanting to reach, reach out and bring it back, you know.

C: Yeah.

H: Reach out and get it.

G: I didn't get any colors or anything. I know I sat in there and played Solitaire, or tried to, with myself for a while

K: O.K.

C: I think that this test, to – oh, well, of course it's impossible, but to know the person before the test would be of more advantage to you, which this is impossible in your type of situation. But, if you, when the people first get here, like in your two months, to give them this.

G: And that's another thing right there. You take a second, just felt like about an hour.

C: You didn't want to be alone, did you?

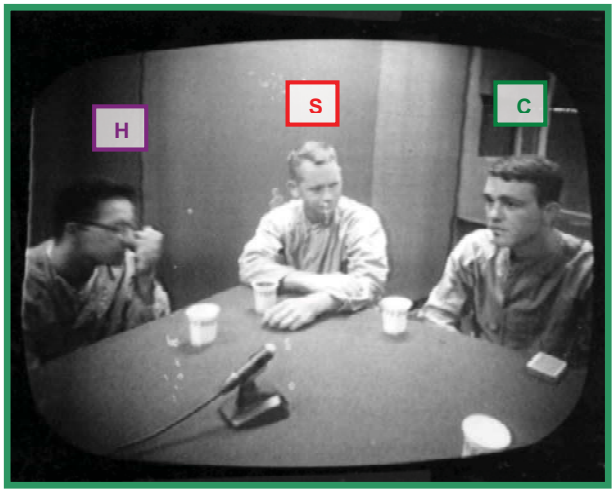
G: I don't guess I did. I don't know. [Still fooling with deck of cards]

C: What do you mean you don't guess you did? You know what you did, don't you? Don't be afraid to say so. Come out with it! Good Grief!

H: You can't keep it in you forever.

C: No.

G: That's true.



C: You don't talk about it now, you just want to talk about it later. You might as well let it be of some use. Don't you remember imagining anything other than yourself and your problems? Didn't you get any good effects from it?

G: I just imagined…no. I didn't. I imagined the people – everybody's against me. Everybody and anybody.

C: Just like a little kid losing a new toy, you know. It's something that you really wanted and didn't want to lose, and it was gone. [to G] Well, what did you feel down inside?

G: That's it. [Laughing] [Looks over at camera]

S: I can't say it for you, G. I know what you mean, but I can't say it for you. [Laughing lightly]

C: Nobody can say it for him. Whyn't you go ahead and say it? It's on tape already, so you might….

G: Yeah.

C: …as well go ahead and throw it out.

G: No. It's out farther than it should have been.

C: Why?

G: Why?

C: Yeah.

[G shakes head in negative as if to say "You're just too much!" S breaks out laughing, which in turn causes the others to laugh. G puts his head on the table, hiding his face.]

G: [To Ketchum] I think you'd better give me another shot so I can go look at the colors. That way I can… [Laughter all around]

K: Are you ready for the colors this time?

G: Right.

…test – and then in the last two months give this test, and see how it affects them both times, to see…

K: I thought of doing that…

C: [To G] Hey! Where'd you get this – I noticed a craving for affection you got during the thing. I know I hear you – yeah, I heard him keep talking about "don't leave me alone, don't leave me alone!"

G: Yeah. That's true. [Starts playing with his slipper]

C: Well, how'd you feel inside? I mean, did you feel like everybody was leaving you, or…

G: Yeah. Everybody was gone. To me, I'd sit in there for hours, nobody around.

C: Well, did you have to have somebody around?

G: Don't ask me. I'd look out the door and I'd see people going this way [uses hands to show directions] and people going that way, shaking thermometers and everything.

C: Why should that bother you?

G: Well, I was in there…

C: Why did it – how did it bother you? I mean, did you feel that you were personally being left out? [G starts playing with juice cup] Or was it something that couldn't be helped, or what?

G: I guess you'd say that.

C: Well, you say it. That's what we're trying to get out of you. I mean, don't – I can't explain it. It was you…

G: Well, you said it. No, but it was – I was left out in a way, I guess you'd say. I was sitting in there; somebody'd be in there; they'd say "I'll be back in just a minute" so I'd sit there two to three hours and nobody's come by yet. It's just that time seemed so drawn out – long.

C: Well, did you feel sad or…

G: Yeah. Sad I guess would be the word for it. I don't find it easy to put words into what I felt.

C: Well, nobody knows the words…

G: Yeah. Well, as I told Mrs. Casillas in that interview out here, she asked me how I felt. I said that it's just like being inside of a little old nutshell. You're in there, you're looking out, you see people on the outside, carrying on their normal activities. You're trying – you try to communicate with them; you try to get out. There's no getting out.

C: Alright.

G: And I told her also, when the drug's wearing off…

C: Well, we weren't there when you were talking to her.

G: …the nutshell just POP! [Gestures with hands in demonstration] The whole world just come FLOP! Right on top of me…. As she said to me, "that's the best way for it to come." [Starts mashing cup between fingers]

C: Well, we understand that. But, I mean, not particularly me, but still…

G: In my mind, he was there.

C: I mean when you looked at him, could you see him, or…

G: Yes.

C: Was he fading off or what?

G: No. He was there. I guess he was.

K: And then the world goes PLOP?

C: Well, it faded with me; it didn't exactly PLOP.

K: It just faded?

H: It faded with me, too.

[G holding edge of cup in fingers, shaking it gently]

G: Did you have anybody working in the latrine during this test?

[Laughter]

K: No. No one working in there.

C: That's a pretty bad place to work.

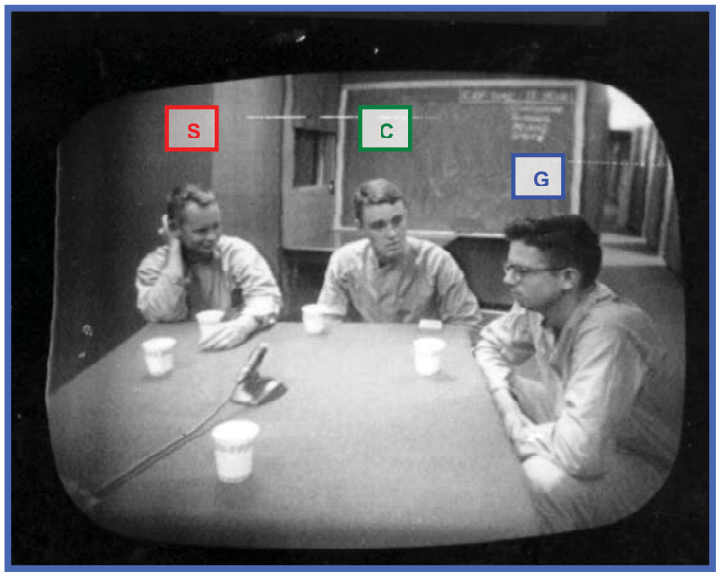
K: We're short of office space, but not that bad.

G: I'll take another shot.

K: You wanta go there, huh? [To G]

C: Yeah. That just got me, when they come in with this "cut the water off" and then all of a sudden BAM! – mass confusion, you know. Bang, bang, clang. [Looks at G] "I need someone! Someone come here! I'm being left alone!"

[G looks at him and laughs, then says "Shhh" and ducks head]



G: [Picking up juice cup again] That's the way I felt though. Just all alone there by myself.

K: Do you feel by yourself now?

G: No. Not now.

K: Looks like you've got a lot of friends.

C: Yeah.

G: No. I'd sit in there and …

C: He had a lot of friends on the test, but he didn't seem to appreciate them then; maybe he will now.

G: I'd sit in there and hear everybody out here playing cards there, just having fun. Seemed to me I was in there – I'd know I was on the drug; it seemed to me everybody else was off of it already. Sitting out there, they're looking in at me in my cell, laughing at him. Old S, he walked by the door there; he and the nurse were going down that way for something.

S: I had the same feeling…

C: We were all living it up.

H: Yeah. Me and C, we'd try not to make fun of you.

C: [To G] Yeah. Cause you seemed to get depressed, you know, and I'd try to get you to come around, and it looked like you'd try, and then you'd look at me and figure "Oh, you're just joking with me."

K: Alright now. I can't stand it any more. I just have to stop. I'll have to go there myself.

H: Well, you'll be hell coming back, let me tell you.

G: Take me with you if the colors are there.

K: You want to go, too? Alright, we'll take another trip.

G: All right. Next week. I'm ready.

H: I'll go on it again, but it'll be after I'm married, not before.

C: It might be worse then. [Laughs]

H: I mean, I just gotta be home, that's all there is to it.

K: You'll make it all right.

H: Well, I'm worried about getting "Delay En Route" going back. I already talked to…

K: Well, I can't help you. I don't do anything about the…

C: He's not the pass man, he's just the color man [Laughter]

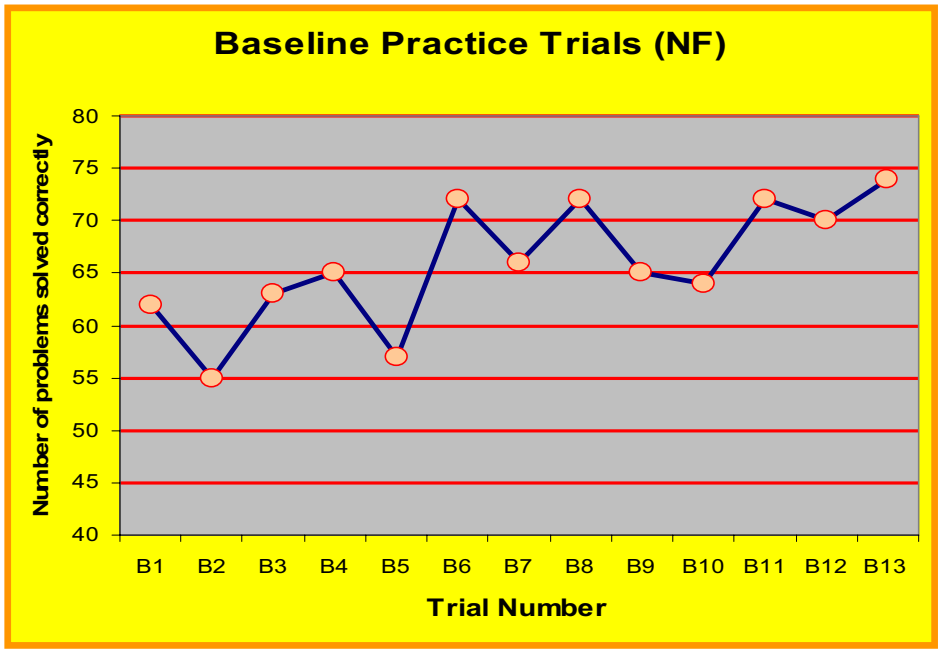
K: Right. I just take care of the…

C: He just takes care of the colors.

[Miscellaneous conversation as group gets up and discussion ends]

About a year later, another volunteer from G's installation said that when G returned to his home unit, he seemed different. No longer shy and reclusive, he had become more jovial and sociably inclined. It seemed that one had to give LSD at least part of the credit.

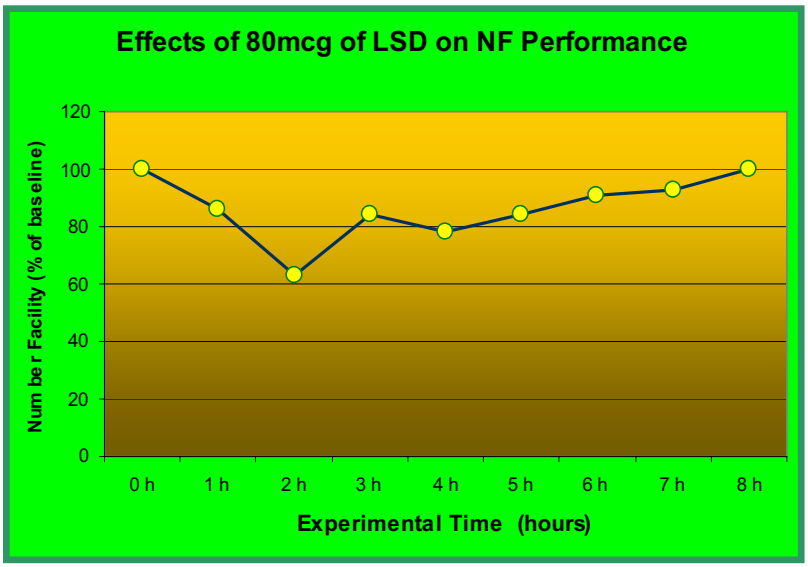
In the early 1960s, practically every LSD investigator in the nation had taken LSD at least once, if only to become familiar with the subjective effects. Many, of course, took it innumerable times, incorporating it into their life style and self-concept. It was not until 1965 that I worked up the courage to try it myself. I knew that Van Sim had taken it who knows how many times, whether he needed it or not, and George Aghajanian told me he had taken it in his dorm room in med school more than once (but only after having someone lock him in). Oscar Bing had taken 20 mcg under George's watchful eye and described the effects as similar to "20 cups of coffee." I decided it was time for me to try it.



Author's learning curve – necessary to establish a baseline for NF performance testing

Before making a final decision, I consulted Dr. Abramson, one of the nation's pioneer researchers on the effects of LSD. When I asked him how much I should take, he casually commented: "if you take 50 mcg, you'll probably get horny, and if you take 100 mcg you'll probably get a little anxious."

I decided to compromise. If I took 1.0 mcg/kg, (80 mcg) things should work out okay. I didn't want to become a management problem or become terrified, thinking I might never come back to the real world. I chose my most reassuring nurse (June Brenneman) and my most easy-going and knowledgeable doctor (Barry Tharp) and decided to go through the test just like a regular volunteer, including taking the NF test as usually scheduled and having my vital signs monitored.



Author's NF performance scores after an oral dose of 80 mcg of LSD

I brought some jazz records and a record player from home, settled down on the Hollywood-style bed in one of the cubicles and swallowed my allotted dose of LSD in distilled water. Nothing seemed to happen for about 45 minutes, although the Modern Jazz Quartet did sound a little more fascinating than usual. Then, it became a bit overwhelming and I turned it off. After that, my cognitive and physiological responses turned out to be very similar to those of the enlisted volunteers. As the effects increased, I started to feel a bit nervous and squeezed June's hand. At one hour, I was scheduled to do arithmetic problems and didn't think I could make it down the hall.

Once I got up, however, it wasn't all that difficult, and my balance was pretty good. Things seemed a little unreal, but I can't say just what kind of unreality it was. I saw no bizarre illusions or beautiful colors. Maybe that was because most of the time, especially while lying on my cot in the cubicle, I was visualizing the cells in my raphé nucleus firing messages to other parts of my brain.

It was all quite interesting, and I thought that perhaps I could figure it all out someday. I can't remember much else, except at the end of the test, I took a Thorazine tab (the fashionable way to come down in those days) and went home.

Maybe it's because I'm not the transcendental type, but sadly, I didn't have any great insights. At the very least, however, I was now a semi-official, semi-bonafide member of the "LSD savvy" brotherhood.

* * * * *

8 WORKING OUT THE KINKS

There is no stronger evidence of a crazy understanding than the making too large a catalog of things necessary.

George Saville: ***Advice to a Daughter***

Kinks are annoying knots that can stiffen up your back muscles. Or, you may think of them as one of your favorite British Invasion bands from the '60s. But in this chapter, I'm talking about still another kind – the knotty problems that bedevil you when you're trying to get something to run more efficiently – in my case, a start-up psychoactive drug-testing program requiring military volunteers. I know there were quite a few such kinks, but it's hard to remember all of them. Memory experts say you tend to forget little frustrations, like flies at a picnic. You don't think about them until you get comfortably settled on a blanket and open up the potato salad.

Fortunately, many kinks aren't that hard to untangle. A hundred-foot extension cord that you didn't take the trouble to wind up properly is something you can straighten out with a little diligence and a few expletives. But others are more abstract. In our fledgling program, for example, one problem was the many variations in performance scores on different tests, scheduled inconsistently and after varying amounts of practice.

I spent a lot of time wrestling with that one. One day, I recalled an ingenious way of combining measurements developed by two researchers, Drs. Pincus and Hoagland, while studying hormonal function in schizophrenic patients. No single measure set schizophrenics apart from normal patients, so they cooked up a kind of statistical stew, using lymphocyte counts and potassium levels instead of carrots and potatoes. They called it the TRI (Total Response Index).

Taking average performance scores, blood pressures and heart rates, and scaling them to correspond to a given dosage range, I ended up with a weighted average. In deference to Pincus and Hoagland, I also called it the TRI. I used a lot of averaging and other mathematical machinations to make the effects of doses (1.0-8.0 mcg/kg of BZ) match up with the TRI scores. Unfortunately, I did not realize that in working out one nasty kink I was creating others.

When the statistically sophisticated psychologists realized what I was doing, they had a field day pointing out my failings – unjustified assumptions, violations of statistical theory and other mathematical crimes. They talked about ordinal scales versus ratio scales and scolded me for not using "analysis of variance" instead of Chi-square and Student's T tests of significance.

Things got so bad that Jim Hedlund, a hiking buddy from Walter Reed days (subsequently elevated to the distinguished role of Psychology Consultant to the Surgeon General), came up from Washington, DC to help resolve what was becoming a prolonged series of skirmishes. I was a pragmatist; the psychologists were purists. I was intent on getting useful numbers; they were in favor of proceeding slowly, studying the measurement problem from every angle and using only respectable statistical methods before drawing any conclusions.

"Have you advised Jim of the usefulness of discriminant analysis?" Hedlund asked the psychologists after we had each expressed our version of the best way to go. They hadn't and as for me, I wasn't even sure what discriminant analysis really was. I knew some statistical procedures, but not that one. The psychologists knew, but they didn't feel like buying into discriminant analysis at that moment, so the meeting ended with the kinks still knotted.

Of course, neither Van Sim nor Doug Lindsey had much interest in this academic dispute – they just wanted to know how much BZ was needed to cause mild, moderate and severe effects. So I continued alone in my stubborn ways. While the psychologists believed in painfully unraveling the Gordian knot, strand by strand, I wanted to cut through it with a sword, as in the ancient myth. I rationalized that if we did things the way the psychologists wanted, we might still be picking pieces of lint out of our navels a year later.

It was arrogant, I suppose, but I was satisfied to be producing usable numbers, even if derived by imperfect methods. Pincus and Hoagland had no problem publishing their results in distinguished journals, so why was I so wrong? Feeling justified, I decided to endure the "slings and arrows of outrageous fortune" and forge ahead, even if I crashed and burned "unwept, unhonored and unsung."

But in the course of a single docile visit to my ward, Dr. Henry Wills, the kindly gray-haired Chief of the Pharmacology Division, induced me to change my mind. He showed up unannounced one afternoon and after a friendly exchange of greetings, inquired if he might examine a few of my charts. I knew right away that he wanted to see how well the TRI matched up with BZ dose in some actual cases.

I predicted vindication, but darned if the five charts he picked at random didn't prove to be less than convincing. The TRIs matched up only roughly with the doses. Henry said very little, but I got his message and elected to retreat to the safer ground of conventional statistics. In the end, estimates of effectiveness came out about the same, but the psychologists had at least won a minor victory.

While theoretical and procedural kinks could be irritating, administrative and organizational kinks were more unsettling. They often persisted for weeks and months. The most befuddling ones sometimes required "help from above" –

i.e., intervention from someone higher in the chain of command.

When I arrived at Edgewood, my basic responsibilities seemed clear. We were supposed to select volunteers, see how they reacted to various drugs, record the results, and make sure the men were medically okay before they went home. After that, we were to sit down, write our reports and promptly move on to the next test.

Above all, we were expected to get along with each other and stay out of the newspapers. If someone needed something he didn't already have, he was to let the right people know and they would do their best to get it for him. It might take a while, but quiet patience was usually rewarded.

Not every time, unfortunately. I've described one of my first knotty problems – getting out on the "playing field" without being perceived as a hyperactive rookie who couldn't wait for the coach's permission. That one I was able to straighten out with the help of Kaz Kimura's good advice.

Another one, however, was tougher to resolve – the casual attitude of some of the psych techs, who sometimes slipped away to the dayroom to play a little pool when they got tired of baby-sitting the volunteers on BZ. I wanted them to write detailed behavioral observations in the chart and consistently record vital signs at scheduled intervals, but they were sometimes less than meticulous and didn't always see the point. I would also caution them not to laugh openly, even at the hilarious things that delirious volunteers invariably engaged in once they were disoriented – like wrestling with their pillows. I thought it was unprofessional. Of course, the technicians were not professionals – that was part of the problem.

The irresistible appeal of the dayroom

Generally, though, when BZ was being tested, the technicians did their best to keep delirious subjects out of mischief and protect them from injury. Unfortunately, one afternoon, an unsteady volunteer lost his balance while under the influence of BZ and fell back against a hot radiator, sustaining a mild second-degree burn to his back. It was just the sort of accident that I (certainly not he) actually welcomed – not too serious, but enough to make the Safety Office nervous.

Pointing out that such events could jeopardize the program, I successfully argued for the conversion of an empty office into an "injury-proof" room, outfitted with padding on the floor and walls. At one end, the carpenters installed a "see-through" mirror. Observers could watch unobtrusively, make notes in the chart and be ready to intervene if anything troublesome developed.

To help with the constant monitoring, workers placed a video camera high in the opposite corner of the room, providing visual coverage of "blind-spots." In addition, a hinged panel below the mirror became a small desk, ideal for administering paper and pencil tests or passing food and fluids to the volunteers.

The room was large enough to accommodate two Hollywood-style beds and two TV-style hassocks. Padded panels lined all the walls and the door, and a one-inch layer of foam rubber covered the floor. Volunteers spent the night before the test in the padded room, completing baseline tests and physiological

measures. This provided time to become comfortable with the surroundings and the medical personnel.

We had improved the setting, but the technicians' relative lack of medical training was still a problem. I realized that we needed to ask for nurses – registered nurses – experienced in the care of patients. Nurses would stick to the protocol and make more complete chart entries, as they had been trained and required to practice in hospitals.

This idea did not sit well with Dr. Sim, however. I think he retained a "locker room" mentality from four years of college football and a year or so as a professional player before medical school. He had unconsciously created a men's club atmosphere. Perhaps he thought the presence of women would inhibit the male chauvinist jokes he liked to share with the staff. Up until that time, it was only men (with few exceptions) who were assigned to the laboratory.

Having nurses was a great advantage

This "super-kink" did not yield to simple untangling. Although I continued to argue that nurses were as necessary in our testing environment as they were in hospitals, my request lingered in limbo. So I pressed the argument with Colonel Lindsey, and also with Dr. Rioch the next time I saw him.

Finally, to my delight, approval for spaces and funding for three registered nurses suddenly came through. The job title was "research nurse." I knew this would be financially appealing to prospective nurses, since it would boost them a step higher on the Civil Service ladder. Applications were not long in coming.

The arrival of the first nurses was a gala occasion for me. Frances Peck, "Billie" Fort and Joan Brenneman were all forty-ish and married to field grade officers on the Post. Most of them had a motherly attitude, which I secretly welcomed. After all, I was only 29 when I began my assignment at Edgewood. Frances, in fact, adopted the habit of calling me "dear boy."

In the ensuing months and years, the nurses proved to be loyal, competent and hard working, dutifully complying with requests that went beyond customary hospital orders. The quality of volunteer care and documentation improved dramatically. Eventually, more than a dozen nurses passed through the program, most of them staying on until their husbands received reassignment orders.

Professional training assures more accurate measurements

Our single padded room soon proved inadequate. We needed additional space, as well as a proper nursing station. I went home and built a cardboard model of an ideal experimental ward. It would actually be a "ward within a ward," with just enough space around the sides to let someone quietly pass by, if necessary. Inside would be a row of six identical cubicles, a well-equipped nursing station and an open area for meals, watching TV, and other forms of relaxation for the subjects.

Rubber padding would cover the entire floor, and line each cubicle. The small rooms would each contain a single Hollywood-style bed (box spring and mattress) and a hassock and the lighting would be out of reach above translucent ceiling panels. I showed the model to Van and then to Doug Lindsey, who brought in a skeptical Post engineer for an opinion.

The engineer, a short feisty guy, said it could be done, but it would probably cost at least $8,000. Only eight thousand dollars? It sounded like a bargain to

me! I bird-dogged it and the proposal finally became a very satisfactory reality. It served as a state-of-the-art experimental setting until a new building required its destruction in 1968.

We were among the first clinical laboratories to have a closed circuit television system. The recorder was an upright piano-sized Ampex console, with two 14-inch spools. They shuttled four-inch wide videotapes back and forth, like the much smaller audiotape cassettes that were just beginning to become popular.

Lloyd Matter, TV engineer "par excellence"

Along with this monster recorder, came several black and white TV cameras, and Lloyd Matter – a talented TV engineer. Lloyd was plump, quiet and totally devoted to his job. He and his assistant, John Day, did their best to accommodate all our requests, whether routine or bizarre, day or night.

One episode remains particularly unforgettable. Sometime in the wee hours of the morning, the nurse on duty called me at home. A delirious volunteer had somehow escaped from the padded room. In a paranoid panic, he had managed to find his way to the day room at the end of the ward area. There he remained ensconced, waiting tensely for "the enemy" to come after him. To defend against the dreaded onslaught, he had armed himself with a broom handle and a heavy glass ashtray. Powerfully built, he intimidated the nursing staff and kept them at bay.

Since I had established a good pre-test relationship with this volunteer, he was glad to see me. I managed to talk him down. Finally, he surrendered his "weapons" and returned to the padded room. His hallucinations did not cease, however, and he insisted on drawing my attention to a parade of vivid scenes.

"You see that sewing machine right there?" he asked.

"Uhh, no," I said, studying the air intently.

"Just take my word for it, it's a sewing machine," he continued patiently, apparently assuming that I was visually challenged. Then he leaned forward and ran his finger along the molding, asking if I could see the strips of bacon.

"Strips of bacon?" I finally realized he was referring to the narrow strip of wood between the wall and floor. Then he suddenly became distracted by the whirring sound of the air conditioner. He gazed at it studiously.

"Hey," he shouted loudly at the grating.

"Who's there?" I asked, showing professional concern.

"Who's there, who's there?" he shouted, taking up the cry and looking anxiously upward through an imaginary shaft. After a moment, he turned his head toward me and reported his findings.

"It's okay, it's just some kids," he said, appearing relieved.

He sat down on the edge of his bed, while I sat on a hassock. For the next twenty minutes, we held what might be called a relaxed conversation. He did his best to express himself clearly, but somehow the words kept coming out wrong.

"Did you answer the phone?" he asked me abruptly.

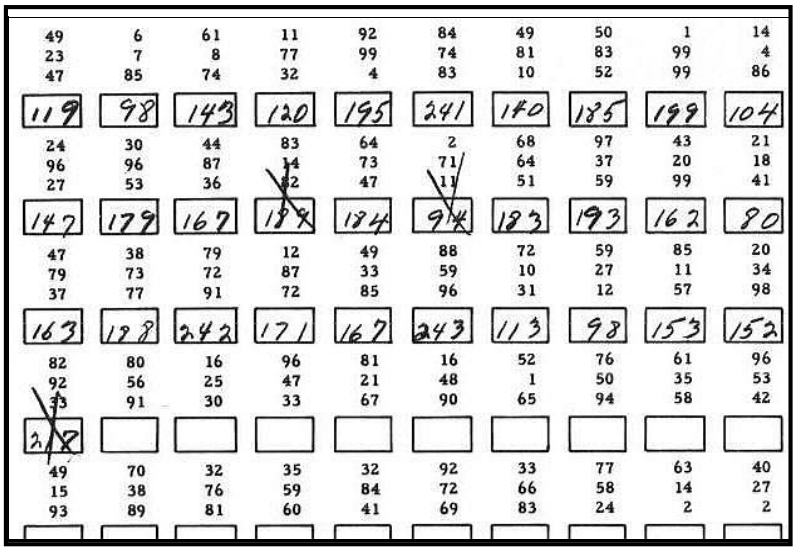
"The what?"

"The phrone, the phrone! If it weren't for those damned kids…" he suddenly stopped, again losing track of his thought.

"The kids?"

"Well what you might call the kids. I mean the kids...well whatever it is. It might be a truck or a fence. Down at the motor pool. Or maybe it might be danger." And so it went.

Little by little, he calmed down. He suggested that I take a nap while he stood guard against any intruders coming down through the air conditioner. I thought this quite gracious of him and since it was about 4:30 in the morning, I nonchalantly lay down on the other bed where I even succeeded in dozing for a few minutes while he continued to perform sentry duty.



The Number Facility 3-minute addition task

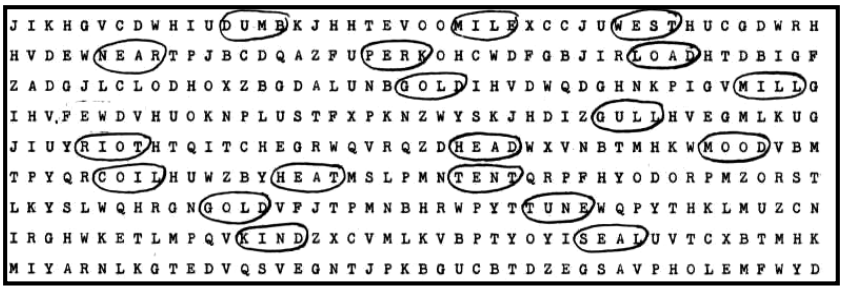
Awakening from my brief nap, I suggested trading places. He did so and gradually drifted into sleep, continuing to mumble, not about his fears of attack, but of home and his mother's cooking. His paranoia disappeared and he soon lapsed into the deep sleep that signals imminent recovery. From this episode, I learned an important lesson: the prevailing emotional state of the individual dictates the content of delirious hallucinations and delusions.

Meanwhile, despite the ungodly hour, Lloyd had traveled from home and recorded the entire sequence without complaint. Indeed, Lloyd would typically drive 15 miles on a moment's notice, whenever something was worth videotaping. Later, we incorporated portions of the recordings into teaching tapes.

On another occasion, I asked Lloyd if he could set up two ceiling-mounted cameras just above two small tables. I wanted to see whether moderately confused volunteers could assemble a 25-piece picture puzzle, working from separate locations. One had the pieces on his table but could move them only when the other told him where to put them. The other could see the puzzle on his TV monitor but had no direct access to the pieces. It was a task that either one could have completed alone in about three minutes

This unusual division of labor produced some interesting results, showing how two partially incapacitated volunteers could add up to one fully incapacitated two-man team. Either could have easily assembled the small puzzle alone, even when drugged, but when they had to communicate with each other to get it done, it became almost impossible. It made an interesting TV vignette to use in official briefings.

We still had a sizable list of procedural kinks. Performance baselines were a persistent problem. Before I arrived, it was considered sufficient to use the highest score from three practice trials on tasks such as the Number Facility (NF) as a baseline. It wasn't really sufficient since practice effects continued right on



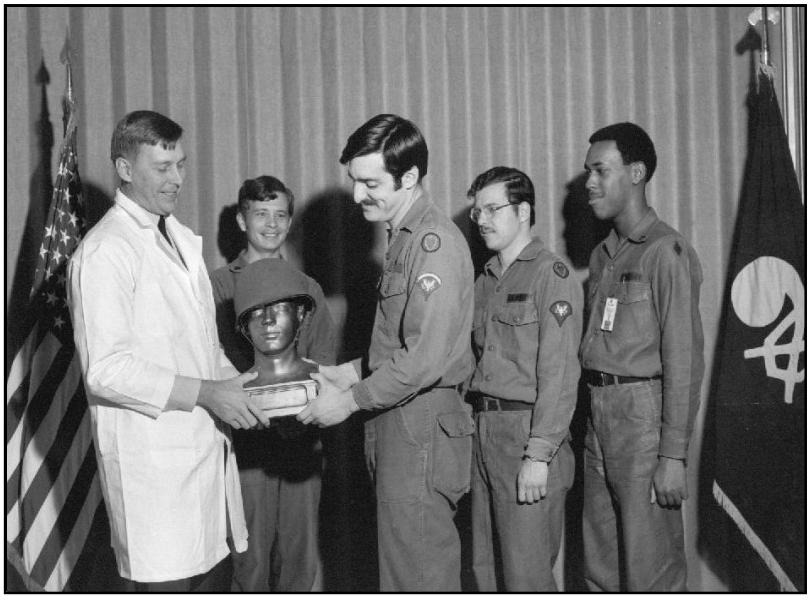
Speed of Closure (SC) — another useful test in the "Texas Battery"

through the drug test, and the scores actually rose above baseline by the time of recovery. So we upped the ante, making the baseline equal to the average of the three highest of ten trials.

This still was not enough to eliminate practice effects over the course of three days of testing, so we finally upped it once more to the average of the five highest of twenty pre-drug trials. This was far more practice than any I had seen described in the psychopharmacology literature, where baselines usually were based on two or three pre-drug practice trials, and compared to a small number of scored trials after drug administration. Such a design probably obscured some real changes.

Still not satisfied that we knew enough about the learning curve, we undertook to study it more systematically and decided to administer the Number Facility (NF) and Speed of Closure (SC) tests as many times as necessary to an undrugged group, until no further improvement was evident. By then we could be reasonably sure we had reached a reliable baseline

Eight volunteers were available and willing. We divided them into teams of four. For five days, they competed in round after round, adding numbers and circling words, striving to outscore the opposing team. The stimulation of competition kept them trying their best at tasks that would have otherwise become intolerably boring. From time to time, we even threw in handicap points to keep the teams close.



The prestigious Head Award for outstanding NF and SC performance effort

Searching for a prize to give to the winning team, I located a plaster of Paris model of a soldier's head, topped with a combat helmet. I put it on display it as the prestigious "Head Award." At the end of the week, we staged a formal award ceremony, with glossy group photographs of the event for each participant. Silly as it must have seemed, the men had all done yeoman duty and we had the learning curve we needed.

* * * *

Where would Don Quixote have been without Sancho Panza? While engaged in one chimerical chase after another, I needed a reality-oriented partner. A personal Sancho for many of my quixotic journeys at Edgewood was Phil Kysor, a bright and dedicated psychology technician, who accompanied me on many of my quests.

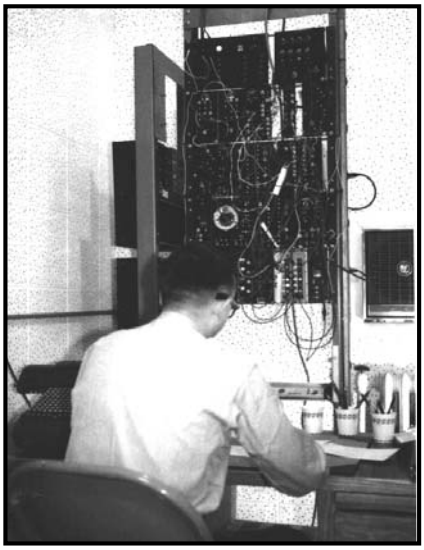
Not only was Phil a good statistician, but he was good-natured. He patiently tolerated my endless tabulations, graph-making and curve-fitting attempts. He also

constructed logic circuits, using lights and relays left over from some rat studies by the psychologists, who used the equipment to explore paradigms introduced by the famed B.F. Skinner and his "operant conditioning" disciples.

Kragg "Phil" Kysor, a great help when "windmill-tilting" was needed

Phil's circuitry skills came in handy when we decided to add an additional performance task to the existing battery. We had nothing that dealt with timing ability, so Phil and I set out to design a time estimation task. Reviewing the literature, we noted that there were four types of timing skills. The one that seemed easiest to automate was "time reproduction."

In a time reproduction task, a signal is given and then, after a prescribed interval, the subject makes a response and gets immediate feedback. We used colored scoring lights that showed whether he had responded too soon or too late. This enabled him to make an adjustment on the next attempt. Repeating the cycle 25 times took about 3 minutes. Scoring was analogous to the total score from 25 shots with a pistol, except that a specified time was the target instead of a circular bulls-eye on a piece of paper.



Phil's jury-rigged VITA set-up

Phil wired up a set of components and connections on an operant testing rack. We named it the VITA (Variable Interval Time Analyzer) as a whimsical parody of an earlier test called "ZITA." It proved quite reliable and sensitive, was easy to learn and scores usually leveled off after about 20 trials, creating a reliable baseline. It could be used repeatedly and required no reading or writing. Scoring was automatic and accurate. As a bonus, the display gave subjects an immediate total at the end of each session. Eventually, we restricted cognitive testing to the NF, SC and the VITA. After a year of use, a "professional" electronic box replaced our jury-rigged VITA, compressing the tall rack into a compact unit about the size of a picnic cooler. The cost: $4,000.

As an aside, the cost of electronic equipment was much higher in those days. Our first programmable calculator, the "Mathatron," was slightly larger than a breadbox and priced at a mere $6,000! It could do simple statistics but only if the operator entered the equations manually beforehand. Since the Mathatron had no memory, the user had to repeat the process each time he turned it on. Compared with today's $10 calculator, it was a stone-age device.

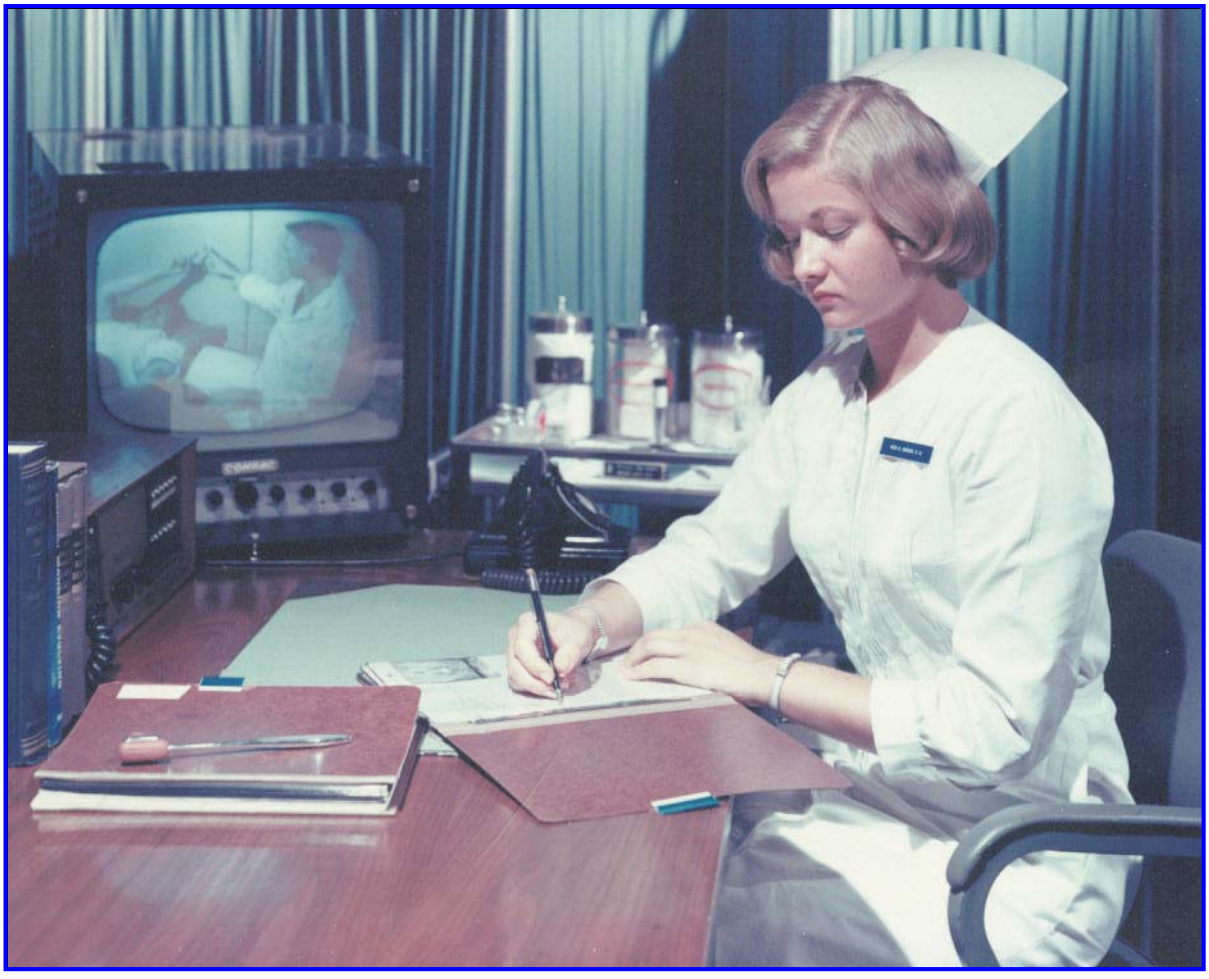
Professionally engineered model of the VITA, our 3-minute time estimation test

The Physiograph, a multi-channel monitoring machine the size of a lunch cart on wheels, was likewise breathtakingly expensive, even though it did nothing but make ink tracings of physiological variables on a moving roll of paper, much like an EKG. This "cutting-edge" device was bargain-priced at $50,000 – Lloyd's TV tape recorder cost about the same. Today, equivalent items would probably sell for about 1% of those prices.

Refinements continued. In 1964, we added a 7 x 6 x 3 foot lighted testing booth on wheels, in which a single subject could sit while taking tests. It contained a built-in desk for paper and pencil tests, and a microphone and speakers for two-way communication with the staff. Lloyd also put a TV camera inside, providing a front view of the occupant. Acoustic tile reduced ambient noise; visual distractions were minimized by having only one small window in the door, which was usually bolted to keep disoriented subjects from leaving during their 3-minute tests. A close-up view of a volunteer in the booth, talking to a "picture within a picture" of the examiner, made for some great video.

We used it to record individual responses to LSD. Not surprisingly, the responses varied. One subject was very irritable. Asked what day it was, he agonized loudly: "What day is it? Wait a minute, wait a minute, don't rush me…what day is it? I can't think! REAPER! REAPER!" We never did know what he meant by that particular expostulation!

Another mild-mannered youth seemed to have landed in Nirvana. He looked beatific. "It's just, I don't know…everything is so great! It's just…I don't know…I



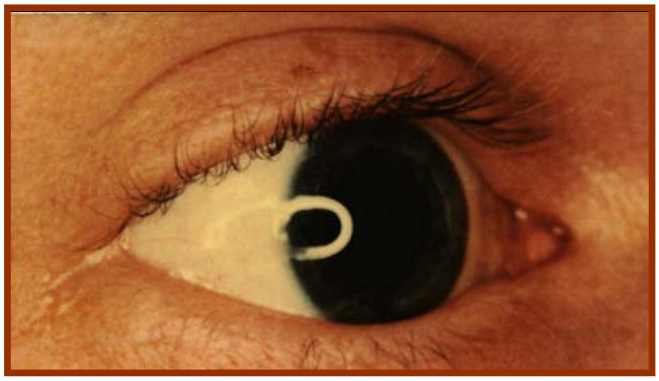
Closed circuit monitor allows nurse to record observations without being in the padded room

just feel…so great!" His bliss made me want to get in there myself.

A third volunteer was unable to stop smiling as if he knew something special. He was eager, and answered everything rapidly, with enthusiasm and uncontrollable amusement. He reminded me of a boy I knew in high school, who couldn't wait to give the correct answers in the classroom.

As studies of BZ continued, we kept revising the schedule of performance testing. Since onset was invariably more rapid than recovery, we scheduled tests at a half, one, two, three, four, six, eight, ten and twelve hours, and thereafter every four hours until recovery. This provided more than enough data points to do curve fitting (which I was forever trying to do, without much success).

BZ and other belladonnoids increase pupil size dramatically, so the nurses carefully monitored these changes along with other physiological "vital signs." To increase reliability, we standardized the lighting to avoid fluctuations in pupil diameter due to inconsistent illumination. Rather than depend on "eyeballing" the eyeballs, we developed a simple "pupillometer" consisting of a round piece of cardboard with black circles of increasing size around the edge. Holding the card adjacent to the subject's eye, one could actually detect changes in diameter of as little as half a millimeter.



Polaroid close-up to measure pupil size

BZ, like atropine, progressively paralyzes the muscles of accommodation, the ones that help the eye to focus on near vs. far objects. Initially, this paralysis caused subjects to have difficulty reading printed material, such as NF problems. At first, we provided simple reading glasses to improve their ability to focus. Later, Dr. Dave Harper, a budding ophthalmologist, devised a way to reverse the paralysis of the focusing muscles, using two types of eye drops in sequence. His technique enabled subjects to see written material clearly without glasses and was subsequently incorporated into the protocol. Another kink resolved!

Taking a delirious man's temperature, however, required some discretion. We found that gently placing the thermometer under an arm was safe and produced reliable readings. We had already figured that placing a thermometer in the mouth might be confusing or threatening to a delirious subject. And of course, the unexpected insertion of glass tube into someone's rectum would be likely to evoke an even more spectacular response.

Rounding Out the Profile of Effects

Scores are good for quantitative analysis, but don't adequately convey a picture of qualitative changes in behavior. And commanders in the field wanted that picture, in order to get a better "feel" for the effects of BZ and other drugs. They needed some verbal descriptions and videotape. We therefore expanded our protocol, including half a dozen additional ways to document the volunteer responses, trying to keep them in a form understandable to non-pharmacologists:

1. Simple tasks during psychiatric interviews to assess mental competence: Repeated subtraction of 7 from some starting number such as 99 revealed difficulty following instructions, inability to stick to a repetitive task, inattentiveness, and other clinical

signs of impaired mentation. One of my favorites was asking the volunteer to sort a pack of cards into four piles by suit. If he could do this, the task would switch to making two piles: high (above 8), and low (8 or less). Often this brought out an inability to shift from one instruction to another. The subject would often start out correctly but then absentmindedly revert to sorting by suit.

Card-sorting as a simple test of concentration

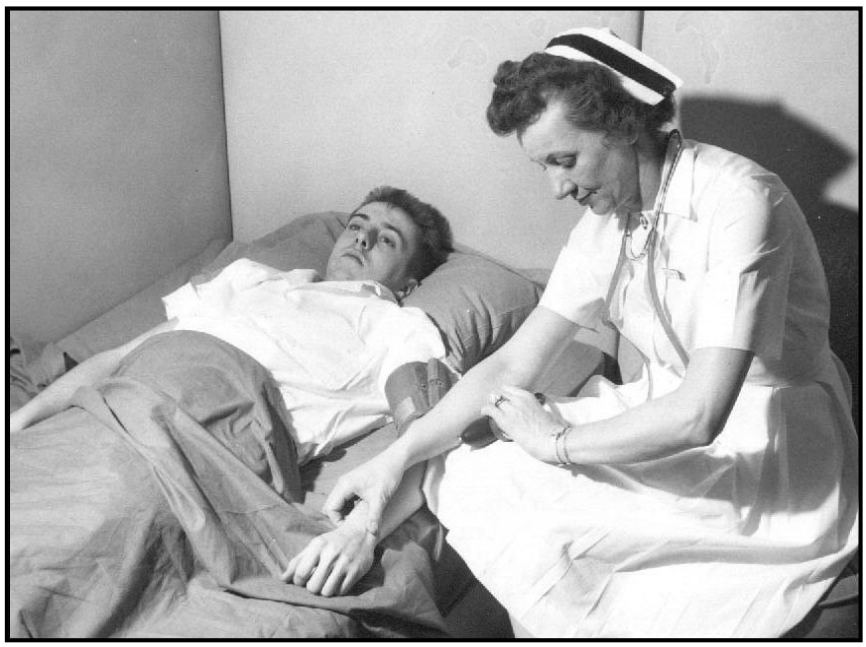
2. Behavior Checklist: We chose about 30 items that seemed to characterize the changes seen in delirium from words and phrases we found among entries made by physicians and nurses in earlier charts. At scheduled intervals, nurses translated their clinical observations into values of 0, 1 or 2 on each item and subsequently added them up to obtain a composite numerical score.

3. Simple memory: A four-part sentence was useful in testing immediate recall. Example: "My name is Joe Green, I live in Cleveland, I work for Goodyear and I make inner tubes. Repeat back." Obviously, not hard to remember (you can test yourself). The name, city, employer and occupation can be changed each time this quatrain is used, eliminating practice effects but keeping the difficulty the same.

4. Draw-A-Man: Described in an earlier chapter, this task requires a pencil drawing of a male figure. The quality deteriorates very obviously as drug effects increase.

5. Symptom Check-List: After recovery, the volunteer rates himself 0, 1 or 2 on about forty descriptive adjectives and phrases previously used by other volunteers in their write-ups. The total is used as a consolidated score of subjective symptoms.

6. Post-test write-up: Each subject is encouraged to describe in as much detail as possible what he can recall of the drug experience and how he thinks he would have performed in combat under its influence.



Nurses assure accurate recording of vital signs

Kinks galore lay ahead, but at least we had unraveled enough of them to make the program go more smoothly. We were now able to collect data much more

safely and efficiently. Years of program development were behind us – but more challenges lay ahead!

* * * * *

9 BUSY AS A BEE ON A DOSE OF BZ

Sisyphus was basically a happy man

Albert Camus

If one picture is worth 1,000 (or some would say 10,000) words, perhaps one detailed clinical record may be worth as much as a summary of 1,000 records. I hope so, because the record selected for inclusion here illustrates, better than most, "The Week that Was" for one BZ volunteer.

Call him John Blake. Not his real name, of course (like all the rest of the names used for volunteers in this book). But everything else about him is recorded precisely as it was entered in his chart. For a 7-day period in February 1963 he spent almost all his time in a padded room, under the influence of an incapacitating intramuscular injection of 7.0 mcg/kg of 3-quinuclidinyl benzilate – the proper chemical name for BZ.

John was teamed with Eddie Clark in a two-part BZ study, designed to show the benefits of continuous physostigmine treatment after a dose of BZ slightly larger than would be required to produce incapacitation in the average subject. An intriguing feature of BZ is that doses below 5 mcg/kg never caused complete incapacitation, while doses at or above 7 mcg/kg almost always did.

John and Eddie each received BZ twice, two weeks apart. Both also received identical capsules containing "physostigmine" at scheduled intervals throughout the test. One of them, however, was getting physostigmine capsules filled with a placebo, while the other was getting the real thing. No one directly

involved in the test knew which was which. When they received their second dose of BZ two weeks later, the reverse took place: physostigmine in the capsules of the man who got placebo the first time and placebo in the one who had previously received the real physostigmine capsules. Such a design is called a "crossover double-blind." In this test series, only two pairs of subjects were involved. With other drugs, it is customary to use more, but this was BZ and in our opinion, giving it twice to more than four subjects under double-blind conditions would be pushing the envelope, both in terms of time and work force required as well as fairness to the volunteers. I believed that they might actually prefer Three Days with the Condor to an extra three days on BZ.

In reality, most volunteers did not consider incapacitation with BZ to be a seriously unpleasant experience, as long as good nursing and medical care was provided. It was pretty much like a lost weekend – 2-3 days of drunkenness, but quickly forgotten. Surprisingly, many described a feeling of well-being following recovery. Both men were quite willing to repeat the test (another illustration of voluntary as opposed to "unwitting guinea pig" participation).

I asked one man who had just returned to normal after 72 hours of BZ delirium how much money he would charge for another go-round. He mused a bit and then gave his final offer: "Twenty-five dollars." I thought it an interesting way of gauging the subjective nuisance value of three days of incapacitation. Civilian researchers were paying more than that to subjects who only had to spend an afternoon taking a small dose of a tranquilizer and giving a couple of blood samples!

Nevertheless, back to John Blake. This was his first exposure to BZ and he was going to be getting placebo capsules, although none of those involved with the test itself was aware of this ahead of time – even though it soon was easy to guess.

I interviewed John two days before we started and decided he was psychiatrically normal. His physical exam, lab work, electrocardiogram (EKG), and electroencephalogram (EEG) were all devoid of abnormalities, and he reassured us that he was free of any physical symptoms.

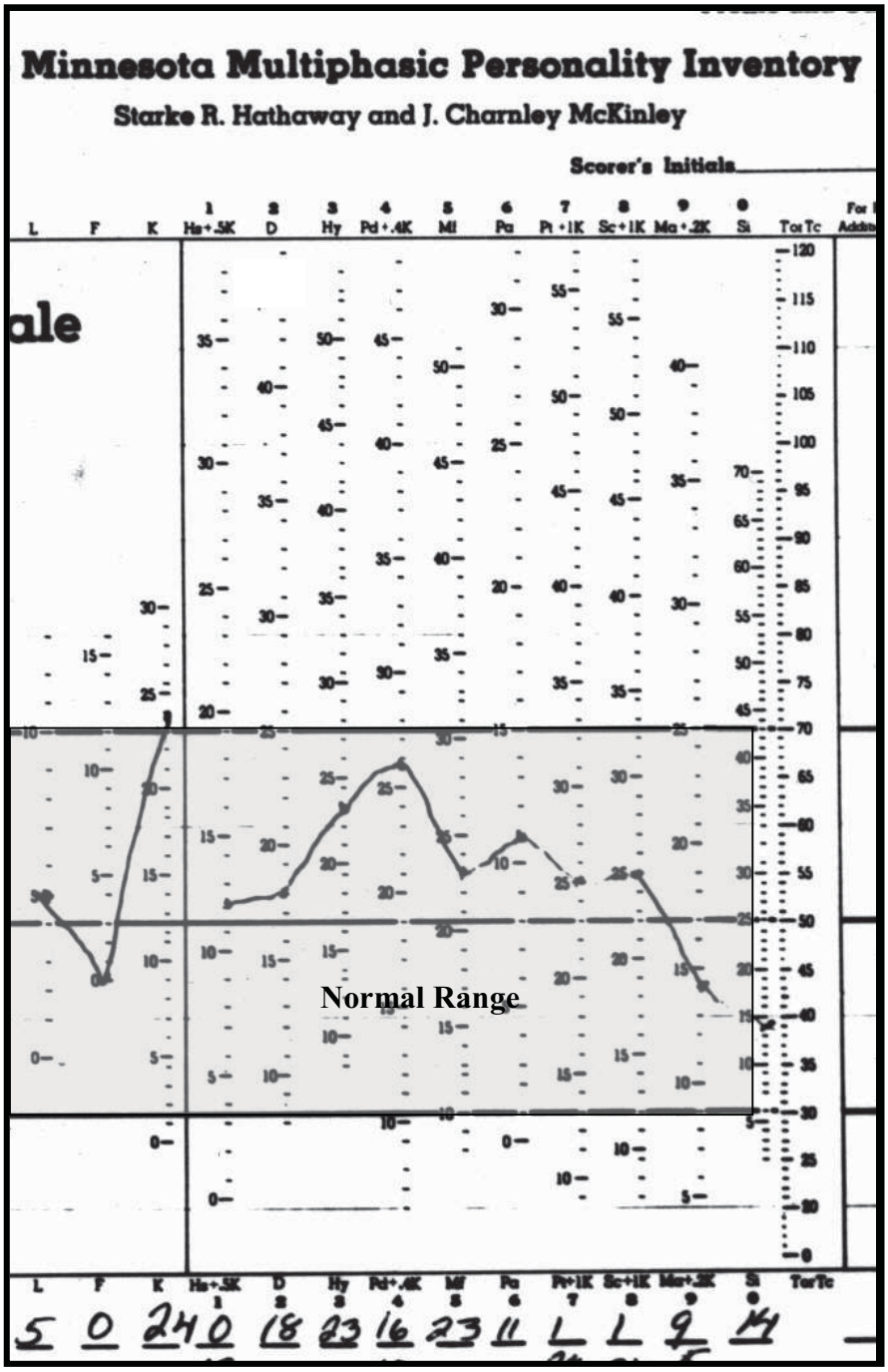
Before joining the Army, John had been a postal worker, like his Dad, and had a special girl friend. A high school graduate, he liked to read and enjoyed various sports, including skin-diving. I asked him what he would do if he ran into a shark.

"Punch him in the nose, I guess" was his smiling reply. Evidently, he was not easily intimidated.

In addition to judging John's interview responses, his scores on the MMPI were also important in estimating his suitability for a BZ study. As shown on the following page, his profile was unremarkable. He also completed all his required baseline NF and SC testing as well as several measurements of his "vital signs" during the day before the test. Dr. Herb Rakatansky drew some blood for a baseline cholinesterase level, expecting that physostigmine would make the level change and wanting to track the changes precisely. To acquire an ample series for analysis, 12 needle sticks would take place during the first 72 hours. Ouch! Fortunately, John wouldn't recall most of them.

To my knowledge, no one has ever published a detailed hour by hour chronological record of a lengthy drug-induced delirium, giving precise times, verbatim quotations and clinical measurements from beginning to end. Here are the chart entries for the 100-plus hours of John Blake's response to BZ (with minor abridgements).

John's pre-test D.A.M.
(Draw-a-Man test)



John's Minnesota Multiphasic Personality Inventory – within normal limits

CLINICAL RECORD for "John Blake"

00:10 Heart Rate (HR) 84, Blood Pressure (BP) 100/80, PS 5/3

00:20 No effects reported by subject. HR 75, BP 100/60 First DAM completed.

00:25 To audiology in soundproof test room.

00:40 HR 80. Back to padded room. Subject states he feels slightly lightheaded and very tired. "Eyes feel very heavy. "

00:45 Performance testing: NF 92%, SC 84%. Feels lightheaded and sleepy during test.

01:00 HR 84, BP 110/40, Pupil Size (PS) 7/4 (dim vs. bright light), NF 92%, SC 84%. Feels lightheaded during testing. Capsule from B package given orally.

Intramuscular BZ at 8:00 A.M.
(00:00 Experimental Time)

01:10 Sleeping, awakened to go to audiology testing. Feels tired and sleepy. Returns to padded room at 01:15. Sleeping through vital signs.

01:20 HR 100, BP 110/60. "Don't mind me if I fall asleep. "

01:30 NF 76, SC 97 DAM test administered. Feels tired and sleepy during tests. Back to bed after tests – fell asleep.

01:45 HR 120, BP 110/60 Sleeping through vital signs. Awake at 01:50 – moving about. Question: "How do you feel?" Answer: "I feel very restless; I feel like I could get up and go. My mouth feels a little dry, too. "

D.A.M. at 20 minutes
appears normal

02:00 HR 128 Restless – moving about in bed – sleeps for short time, then restless again.

02:05 To latrine with assistance. Voided 150 cc. Gait unsteady – eyes bloodshot.

02:08 To audiology for hearing test – needed assistance while walking.

02:12 Back to padded room.

02:15 HR 132, BP 115/70, PS 5/3. Sleeping at short intervals – restless.

02:30 Performance testing. NF 50, SC 61. Items on Behavior Checklist (BCL) recorded – gait unsteady. Appears to be very sleepy. Question: "How do you feel?" Answer: "Lousy. I feel very, very tired and my mouth is dry." Went to sleep immediately after lying down.

Drowsiness setting in at 3 hours

02:40 Interview with MAJ Ketchum. His note: "Reflexes slower – felt he couldn't do his job. Serial 7's tested and performed slowly. Repeated four part sentence correctly. Stated, "I feel a little unsteady. With eyes closed, a little more unsteady " Went to sleep immediately after lying down.

02:45 Appears to be sleeping – moving extremities spasmodically. HR 124, BP 110/5003:00 HR 120 "I feel very tired and loss of coordination also. I can't keep my legs still. I feel like I want to go, go, go." To latrine at 03:05. Voided 260 cc. To Audiology at 03:10. Back to padded room at 03:13. Walked with assistance.

03:15 Restless. HR 104, BP 120/80, PS 8/5.

03:30 Performance testing. NF 16, SC 31. DAM completed. Does not seem to be too much affected except for being "extremely tired."

Early deterioration of
D.A.M. at 03:30

03:45 Having great difficulty lying still. HR 120, BP 125/90. Has to move about – standing up. Rubbing eyes. Walked to door, looked out. Question: "What did you see. " Answer: "Carpenders (sic)."

03:55 10 cc of blood drawn for cholinesterase level (indicative of physostigmine effect).

04:00 Capsule given orally from B package. HR 120, BP 124/80.

04:15 Interview with Dr. Ketchum. "Performs dexterity test rather slowly. Able to sort cards correctly."

04:20 To latrine, voided 160 cc. To audiology for testing.

04:28 Back to padded room. "I feel restless as hell. Boy this is something. I have got to walk up and down the hall after this. It's starting to get to me."

04:45 HR 132, BP 120/80, PS 9/7. "This is driving me crazy. I'll be dead in a few minutes. I am not used to this." Walks up and down hall slowly, did not need assistance. Then wanted to go back to bed. Question: "I thought you wanted to go-go-go?" Answer: "I did but I want to go back to bed now. My mouth is very dry." Closed eyes for a few moments. "Where did it go?" Question: "What?" "Answer: " Oh, I must have been dreaming." Closed eyes again. "What time do we have to get up in the A.M.?"

04:50 Mumbling to himself. Reaching into the air at imaginary objects.

Comment: At this point, Blake is showing the first signs of delirium, and losing contact with the environment. This is about the usual time that ability to distinguish real objects from those in the mind begins – very much as takes place in ordinary dreaming.

D.A.M. essentially impossible at 05:00

05:00 Performance testing. NF 0, SC 3. Had difficulty taking test. DAM.

05:15 To audio room for five minutes.

05:30 Subject has lost total recall of persons and of recent past. Killing "bugs" with slipper, pretends to be drinking and smoking. Hostile while in audio room. Seems to be getting sleepy, but just when you think he is relaxed, he jumps up. Inarticulate speech, sometimes directed to someone and sometimes just talking. Hallucinating, disoriented, face flushed. Subject said he thought Mr. Khrushchev was here. Says he is a genius but is using it the wrong way. Said he talked to him yesterday.

05:45 HR 128, BP 110/70. Awake – restless – can hardly lie still to have vital signs taken – sitting on bedside. Picking at bed clothing – eyes partly closed. Appears to be very sleepy but moves about continuously.

06:15 HR 132, BP 100/60. Would not lie down for vital signs. Moving about continuously – hostile and not very cooperative – unable to understand anything.

06:45 5 cc. of blood drawn by MAJ Ketchum. Unable to get any more blood. Subject would not lie still.

Observing something not visible to anyone else.

06:55 BP 118/60, PS 10/8 Cap (No. 3) given orally from package B. Interviewed by MAJ Ketchum and CPT Beason. Unable to understand anything subject says. Continuously hallucinating, completely disoriented.

07:45 HR 130, BP 124/80. Sitting on bed most of the time. Refused juice. Reaching for objects. Mouth very dry. Interviewed by Dr. Ketchum, who records: "As he is propped up on one pillow, eyeballs tend to roll back and lids close as he repeatedly seems about to fall asleep. Watching movements observable in eyes when he is staring. Pointing and grasping movements with fingers. Quite irritable – profane when any procedure is attempted, e.g., venepuncture, mouth care. This is a striking reversal from his condition at 4 hours, when he seemed relatively alert and in better shape than his fellow subject. Now the roles are reversed. Impression: Severe reaction nearing peak phase. Semi-stupor."

08:15 HR 108, BP 130/84. Had to be asked several times to lie down on bed for vital signs. Put both hands loosely around nurse's neck, as if choking her, for a second; then removed them. Laughed out loud once – sitting on edge of bed now, lips are moving as if talking, but is not making noise. Reaching for other subject's feet, picking at floor and pants leg. Sneezed about four times in past half hour. Eyelids look heavy and drooping. Does not have the same alert expression on face as other subject at this time.

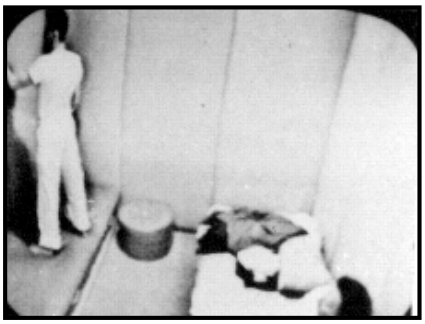
08:45 HR 120, BP 124/78. Very uncooperative – wouldn't lie down for vital signs. Hit nurse lightly on the shoulder when she suggested he lie down for BP. When lights were turned down for PS, he yelled "Hey, who turned those lights?"

09:30 PS 9/7. Interview with Dr. Ketchum. Unable to identify cards at all – did not seem to respond to questions. Smiled vaguely when asked what time it was. Speaks out of context. Dropped cards when they were handed to him.

09:45 HR 100, BP 130/82. Lay down on bed after being asked several times. Is talking more now – calling out occasionally to imaginary people.

10:00 Blood sample #4 drawn – capsule B given. Does not respond to requests readily. Refused toast when offered to him.

10:30 Sitting on edge of bed talking to himself, mostly unintelligible mumbling. Drinking from empty hand, looking around slowly, laughs occasionally. Uses foul language if he becomes angry with nurse's request to lie down, etc.



09:30 An unusual interview

11:00 HR 92. Had to be asked several times to lie down again. Other subject said: "That's an order!" This subject looked at nurse and said, "Yes, sir, soldier." Nurse asked if she looked like a soldier. He looked up and said "No, you look like a nurse." Subject is still unsteady on his feet – has misjudged distances when sitting down and lands on the floor. Does not appear to be hurt by these falls.

11:30 Sitting on bed with other subject, watches him play cards for a few minutes, then begins picking and investigating again.

12:00 HR 108. BP 114/72. PS 8/6 Standing on bed, then walking around room. Very active. Responds poorly to questions like "When I try to take your blood pressure, why do you pull away?" Said "What are you, a nut?" Still mumbling, mouth is dry refuses fluids – seems more incoherent than other subject at this time.

0930 Playing cards in disarray

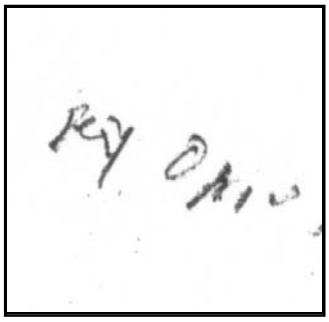
Comment: Blake is now fully delirious and will continue to be out of touch with reality for many hours, although brief moments of lucidity do occur from time to time. This is a characteristic feature of delirium – variability and occasional awareness of the environment, sometimes with surprisingly appropriate comments or behavior followed by a prompt lapse into total disorientation. As opposed to the normal awake state, in which thoughts and inner stimuli are sometimes distracting, in delirium, the opposite is the case: the inner world (although confused) is sometimes invaded by the outer world.

12:30 Unable to do NF, SC or Draw-a-Man. Unable to concentrate, would not take pencil when asked to. Began to write in air with an imaginary pencil.

13:00 Blood #5 drawn. Capsule 6 given with water. Mouth still dry, skin warm. Sitting in middle of floor, staring. Speech is nonsensical. Does not respond to questions or requests.

13:30 Subject said this place was "as bad as transit" and for other subject to go get "his own woman."

14:00 HR 108, BP 112/72. Would not cooperate for aid man to take vital signs. Lay down immediately when nurse asked him to. Became abusive when nurse put hand on his shoulder lightly to have him lie down again – "Don't push me around – listen – stop it!" Seemed to forget this immediately, then became friendly. Took a sip of orange juice with urging, then pushed nurse's arm away from face and said "Listen, you're getting just too G.D. personal."



12:30 Attempt to Draw-a-Man

13:30 Moving carefully, for reasons that are not apparent.

14:45 HR 100, BP 112/74. Interview with Dr. Ketchum. Unable to cooperate. Out of contact. Sitting for vital signs. Refused to cooperate about lying down on bed.

15:30 **Midnight, February 8**

16:30 Responds to questions. Offered orange juice. Stated "That stuff is turning my stomach." Picking at imaginary object. Playing imaginary violin. "Trying to get to sleep and that fellow…"

17:00 HR 100, BP 100/70, PS 10/10 (i.e. maximally dilated, non-reactive to light.) Offered juice. "Why do you people keep bringing me things I don't want. Why don't you stick it!"

17:20 Becoming more active. Walking rapidly about room. Stands in corner for a few moments, and then moves about again.

17:30 NF 0, SC 0 Unable to do performance tests. Standing with hands held out in front of him. Asked what he was doing and he said "Reading the paper." Asked what the headlines are. "Vietnam is getting us in trouble."

17:55 Banging on wall. Stopped and put hands on hips and shouted "Yes, he is senior man."

18:25 Writing imaginary letter on shelf of window. When asked "who are you writing to?" he responded "Work -------- mumbles -------"

18:35 Nurse asked the aid man how to spell "convenienced" and subject responded: "CONVENIENCESHIT!" Smoking imaginary cigarettes. Sitting cross-legged on floor. Picking at army blanket. "Let us spray (sic)."

18:55 Putting on imaginary GI boots. Speaking about a buffer yesterday morning and this morning. "Hurry up, one half hour to go." Tripped over hassock but kept his balance. Turned around and gave hassock a kick and said "Jesus Christ."

19:00 HR 100. Requested nurse not to put down 100 for pulse. "Try 95. Ask Mrs. Fort to get her OK."

19:30 Quieter – sitting for longer periods. Apparently listening and responding by mouthing the words. Not vocalizing. Sitting on hassock. Driving an imaginary truck. "All those god damn people." Looked at other subject and said "Three strikes you are out." Other subject said: "My hands and feet are red." Subject said "Mine are too." "Man, get out of the way, we're playing a game" "This is the center of the earth." Made a circle with his arms. Trying to climb wall and said "Jesus, what is this for?" Then put hassock on other subject's bed. Said "We just talented working on Reds and serve spaghetti and meatballs stop me if I'm going too fast." Folded blanket and said "I'm a sonofabitch."

Comment: It is 20:15 experimental time (i.e., elapsed time since the BZ injection) but the real time is about 6 A.M. On this, the second day of the test, Blake will be very busy, but not with any logical purpose. This sort of active behavior will continue for another two days. Since it is often highly repetitious, we will skip some of the record for the sake of brevity.

20:15 Once again stated that his hands and feet were very red. Stated he had eggs for breakfast, and talked of his field jacket. "It isn't mine and don't push me brother!" Smoking an imaginary cigarette.

20:23 Drawing on the wall. "You know where they are, don't you, Buddy? They are underneath the blanket." Flying a plane.

20:30 "Isn't it raining?" Extended his hand and shook with other subject. "What are you doing with this fireworks shit?"

20:35 "Yes, so can I." "Uh, geez." Scratching his back. "Holding up traffic." "Search" "That's enough you sonofabitch. Huh. We'll go to the gym or something." "That's a par. Oh shit." "Better turn it on. What the hell is this here for? Bull shit." "See this? See this down here? The food isn't half bad. It isn't as good at headquarters."

20:47 Picking his nose. Smiling. "Oh God, that penetration was wet. Oh mother!" Urine stain on trousers. Urine on floor. Apparently has voided. Scratching his head.

21:00 HR 120. Tying something around his waist. Scratching his ear. "Do you want to talk to my old Dad?" "Okay, hold on now." "Where does he work?" "Straight from the transit hut up the street. I hurt my eye." He poked his right index finger in it. "I saw it before in -----" Buttoning his jacket and working with a pillow. Hitting a punching bag.

21:15 Breakfast – ate half a slice of toast, 80cc water.

21:35 Having difficulty returning subject to room. Listening to his dog bark.

21:55 HR 84, BP 120/60, PS 10/9. Standing in corner. Says "Oops, there we go." Throwing imaginary objects against the walls. Beating on wall. "You'll hear a better one when I get in the house with Janet." Stands looking at wall. "Nice guy, huh?" Talking about bugs and mice with other subject. "By that time my sister would have been up the third wall of the house." Cooperative during pulse and blood pressure.

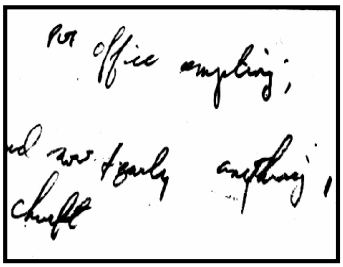
22:00 HR 84, BP 120/60, PS 10/9 Gets up and walks over to air conditioner. Calls other subject "a rat." Starts picking at his bed. Says "I'm going to put the whammy on you." "Hello Robert, how you doing? I haven't seen you in a long time." Stands on bed and kicks at wall and says "Watch out." Lips are still dry but seem to be improving.

22:25 (Friday, 8 February 1963) NF 0, SC 0 Untestable on performance tasks.

23:15 Took subject to give him shower. He had no difficulty in washing; however, experienced much difficulty in dressing and I had to almost entirely dress him. He hallucinated some of the time. Took off an imaginary watch and handed it to me. He also appeared to be smoking and picked at clothing and at his hands and threw imaginary things into trash basket. Subject used toothbrush to comb hair until I inserted toothbrush into his mouth at which time he got the idea and brushed his teeth. He talked most of the time and had a general flight of ideas. Walking about room talking continuously and hallucinating. Disoriented. Smoking imaginary cigarettes. Eating imaginary food. Looking for a way out of the room. Continuously moving.

24:00 HR 88, BP 110/70 "Hi there, where's my pate (sic)? And I drove the car back for her ----" Kissed the nurse on the cheek. Subject is completely disoriented. Hallucinating continuously. Talks out of context. Ate one piece of apple butter and toast. When toast was being fed to him he said "Smells like a French whore." "Look, look, look, what are you? Some kind of nut?" Walks over to window. "What loot I have I have to save." "Oh, boy!" Cooperates well when he understands what you want him to do. It takes quite a long time to get through to him.

Comment: It is now 09:30 on the morning of the second day. Blake has been up all night, hallucinating, talking nonsensically and totally disoriented. He has taken a small amount of food and fluids, but appetite is definitely suppressed as is common with BZ and related atropine-like drugs. His vital signs have returned to normal, with the exception of pupils, which are still maximally dilated and almost completely non-reactive to light. He cannot draw or perform any tests. The record will skip forward a few hours to when he will begin to show noticeable signs of improvement, although speech and behavior will remain nonsensical.



30:00 D.A.M. effort shows some return of function

31:00 Interviewer not getting much response

29:20 HR 74 Very cooperative about lying down for vital signs. Able to name playing cards correctly. Dr. Ketchum: "Sort out cards in the four suits." Subject sorted out several piles, all incorrectly. Subject: "Get that song out of here. Hail to the Chief." Did very poorly on memory test. Question: "How long have you been here?" A. "I don't know. I'll find out in a day or two." Q. What would you do if lost in the woods?" Subject mumbles on and on. Most of speech not understandable. Answers that are understandable are irrelevant. "Timber!" Dr. K: "I'll see you later." This subject sat beside other subject while he was being interviewed.

29:55 HR 76, BP 110/60 Lay down for vital signs. Unable to perform on tests, but did write some words when asked to Draw-a-Man. 10 cc of blood drawn (3 heparinized, 7 clotted).

30:30 Capsule given orally from B package. Subject seems to be very sleepy and tired but continues to walk around room and mumbles continuously. Incontinent of urine. Clothes changed.

31:45 HR 76, BP 126/62, PS 7/5. Mumbles incoherently. Had to be asked several times to lie down for BP vital signs Blood sample drawn. Capsule given orally from B package. Ate a full dinner: fish, peas, potatoes, but had to be fed. Wandered around room while eating. Talking continuously

32:30 Performance tests not given as subject is incoherent and unable to follow orders that require thought as his concentration span is extremely short. Subject spends majority of his time moving slowly about the room muttering and hallucinating. He stops at times and stares ahead but makes no sound or movement and appears frozen, then goes back to his flight of ideas manner.

33:30 Subject sat on bed of other subject and approached other subject after corpsman came in, he patted the guy, then sat on the hassock. Subject seemed to be undressing.

34:00 Very cooperative when asked to lie down for vital signs. Remained lying down with lights low for about four minutes, then got up and started moving about room again. Climbed in bed. Then down again. Talking out loud most of the time. Shouts and laughs.

40:00 To corner of room. Started to take trousers off. "I'm here all day and don't you forget it." "Not the Murphys. Maybe the Calhouns or Blakes but not the Murphys. Voided incontinently. Trousers changed. Fell onto bed. Laughed and said "I thought that would shake you up." Called nurse by her real name when she entered room. Picked up blanket. Held it at arms length, reading it like a newspaper. "First we tried to figure out what street we went down to find the car." Sitting on bed. Quiet. At a ball game. "Threw the ball." "To you." "I've got a hobby Joe. Just being nice." Motions appear to be spit-shining his boots.

40:55 HR 92, BP 112/70, PS 10/8 Stepping very cautiously about room. Dropping pillowcase over back and round shoulders. Appears to be putting on pack. "Go ahead, take it (BP) while I play with the kittens. Nice kitty." Fed ice cream. "Gordon will build them if anyone will." "This country better hurry up or we'll be in another depression." "When in doubt, blow it out." Standing at window smoking imaginary cigarette.

41:20 Untestable on performance tests: NF and SC.

43:00 Enjoyed a cup of warm bouillon. Standing in middle of room, hand on hip. Holding imaginary cigarette in other hand. Staring as if to the sky. Making motions as though driving a truck. "It's spinning and I can't stop it."

43:35 Playing with small imaginary animal in palm of hand, telling it to be good. Removed sheet from bed. Picked up mattress and put it off angle to box springs. "Holy hell, I've got to get home and help milk the cows." Driving a truck. "I'll tell you it ain't easy as hell to drive" Yelling: "Be careful you'll hit the tree." Whispering: "I don't want to hear that word 'Attention' again."

43:50 HR 72, BP 122/74

44:15 Refused to drink bouillon. Working on window sill. Not speaking as much. Sitting on bed. Called to someone: "Yes, take it out of petty cash." "Give me a call on Saturday. I know damn well you won't be getting up early and neither will I."

44:45 Sitting on floor. Appears to be repairing a truck. Bouillon 180 cc. Sitting on side of bed with both eyes closed. "That's the way we've been living all summer long – like beatniks." Jumped up from bed and ran to hall. Sitting on floor eating an imaginary meal from the hassock. Jumping on bed.

46:00 HR 98, BP 130/70 "We don't need a king, we can't use a king. Understand, boys?" Still completely disoriented.

46:45 Ate fairly good breakfast

47:00 NF 0, SC 0. Performance testing with glasses. Tried to circle a few words that were actually words, but made the circle either too large or too small, completely out of proportion. Finally took shower with much insistence.

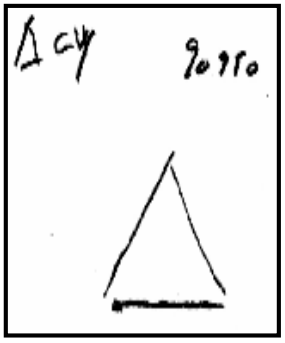
47:30 HR 84, BP 110/60, PS 9/7. Lay down with much insistence for vital signs. It is very difficult to get subject to do anything at this point. "I'm not sorry I'm married to you. Really I'm not." "Here comes Caroline." Smokes imaginary cigarettes. Talks to imaginary people. While standing, looking at wall, grabbed nurse's cap while she was sitting on stool. Twisted stethoscope around her neck. "Oh, I thought you were a truck driver." Walked over to window. "I hope they don't have this damn door locked." "Hey a package of cigarettes, if you can read Mexican."

48:00 **Saturday, 9 February** HR 72, BP 110/50. Interview with Dr. Ketchum. Subject tried to move table. Walks over to wall. Tries to climb wall. "Hey, come over here on the double." "Hey, Jank, over here." "I couldn't get in there to get my suit." "So you know what happened." Walked to where Dr. K was interviewing other subject. Seemed so tired. Seems about to go to sleep standing up. Sat on Dr. Ketchum lightly. Got up, went back to window. "Hey, me too." I'm glad you don't want to cause I don't either." "Hold on to your bacon." Trying to climb walls. "That's two hours and fifty minutes, isn't it Sir?" "Sit on the bottles and paint it green." Dr. Ketchum: "Come over here. I want to interview you." Subject stood on bed, staring at wall. Sat down in chair. Shuffled cards for some time. Dr. K: "Sort cards in 4 different suits." Starting sorting in four different piles, but not in four different suits. "This is what I'm afraid of."

49:30 "Walked to where Dr. K was. On memory test got one card correct out of six. Placed three cards correctly, but couldn't put 4 cards in correct suits. Attention span short. Talked to wall – "Hey, why didn't you get canned for that?" "Well, put that in your pipe and smoke it." "Hey, I'd like to fuck that." "Hey, hey, hey, Holy mackerel, Andy." Talks so rapidly. "It is breathing, it must be someone we know." "It's true, I've been hitched." Lay down on bed for vital signs with much persuasion. Lights turned low in room to encourage sleep. Subject got out of bed – continues to walk and talks to wall – converses with other subject, sometimes talking to wall. "He looks fairly sober to me." "I don't know whether to kill him or maul 'em." Sings song in German accent. Tries to walk through window. "Didn't have it now – didn't have it." "Oh it's nice in here."

Comment: Very little has changed and it is now 09:30 on the morning of the third day. Blake remains active, talkative and disorganized. His performance is still essentially zero. He is, however, able to make efforts to draw a man, rendering very primitive approximations. Although he has not slept (in the ordinary sense) in two and a half days, he shows few signs of slowing down. This will continue for another day or more, with a gradual return of his cognitive abilities.

43:30 Singing and laughing



48:00 not much improvement on D.A.M.

50:00 D.A.M. test yields female form, illegible writing, but no male drawing

60:00 D.A.M. effort is worse, if anything

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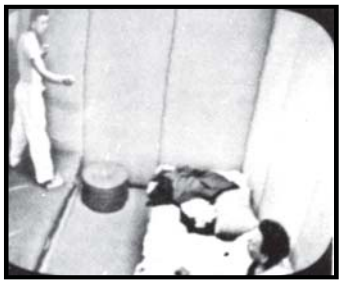
60:00 HR 76, BP 110/68 No change in behavior in past hour. Makes circular motions with his hands. Climbs on bed then runs rapidly to another corner of the room. Smokes imaginary cigarettes. Lights imaginary matches. Stumbles on mattresses several times but doesn't lose his balance. Pounding hard on wall. Begins a sentence but end of sentence is inaudible because of mumbling. Fell on floor and said: "all right, who stole the other pencil. I ate it, I ate it." Unable to draw a picture. Still walking around room. Fell and remained on floor as if he would sleep but then got up and became active again. Periods of inactivity are increasing in length as subject becomes more tired

61:00 Talked like Yogi Bear. Became very active for about four minutes. Fell a few times, sat up immediately and laughed. Then sat on edge of bed and became quiet. Up again. "I was going to do something today but I can't remember what it was." Said this in a sing-song fashion. Speech is very rapid – difficult to distinguish. Yelled "Dumb."

61:30 Becoming more oriented – knew he was a Med Vol, stated his MOS [Military Occupational Specialty], answered when his name was called. Thought date was 7 Feb. Still walking around actively. Asked why he was here. "To see how the drug works – the effects."

62:30 **Midnight, Sunday, 10 February** Walked into padded wall with force and appeared stunned. Complained of neck hurting. Examined by Dr. Bing – is able to move without apparent difficulty. Remained lying in bed for a few minutes. Capsule B given. Up walking around room again. Took pants off but allowed them to be put on again.

62:50 Standing in front of wall – "watching TV." Pointed and stated "I saw that part before."



62:50 An unorthodox interview

63:10 HR 102, BP 116/64 Difficult to obtain vital signs – does not lie still. Became romantic with nurse – hostile with aid man. Picking at nose – looking into space. "Let's see, yesterday was Thursday." Scratching head and wall. Appears to be sharpening an imaginary knife – fell to the floor straight down – sitting cross-legged, Indian style. Closed eyes, head started to nod. Jerked himself awake – started to seem to shave self. Remarked "Oh I forgot to shave." "I don't like this asshole." Standing – appears to be eating. Walked toward mattress, tripped over it. "Oh, it's handy if nothing else." Got right up – stood still, smoking imaginary cigarette.

63:25 Fell down from mattress. "It's not my fault you dropped me down." Standing – watching wall intently. Appeared to grab a doorknob and walk through wall. Went through frantic excited motions and returned to staring at wall.

63:40 "Ya, might as well." "Go ahead." "You going to let me drive today?" Speech loud and distinct. Continues talking toward the wall. "I don't know what the hell it is; it comes and goes." Appears to be smoking cigarette and blowing smoke rings. "Hey Joe, you want us to bring 'em or not?" Speaking to an officer apparently. "No, I wasn't anywhere near that fight." Appears to be washing or scrubbing walls with a circular arm motion. Fell to floor. "I don't know why I'm being pushed like this. What did I do?"

63:55 "There's no one here on Saturday. You might as well make your bunk and go home." Sat down on edge of bed and begins motions of eating and chewing. "Gravity! Ah, he disproved that long ago." Standing again – continues

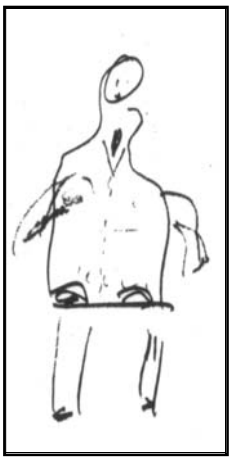
disjunctive talking. Appears to pull string between hands and untie knots. Tries to sing (?) Scratches head and neck occasionally. "Are you going to stay with wife tonight or come bum with us?"

Comment: After approximately 72 hours with little sleep, Burns is now intermittently in contact with his surroundings. He will spend much of the next 24 hours alternating between periods of sleep and semi-oriented wakefulness. Some episodes of delirium will continue, followed by a rapid return of awareness and improvement on his Number Facility and Speed of Closure scores, as well as his ability to conceptualize and draw a normal picture of a man. Incapacitation was longer in this case than in most, by at least 24 hours. A graphical illustration of his time course appears at the end of this chapter.

70:15 HR 72, BP 110/70, PS 7/5 BP and pulse taken without awakening subject, and turned him on his side due to oral breathing and dryness of the mouth. Body movements have decreased. Remains asleep on floor.

71:00 (Sunday, 10 February 1963) HR 70, BP 90/60. Awoke when vital signs were being taken. 10cc of blood drawn for cholinesterase level. Capsule given from package B. Ate breakfast fairly well. Shaved with electric razor. "They stand there and get the ass picked off them. The Navy was probably on the wrong island and the Marines probably landed somewhere in South Jersey." "That's a lot of engine, boy." "Hello Stuart." "She had the oddest expression on her face – came out of the house." "What did he give you?" "I thought that was nice of him. How did he know you wanted that?" To Dr. Ketchum: "You have to wear a three-quarter coat like Kildare." "Yeah, that coat is okay. It's up around your ass – hell if it was any shorter – you know what." Laughs. Interview with Dr. Ketchum: "How do you feel?" "Great, good. Raring to go." "What's the longest you've ever gone without sleep?" "I don't know." "Is this the first time you've ever been in this room?" "Yes, I've been in a couple down the hall." "Do you know who I am?" "Yes, Dr. Rakatansky." "Could you go to work right now?" "Yeah." "Without much sleep?" "Yeah." Named cards correctly. Did not sort cards correctly in four piles the first time. "Hey, wait, I'd better start all over again." Tried second time – "I'm doing it again." Starts doing it right then does it wrong again. Dr. Ketchum: "You started off right – what are you doing now?" Finally managed to sort them almost right. Serial sevens: starts subtracting wrong. Talks on and on very rapidly, many irrelevant intrusions (e.g. "'ll kill him") but sticks to task for more than a minute.

73:00 BP 110/70 NF, 8 SC 9, PS 7/5 Performance testing. For the first time, is able to get a positive score. Took shower and brushed teeth. "Holy shit." "Holy Christ." "You can see that they are not air tight." Lay down for vital signs. Seemed to be going to sleep but got out of bed quickly "May as well get some of this." Exploring walls. "Headquarters Company." "Yeah I'll let him suck my cock." "Yeah, didn't she?" "This is it." Whispers to wall: "All right. Let's go. How come you here, girl." "I doubt it." "Hey Mom, if that's the hot coast, have him look around. I lost my wallet – I know I had it when I got up this morning." "Oh, you sonofabitch. You'll get thrown right out." "Okay, this is for advertisement – fuck it – put it down or you'll get it right on the block." Had difficulty getting subject to lie down for vital signs.



64:00 D.A.M. effort, showing partial return of ability to render a male figure

74:00 HR 82, BP 110/50 "I went out with her three times and I think she is knocked up." "No, hell, I didn't do it." "Oh, your father's tits!" "Where are my boots? I've got to get my boots to get some chow." "Where bouts?" Continuously moving about the room, very busy with his hands picking up imaginary objects from floor and from walls. Laughing. "Holy shit! Did you see his face?" "See these rats, too?" Put his pillow case with pillow on it, on his right leg – took it off then tied imaginary shoestrings on both feet. "All right gentlemen, here is the scoop. If you want a pass the gentleman is down stairs." "Huh? You don't have to." Who's that?" "Did it itch or what?" "I'm due for an IG inspection any minute and if you don't pass, your ass is grass and so is mine." "What the hell? And I ain't even got time." "Shit, who is it?" Very busily cleaning up room – seems to be moving imaginary objects around. "Come on, bomb, that's my ass. Do you know what this means to me?" Standing at attention. Arranges clothing as if being inspected. Seems to be listening to someone talk. Stood at attention until asked to come out to lunch. Ate large amount of lunch of fried chicken, peas, rice and gravy.

73:15 Beginning to concentrate better during serial subtraction by 7's from 100

Comment: Recovery is close at hand. He has had several hours of good sleep, a reliable sign of the ending of delirium.

82:00 Has been sleeping restfully and soundly. Respirations are regular, no muscle twitching.

84:30 HR 68 Was awake when nurse entered room – seemed alert, not drowsy. Asked what day it was – seemed surprised when told it was Sunday. Said "I sure have slept a long time." Remembers the nurses that were on before the test started and when the test started. First remembers uncomfortable uneasiness and restlessness soon after original injection. Remembers other subject laughing uncontrollably and says he remembered nothing more until now. As he talked he remembered "dreams I had while sleeping." He thinks he has been asleep since Thursday. Remembers a "dream" in which nurse tried to feed him orange juice. He remembers saying "Oh, I don't want any of that, it's coming out of my ears." Only remembers the pill he got today at 1630. Talked about a dream in which he ran off to the dayroom – thought he was gone about 15 minutes, but says he was really gone for 6 hours. Dreamed he was in room at barracks and tried to get out to see his father, but three guys held him back. Thought wall in the padded room was a blackboard that he had erased as a prank. Seems alert, oriented and does not appear to be hallucinating.

84:00 Body image and drawing control showing great improvement

85:30 NF 31, SC 45. Did performance tests and Draw-a-Man. Ate toast and juice and went back to bed.

88:00 HR 72 BP 112/70 Awakened for vital signs. Pleasant and cooperative. Greeted nurse with "Hi!" and a smile. Returned to sleep after vital signs. Sleeping restfully. No muscle twitching noted.

89:00 Sleeping soundly.

90:00 Sleeping soundly

91:00 Sleeping soundly.

92:00 HR 68, BP 100/52, Wgt 131.25 Awakened for vital signs. To latrine and voided 350 cc. Stated he sure has lost weight (136 before test started – he lost almost 5 pounds). Measured own urine and then rinsed out urinal and graduate cylinder. When he left the padded room he turned in the wrong direction. "Oh boy, I sure have lost all sense of direction." Back to bed and to sleep.

93:00 Awakened for breakfast. Slow in getting up. Appetite good. Said "Everything okay? Was I combative? Can I see the TV films? I was televised, wasn't I? I can remember standing inspection without my boots on. I had the General all snowed that I had a physical disability to allow me to go without shoes. Then someone came up and squealed on me – he and I had a fight."

93:45 Sitting in room reading a library book while waiting to take a shower. Pleasant and cooperative.

94:30 HR 66, BP 110/60, PS 8/5, NF 71, SC 77 Up walking around. Taking performance tests.

Monday, 11 February Started writing resume.

96:30 Putting jigsaw puzzle together. Says he remembers having Inspection yesterday afternoon. He actually went through the actions of inspection yesterday but kept talking to "the Colonel." Today he says the man inspecting was a general. When subject was told what a good subject he was he said "I will go on the test again – anytime – just ask me."

97:15 Ate a good lunch – Two wieners, large amount of potato salad and corn. Drank two glasses of milk.

97:30 When told he could lie down and sleep awhile or work on the puzzle, he preferred working on the puzzle.

98:30 Audiology test given by Mrs. Schuette.

99:15 NF 60, SC 68 Performance testing. Continues to put jig saw puzzle together.

104:30 Ate supper. Seems to be in a good mood.

105:00 HR 68, BP 100/56, PS 7/5, NF 76, SC 57

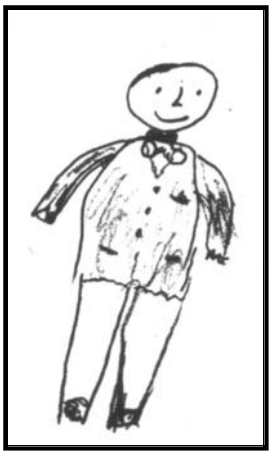
109:00 Has been working on puzzle all evening. No inappropriate behavior noted. To bed.

118:45 **7:15 A.M. Tuesday, 12 February** HR 68, BP 114/62, NF 97, SC 94

Subject remained on ward all day – no symptoms. Regular schedule of measurements discontinued

142:45 **7:15 A.M. Wednesday, 13 February** NF 89, SC 114 Remained on ward. No scheduled measures.

144:45 NF 105, SC 105 Performance scores both above 100% of baseline. Subject discharged by Dr. Ketchum.



92:00 D.A.M. Now shows a firm hand and more detail, but NF and SC not yet back to baseline

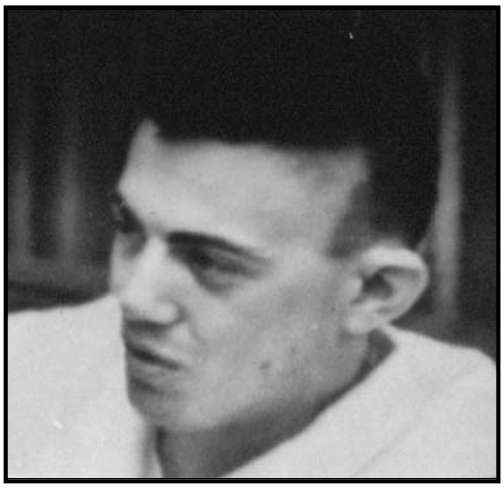
122:00 Smile on face of D.A.M figure as scores on NF and SC finally return to baseline

John wrote up his experience at the end of the test:

On Thurs. morning at about 8:30 AM I was injected with a drug. I felt no different at that time; about an hour later I felt very restless and I wanted to get up and walk around but the nurse said I had to stay flat on my back. I have no idea of when I fell asleep but it must have been between 8:30 and 12 noon because I cannot remember eating lunch. In fact, I cannot remember eating or drinking during the entire test.

I will now describe some of the dreams I had. There was supposed to be an inspection in the barracks by a General and I had just come back from leave. I was trying to get ready for it. The only difficulty I had was that I could only find one boot so I put on a pair of shower shoes. When the general saw them he asked why I was wearing them and I told him that I was under orders from a doctor not to keep my feet enclosed but to let the air at them. He believed me and left the room. In this same dream I had a girl waiting for me down the hall. I wanted to go out and see her but the nurse wouldn't let me so after trying to fight my way out and failing I called the MP's who promptly arrested them. After that I found out that they were going to beat me up so I tried to make friends with the one who appeared to be the leader. It must have worked because I don't remember a beating.

In another dream I remember that I kept falling down. I told everyone that I had lost my balance but I really felt that something was seriously wrong with me. I remember taking only one fall that really hurt me; the others weren't very bad. In another short dream I can remember red lights blinking on and off but that's all I can remember about it. I can remember no written tests or anyone taking blood.



Feeling pretty good after his long test, John and his partner agreed to repeat it two weeks later -- as part of a double blind crossover, he received physostigmine treatment instead of placebo and remained close to baseline all week while his partner got placebo and was incapacitated..

Another effect of the drug besides being restless was a slight headache and a feeling of being very light-headed and having trouble focusing my eyes.

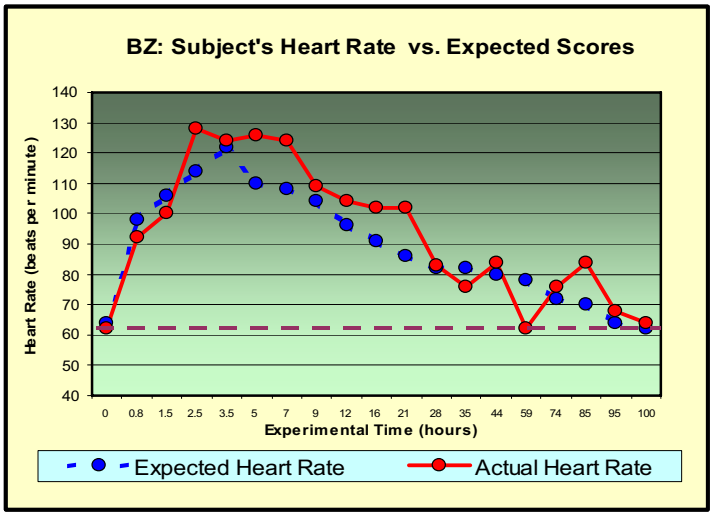
To the best of my knowledge [the other subject] was in the room when I fell asleep but when I woke up he and his bed were both gone. I can remember eating a meal; I don't know what meal it was but it consisted of beans, cold cuts, and for desert I had peach ice cream. [This was Sunday, Feb 10, 1963] I seem to remember Mrs. King and Mr. Stearn being there for a while, about what I don't remember.

In another dream I met a girl whom I had known for some time. We had been going out quite a bit together but then I broke off with her. She didn't look right to me and I asked what was wrong but she started crying and wouldn't tell me. Finally she admitted that she was pregnant. I didn't ask her anything else and then the dream ended. I could not understand why; she was always so careful not to go that far. This girl I speak of is [—], a girl I went with for about 2 years. I stopped going out with her all together in June of 1960 but in the dream I wanted to go back and take her out again. If there were any tests taken while I was under the drug I don't remember them at all nor do I remember eating or drinking anything except for the one meal that I described before.

I do remember refusing to take orange juice and getting mad at whoever tried to give it to me. I also remember trying to break out of a room, probably the one I was in but I'm not sure. I tried to rip some of the walls or padding off. Another incident I remember was sneaking out of my room and going for a walk. Also, when I woke up this morning I noticed that there were white sheets on the bed but before I was injected there were green sheets.

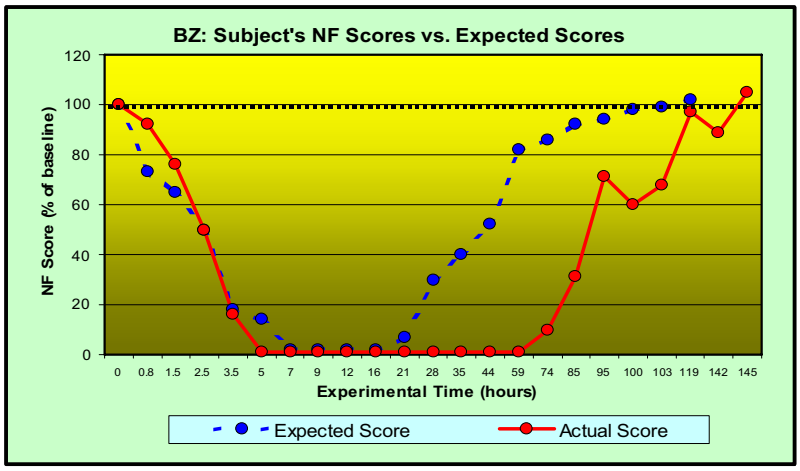
Now that I think back I can remember blood being taken once. It seemed to be very, very painful. I also remember my hands and feet being red in color. At one time I seemed to have a very sore throat; it was then I asked for and received a drink of water.

(Resume rendered exactly as written by subject.)



John's response to 7 mcg/kg of BZ was longer in duration than the average, as can be seen by comparing the expected with the actual scores on NF as well as the somewhat higher heart rate.

When retested two weeks later, he received physostigmine repeatedly and after the first few hours, his NF scores and heart rate measurements were maintained close to the baseline values.



And so ended "the week that was" – for all of us!

* * * * *

10 MORE BREEDS THAN AT A DOG SHOW

Since we cannot know all that is to be known of everything, we ought to know a little about everything.

Blaise Pascal (1623-1662)

I almost have to dream myself back and forth to recapture all the interesting happenings during my first five and a half years at Edgewood. I've got a stack of reports, a pile of data sheets filled with rows and columns of numbers, personal and official letters, family and workplace photographs and…my memories.

People came and went. Chiefs and organizational charts seemed to change moment by moment. New chemical agents pushed older ones out of the spotlight, until they too were displaced by something that might work even better. One week it would be a more potent molecule, the next it would either be one that was faster acting, but less potent, or very potent but too long-lasting. Comparing and judging them was as complex as picking "best in show" at Madison Square Garden.

And it wasn't just breeds of drugs. I found myself sorting out people and places, too. Not that one person was better to work with than the next, or that one location was more worth visiting than any other. Although we were becoming more familiar with the drugs, we still had to choose with whom, as well as when and where, to concentrate our efforts. Obviously, there was no way to come up with foolproof formulas or protocols for such decisions. As in any endeavor, the unpredictable flow of events and opportunities often imposed the decisions upon us.

When not too busy, I spent some time during 1961 in Edgewood's medical library. What I read took me back a few years to the work done by others. As Horace once said, "Vixere fortes ante Agamemnona" – "Brave men lived before Agamemnon." It would be overly grandiose to suppose that I had personally invented incapacitating agent research!

But talk about high doses! In 1958, under an Army contract, Dr. Gerald Klee had paid each of several volunteers to take LSD four times, with at least a week between doses. In random sequence, he gave each subject 2, 4, 8 and 16 mcg/kg, which in an average-sized male would equal total doses of 150, 300, 600 and 1200 micrograms! It was a double-blind study – neither the doctor nor the subjects knew who had received what until after the experiment was completed.

The results, summarized in tables and accompanied by the customary statistical tests of significance, indicated that dosage correlated with intensity of effect – not a very surprising conclusion, considering the 8-fold range of doses. At the higher doses, confusion, anxiety and paranoia were much more likely. Apparently, there were no serious complications requiring extended care. It was a good design, but the methods section said relatively little about setting or safeguards. There was no pre-test or post-test overnight stay on the test location, and the subjects were released as soon as they returned to everyday reality (as opposed to the "true reality" sometimes glimpsed by psychedelic drug-users during LSD trips).

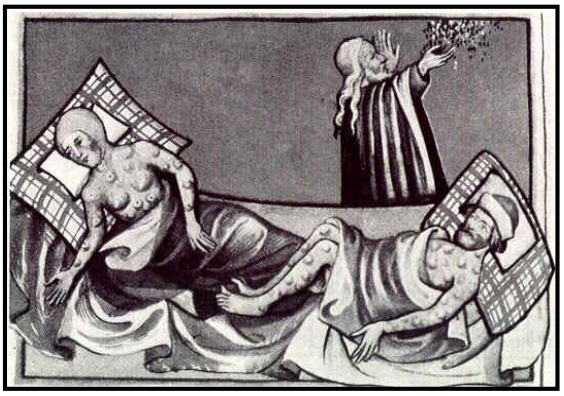
It amazed me that Edgewood had allowed Klee to publish the results in the open literature. If he had conducted the same tests in our laboratory, the Security Office would have promptly stamped his reports "Secret" and locked them up in a steel file. Nevertheless, both the editor of the journal and the security gatekeepers at Edgewood approved Klee's publication, apparently without a blink. One might conclude that they treated hired contractors and in-house investigators as different breeds when it came to classifying their work.

Media critics were predictably more interested in drug studies done in a military setting than those conducted within the hallowed halls of academe. Their reporting would have been less biased if they had noted that we never gave more (and usually much less) than 300 mcg of LSD to any of our volunteers. The problem, of course, was that Edgewood kept reporters in the dark by classifying most of our work, thus keeping it out of the public's purview.

Professor Klee had administered up to four times as much as we ever did, on up to four times as many occasions, without evoking a peep from the media. I think the Romans had it right: "O tempora, O mores." They should have added that "who and where also make a big difference."

The security-conscious librarian allowed me to read only a small number of highly classified reports during my time at Edgewood. Although I had a Top Secret clearance, unless I could demonstrate a "need to know" many documents were inaccessible. "Need to know," incidentally, had nothing to do with intellectual curiosity. Higher authorities made the decision based on personal judgment.

I did manage to read a classified intelligence report gathered by covert sources in Europe. It stated that the Soviet Union had imported trainloads of ergot from certain Balkan countries. Ergot is produced by a fungus that sometimes infects rye and other grains. At the time, it often served as a starting point for the production of LSD. A devastating 14th century epidemic of



Depiction of the "Black Death"
(From the Toggenburg Bible, 1411)

"ergotism" in Europe resulted from consuming rye that had been contaminated with this fungus.

Ergot by itself, in sufficient amounts, can wreak terrible havoc upon the body. A powerful vasoconstrictor, it shuts off the blood supply to fingers, toes, arms, legs and internal organs. In the brain, it also causes madness, due to its neurological effects. The "Black Death" scourge in 1347 was a massive epidemic, during which thousands of victims, if not already crippled or dead from massive gangrene, raved psychotically in the streets. The infection also produced large blisters and purpling of the skin which some observers called "Saint. Anthony's Fire."

Since it was doubtful that the Soviet Union was planning to inflict such horrors on its own population, it seemed that the only explanation for their massive ergot acquisition must have been a desire to make large quantities of LSD. And obviously, they were revving up their efforts to produce such incapacitating agents. This was fair warning that we too needed to get busy with our own program.

I have no doubt that reports of this type catalyzed the acceleration of our research activities. Happily, it also opened the coffers of government funds more widely. Other intelligence reports indicated that the Soviet Union was spending ten times as much as we were on the development of its chemical warfare capabilities. This fueled the sense of urgency regarding our efforts in the lab and strengthened the belief (mostly an illusion, as we learned later) that we had to go all out if we wanted to stay ahead of the Russians. As much as anything, this belief imparted a patriotic fervor to our efforts.

I viewed a film showing some of the LSD experiments at Fort Bragg in 1959. Edgewood investigators had given volunteers 150 mcg and tested them with the same military tasks as the ones they had performed without difficulty before the drug. After receiving LSD, they failed in efforts to survey a section of road, track an aircraft through an anti-aircraft gun sight or relay messages properly from one troop leader to another. Soldiers who had performed smartly when given drill instructions before medication, wandered in all directions after taking LSD, many of them giggling and clowning in response to orders.

Dr. Harold Wolff was Chief of Neurology at Cornell while I was a student and was one of our most admired teachers. In 1955, when I was in my third year, I described a delirious patient I had seen and he gave me a mimeographed copy of his 1935 monograph entitled "The Dysergastic Reaction: Delirium and Allied States." It enumerated over 100 different diseases and drugs that could produce a delirious state. Little did I imagine that I was destined to specialize in drug-produced delirium seven years later. One might call that an uncanny coincidence. I have referred to his comprehensive review repeatedly during the last 50 years.

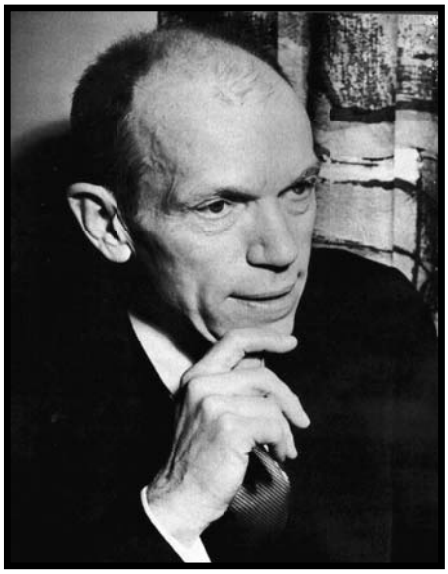
Dr. Wolff was also a supervisor during my neurology rotation. One day I learned that he loved the game of squash and asked him if we might have a game together. Thereafter, we played frequently on the 24th floor of New York Hospital, adjacent to the med school. He was a stickler for punctuality. After exactly three games, he would hasten to use the shower first in order to hurry to

his next appointment. Even the way he dried himself was precise, always ending with a sharp flick of his towel between the legs – an image I'll never forget!

One day, while we were dressing and making small talk, he spontaneously commented: "Some day people like you are going to make a difference." I have no idea why he said that, but it certainly was an ego-boosting compliment, coming from a man who rarely wasted words.

I had no idea at the time that during my last two years of med school, Harold Wolff was secretly under contract to the CIA. He received funds by way of the Geschicter Foundation and the Human Ecology Fund, front organizations set up to launder money for LSD research. Wolff was only one of many prestigious professors and research pharmacologists partly supported by the CIA in the early 1950s.

One could compile a long list of universities and pharmaceutical laboratories that readily accepted Geschicter Foundation contracts. Many of the investigators, however, did not know the real source of the funding. These world-class pharmacologists and research physicians were engrossed in studying drugs – particularly LSD – at the biochemical, physiological and behavioral level. Their published results were seemingly nothing more than interesting and legitimate scientific reports. The CIA, however, was watching their work closely, drawing inferences from their publications and planning operations that could make use of the new information in its efforts to find a mind-control agent.



Harold G. Wolff (1899-1962)
Professor and Chairman of Neurology at Cornell University Medical School and consultant to the CIA and US Army

Unlike some, Harold Wolff was willing to take an active role in what he considered valid CIA activities. They asked him to chair a secret committee, brought together to evaluate LSD as a possible military incapacitating agent. In 1955, the "Wolff Committee" (as it came to be called) submitted its report to the Chemical Corps. Among its recommendations: a proposal to study military performance in a field scenario, before and after administering 150 mcg of LSD to a squad of trained volunteers. I was pleased to note that Wolff placed great emphasis on safety, insisting that the experiment not hurt anyone.

The Chemical Corps had great respect for Harold Wolff, but they were not the only ones who admired his imposing intellect. As students, we also regarded him with awe. His lectures were always crisp and precise, and he presented information so clearly that we all considered him a pedagogical phenomenon.

Without modifying his countenance, he could instill anxiety into any student who was not prepared to answer his incisive questions. In my third year, I presented a carefully prepared case history to him as part of a class assignment. When I finished, he paused and then quietly asked, "If the patient were to

respond favorably to your treatment, would you conclude that the theoretical basis of your therapy was validated?" I hesitated, but finally said "No." Later, I was relieved to learn from his secretary that he thought well of my presentation. "No" was the response he wanted to hear.

In John Marks' widely cited The Search for the Manchurian Candidate, an investigative book about the CIA's involvement with LSD, he describes Wolff as simultaneously both highly respected and quite intimidating. Marks quotes one of Wolff's longtime associates: "From the Agency side, I don't know anyone who wasn't scared of him. He was an autocratic man. I never knew him to chew anyone out. He didn't have to. We were damned respectful. He moved in high places. He was just a skinny little man, but talk about mind control! He was one of the controllers."

Despite this double-edged characterization, Harold Wolff was, in my opinion, a force for good. As Marks acknowledges, Wolff was always clear in his insistence that no one be injured by any experimental procedure.

In December, 1961, when I went home to New York for the holidays, I decided to call him. He invited me to visit him at the medical school. It was Saturday morning and Professor Wolff was making rounds with the medical students. He greeted me warmly but explained that his time was limited because he had to catch a train in the early afternoon.

The Simca, in better days

When it was time for him to leave, I offered him a ride to Grand Central Station. We were so engrossed in conversation that neither of us noticed we were walking down the wrong staircase. We eventually made it to my little Simca. There was snow on the Manhattan streets and the weather was bitter cold. I had (bizarrely) taped plastic film across the windows for insulation. As we drove toward the station, I suddenly realized I had been too busy talking to make the correct turns and we arrived at the station just in time for him to run to his train. Considering his usually impeccable planning, my ineptitude must have been maddening, but he was kind enough not to show it. Before he left, I asked if he would visit us at Edgewood and he readily agreed to come early in 1962.

Two months passed and I forgot to follow-up on my invitation. Van Sim came to work one Monday morning and told me that Dr. Wolff had just died – within hours of Valentine's Day – while they were both attending one of the secret meetings in Washington. In the course of a group discussion, he had collapsed with a massive stroke, but was still conscious when Van, of all people, had rushed to his side. Purportedly, Wolff looked up and said "Oh Van, I'm so glad it's you." An ambulance rushed him to the hospital but he died en route.

As I listened, I thought the story apocryphal and terribly ironic. I remembered that in December, I had spoken to Dr. Wolff about Van and mentioned some of his limitations. He commented that Van "seemed to be a rather ordinary man." For the great professor to have spent virtually his last moments of consciousness in the arms of my "rather ordinary" boss at Edgewood was mind-boggling.

In addition to sadness at his death, I seriously regretted not taking advantage of his generous offer to visit our lab. I thought back to Cornell, where our graduating class had voted him "most inspiring teacher." In my opinion, he had patriotically served both the Army and the CIA. One of a very special breed, he was dead at the age of 63.

Before long, however, the aforementioned Colonel Doug Lindsey, scion of an equally special breed, diverted me from such depressing thoughts.

"Jim, we've had a special request from SHAPE, in Paris."

"SHAPE?" To me it was an unfamiliar term.

"Supreme Headquarters of the Allied Powers in Europe," he explained. "They're meeting in May and they want an update on our research program. I'm putting together a briefing team to go over with me and tell them what we've been doing. I want you to go along."

"Wow," I said. "Just what is it you want me to do?" I had never been to Europe, much less Paris.

"For starters, get together a one-hour presentation on your work with BZ and LSD. Then I want you to put together a six-minute film."

"A film?"

"It should hit the highlights and bring out the nature of the psychochemical threat."

"This is not like something for the Journal of Irreproducible Results?" I temporized, trying to get back to my emotional baseline.

"Nothing that sophisticated," he grinned. "But it should be accurate, hard-hitting and informative. It's got to be short because I want all the NATO generals and admirals to be able to view it individually."

"Do they all speak English?"

"No, but the fabrication shop can make a special kiosk-like viewing station, with four rear-view projectors, pointing outward in four directions from the center. That way the generals can watch the film through any of four openings. The visual part will be identical in all four, but the voice over languages will be different. Whoever wants to see the film can pick the projector that speaks his language."

"Sounds neat. You do realize I haven't made a whole lot of movies." (To be precise, I should have said "any movies at all.")

"Not to worry, Lindsey assured me. Just pick out a six-minute sequence of scenes and write a synchronized narrative. You'll have the full support of the Graphic Arts people."

First visit to Paris

So off I went to tackle this new assignment. I wondered if there were sufficient stock footage in the Graphic Arts files to make a coherent six-minute film. I looked at it all, and saw that there were plenty of good clips to work with.

The camera team was needed only to shoot a couple of new scenes – in the case of a lethal agent, for example, a soldier staggering as VX takes hold, and another where he injects his own thigh with the antidote.

Writing the narrative was a challenge but, once started, it came fairly easily. Toward the end, I even fell into an Archibald MacLeish rhythm, mimicking the

timbre of his alliteration: "This armor for the inner man must be fabricated from organic molecules, not metals. To meet the psychochemical threat we will need a psychochemical defense!" Dramatic, modern, impressionistic music up to climax!

1962 – Sleepy May afternoon in Paris

Later I realized that I was unwittingly formulating U.S. chemical warfare policy by announcing that "a psychochemical defense" was what we would need "to meet the psychochemical threat." Apparently, it was okay, however – a year later, a higher-up from Washington confided that Secretary of Defense McNamara had watched it during a staff meeting and commented "Good flick!" It also went over well with Doug Lindsey and the NATO delegates at the conference. On top of all that, I got to spend a great two weeks in Europe in the merry month of May.

It was my second year at Edgewood and the pace was heating up. Even before we could finish all the individual BZ studies designed to fully characterize its effects, the chemical breeding kennels were delivering new litters of BZ-like chemicals to be tested.

The first was EA 3443, a molecular relative that had almost exactly the same time course as BZ, but 50% more potency and relatively less effect on peripheral bodily functions such as heart rate, blood pressure, salivation, sweating, and vision. At just the right dose (about a third of a milligram), it could produce the "mad as a hatter" features of classical belladonnoid intoxication. Although the "madness" would indeed be there in full force, it might confuse a diagnostician looking for peripheral signs, such as rapid heart rate and hot, dry skin.

At higher doses, these features became more apparent, but at or below the incapacitating dose, they were virtually absent. We began to realize that absolute potency was not the only way to describe belladonnoids, and we adopted the term "relative central potency" as another way to compare them.

EA 3580 came along next. It was similar with respect to relative central potency and was equally incapacitating at approximately the same dosage as EA 3443, but lasted only half as long.

Next in line was agent CS 27349 – short acting but not very potent – and 302196, which was only a quarter as potent as BZ, but worked in minutes and wore off in 2 or 3 hours. Still other new glycolates came along later, each with a distinctive profile.

It seemed like we were rapidly acquiring a crowded kennel of chemical breeds, sufficient in number to parade past the military judges. And even more were in the offing. Some were from other chemical families and had different effects, but their potency tended to be too low or they failed to meet some other practical requirement. They might last too long, for example, or have too many side effects.

Returning to the glycolates, it might help to convey the similarity in mental effects between EA 3443 and BZ by providing some excerpts from the clinical records. Here are some samples of alterations in speech, perception, behavior and self-descriptions for some EA 3443 subjects. Similarities to BZ should be obvious:

Examples of speech disturbances after exposure to EA 3443

Case # 779 3.2 mcg/kg i.m. **Experimental time: 2000**

"Are we going to do that, what day is it, what time is it, jazzy again?"
"… catching myself talking to people. But I forgot it was Halloween."

Case # 538 3.4 mcg/kg i.m. **Experimental time: 0450**

When asked what he had in his hands, said "All propaganda, no truth to it." When asked "No truth to what?" said "Oh cars, houses, TV."

Case # 333 3.4 mcg/kg i.m. **Experimental time: 0450**

While looking at a notebook binder, said "Is that the new air conditioner? At least it keeps the folks well."

Q "What are you looking at?" **Experimental time: 0545**
A. "A bunch of trucks pulling a trailer."
Q. "What are they doing?"
A. "I imagine they're going swimming by now."

Perceptual disturbances were vivid and at times amusing. Unlike the pseudo-hallucinations of subjects under the influence of LSD, they were ordinary and included everyday scenes and memories.

Examples of perceptual disturbances after exposure to EA 3443

Case # 690 Aerosol Ct 54 (equiv. i.m. dose 5.3 mcg/kg) **Experimental time: 2000**

Complained that his "cigarette" was heavy – he was "smoking" his pencil.

Case # 333 3.4 mcg/kg i.m. **Experimental time: 2200**

"I gave up trying to eat that food. Every time I turned around I had to pick a whole mess of bugs out of my mouth."

Case # 538 3.4 mcg kg i.m. **Experimental time: 0450**

Saw three baby bats on the floor and a 6-yr old baby running around in cubicle.

Experimental time: 1220

Said everyone had on a brightly colored hat

Experimental time: 2755

"I went to the men's room and saw Ernest Hemingway come out. Hemingway was wearing Bermudas."

Case # 685 Aerosol Ct 118 (equiv. i.m. dose 13.4 mcg/kg) **Experimental time: 2400**

"My hands and arms, as well as everyone else's, appeared to be yellow …Any white or light colored spot on the floor or wall seemed to sparkle like diamonds. On closer inspection by me the spots seemed to be covered with tiny bubbles [which] disappeared whenever I touched them."

Case # 332 2.4 mcg/kg i.m. **Experimental time: 2400**

"My friends came through the wall and talked to me. I have to go around the other side because I can't go through the wall. I just don't see how they do it."

Occasionally, subjects who were disoriented and frightened expressed anger – rarely violently, but often unpredictably and at times bizarrely. These incidents were rare and were usually handled without difficulty since the volunteer's attention span was extremely short and he would generally forget what he was doing or intending to do. Amnesia almost always erased recollection of these outbursts.

Examples of hostile, destructive or violent disturbances after exposure to EA 3443

Case # 333 3.4 mcg/kg i.m. **Experimental time: 2200**

Subject broke a wooden chair and smashed a hole in the wall after tearing down a 4 by 7-foot panel of padding. Subject suddenly raced for the door. After a brief struggle, four of us subdued him. He was clearly terrified and convinced we were intending to kill him.

Case # 641 Aerosol Ct 273 (equiv. i.m. dose 21.2 mcg/kg) **Experimental time: 1000**

When nurse attempted to take blood pressure, subject took a swing at her – did not want to be bothered. Says everyone is against him and will not let him sleep. Would not allow nurse to check vital signs.

Case # 780 3.2 mcg/kg i.m. **Experimental time: 3200**

He asked what nurse was on and when told who, said "OK, but I'm laying out for the other one." States he "really has it in for her."

Case # 335 3.8 mcg/kg i.m. **Experimental time: 1400**

Was asked to leave cubicle of other subject. Walked past aid man, then turned and ht aid man in face with fist. Walked away without any response.

Experimental Time: 1745

He was antagonistic toward aid man, had his drawn hand back and was making a motion to strike several times.

I well remember the EA 3443 volunteer (case # 333, above) who managed to break out of the padded ward and run down the hallway in an effort to escape. Reliable Master Sergeant Owen Jones (age 48) ran him down and tackled him while the rest of us piled on to temporarily immobilize him. The runaway quickly forgot that he was frightened, and we were able to guide him back to his cubicle without difficulty. Thereafter, he remained generally cooperative. No injuries had occurred and he could not even recall the incident after the test was over.

The abnormal appearance of the skin mentioned by one subject, as well as his attempt to rub "blood" off his fellow test subject, was also reported by other volunteers. For some reason, never explained, those who received high doses of glycolates often saw red coloration on their skin and other objects. Sometimes, at the sink, they even thought they were washing blood from their hands. This visual disturbance was always temporary, and disappeared by the time of recovery.

When asked to estimate on a scale of 0 to 100 percent how well they believed they could have functioned under EA 3443, most subjects gave a percentage strikingly proportional to the dose they had received. Subjects who had received physostigmine treatment were just as accurate in their estimates.

It is interesting that most volunteers do retain such an accurate impression of their impairment, even though most of them develop amnesia for the details of their experience. (They did, however, remember quite a few additional details immediately after recovery, just as people remember dreams best just after awakening.)

Examples of subject's own estimate of military incapacitation after EA 3443

Case # 780 3.2 mcg/kg i.m.

"It was like having no control over mind or body," "… all I wanted to do was get away from whatever hallucinations I was having."

Case # 333 3.4 mcg/kg i.m.

"I began hearing voices… I also saw… bugs, worms, one snake, a monkey and numerous rats… I thought my skin was yellow… I attempted to wipe the blood away [on nearby subject] but there was no blood."

Case # 690 Aerosol Ct 54 (i.m. equiv. dose: 5.3 mcg/kg)

"I think that a soldier under these conditions would have two large obstacles: He would have a great time trying to understand any orders given him and if this soldier would even try to perform his duty, he'd be more of a hindrance than a help to his fellow man."

Case # 636 Aerosol Ct 71 (i.m. equiv. dose: 6.6 mcg/kg)

"If I had been at duty when I received this gas, I would not have been able to perform for about 10 hr. If I was in combat and received this gas, I would not be able to function and would be wide open for attack."

Case # 684 Aerosol Ct 127 (i.m. equiv. dose: 11.9 mcg/kg)

"I had a great urge to smoke and, when I thought about it, a lit cigarette appeared in my hand. I could actually smoke the cigarette…when I wanted to get rid of the butt, all I needed to do was roll the butt in my fingers and it would disappear."

As mentioned, one of the appealing attributes of EA 3443 was that it had more "relative central potency" than BZ. This would seem to confer an added measure of safety, since sweating is less impaired, and effects on the heart (the usual cause of death) are minimal. Previous pharmacology textbooks often stated that central (i.e., brain-regulated) respiratory failure was the probable mechanism of lethality – our studies suggested otherwise.

Having observed a decrease in appetite and thirst when testing BZ, we decided to measured caloric and fluid intake more precisely in the EA 3443 series. At the incapacitating dose, calories ingested and fluid consumed both dropped by about 40%. Sleep duration, also measured, increased at the lower doses but seemed to drop precipitously at the incapacitating dose. This seeming insomnia, however, was illusory. Delirious subjects appeared physically awake, but were "asleep" in terms of brain electrical activity – the so-called "pseudowakeful state."

Had the Chemical Corps not already decided to make BZ the standard incapacitating agent (approved for weaponizing) it is likely that it would have chosen either EA 3443 or EA 3580. The choice would probably depend mostly on whether a duration of 1-2 days or 3-4 days was preferable.

The glycolate pipeline continued to supply new candidate agents, each one a related compound with differing properties, and they all seemed deserving of clinical evaluation. It seemed necessary to study any compound that an enemy might conceivably use against us. We felt it important to know whether any of them possessed some unique type of toxicity, requiring novel medical countermeasures.

On the other hand, the development of more effective weapons, including better incapacitating agents, was a proactive national defense goal. I had no problem with this latter objective, since I believed that incapacitating agents were potentially life-sparing weapons, and we should have the most effective and least toxic ones available. Unfortunately, once BZ was "standardized," the other agents were not considered worthy of production, in spite of their apparent superiority from a "life-sparing" standpoint.

EA 3167

When it came to testing this agent, we faced a drug whose effects lasted longer than any we had examined before. We knew it was potent, but not exactly how potent. We also knew it had long-lasting effects, but not how long. In addition, we didn't know what its relative central potency was.

EA 3167 proved to be as potent as the most potent glycolates we had studied and its duration was much longer than any. One subject required antidote treatment for more than two weeks to stave off delirium. During that period, he received a total of 231 mg of physostigmine (a single dose would be 2-4 mg).

Starting in 1965, the rate of testing exceeded our ability to house all the subjects. This was largely because as much as 10 days of "bed occupancy" was sometimes required to observe the course of EA 3443 effects because of the slow absorption of the drug when placed on the skin. Accordingly, Edgewood arranged to do some of the testing at Holmesburg Prison in Philadelphia, under a contract with the University of Pennsylvania.

Selection criteria were essentially identical to those used for enlisted volunteers. One obvious difference was that inmates have a criminal history, but we restricted our choices to those whose crimes were non-violent, such as theft, fraud or drug-related offenses. We also excluded inmates recently addicted to street drugs and those awaiting release in less than six months.

We compensated the inmate volunteers monetarily for their test performances. For example, they received three cents per correct NF answer, which meant an average reward of about eighty cents for each three-minute test. In a maximum-security prison, this was a substantial incentive.

Because of concern about possible residual effects on personality profile or cognitive function, we not only gave the MMPI (Minnesota Multiphasic Personality Inventory) and IQ tests prior to selection but also repeated them one and six months post-exposure. Although there were a few differences in the MMPI scale scores one month post-test, they were close to the pre-test values when the Inventory was repeated five months later.

We eventually studied more than a dozen different glycolate compounds. I thought it would be nice if we could have a single term to refer to these pharmacologically related drugs. Our preference was "belladonnoid" (as we argued in a 1973 publication). We were following the example of Dr. Jerome Jaffe and others, who, in the 1970s, used the term "opioid" (opium-like) to refer to all drugs with effects similar to morphine, whether derived directly from opium or synthesized in the laboratory. "Opioid" is now a widely accepted term.

Regardless of terminology, one should remember that despite differences in intensity and duration of action, all atropine-like compounds have structural similarities and produce a common pattern of pharmacological effects. In other

words, BZ, 3443, and the other dozen or so belladonnoids we looked at may all be considered distinctive "breeds," but they are all members of the same "genus" and each could vie for "best in show," depending on the particular features the "judges" consider most important.

By 1968, we had pretty much reached the end of the list of drugs likely to be of military interest, either to an enemy or to our own forces. Nevertheless, studies of their military effectiveness under field conditions would continue. In the following chapters, we will portray some of these in detail. The best lies ahead!

* * * * *

11 TAMING THE FRACTIOUS BELLADONNOIDS

We must ask where we are and whither we are tending.

Abraham Lincoln

Like the bucket-carrying brooms in Fantasia, once BZ molecules began to flow into the body no one, in 1961, seemed to know how to turn them off. They moved easily into the brain, largely unimpeded by the blood-brain barrier that blocks out many unwanted substances. Their high degree of "relative central potency" enabled them to gain access to nerve cells in the gray matter.

Once in the brain, the BZ molecules sought out receptors designed to accept acetylcholine, the natural neurotransmitter that triggers physical and mental activity. Shoving the acetylcholine molecules aside, the BZ interlopers took up residence on their receptors and, like dogs in mangers, crowded out the transmitter molecules essential to normal thinking and acting.

Once they reach acetylcholine receptors, BZ molecules hang on for dear life. So tenacious is their grip that they take hit after hit from the weaker acetylcholine molecules. For tens of hours acetylcholine is unable to exert command and control of mental activities. Like sugar in a gas tank, BZ "gums up the transmission." The result is incapacitation.

As might be expected, the constant bombardment by acetylcholine molecules eventually takes its toll and, one by one, the BZ molecules lose their grip. They bounce around in the brain fluid surrounding the cells until by chance they run into and right back through the blood-brain barrier, returning to the bloodstream. Then, unless they accidentally find their way back into the brain again, their fate is sealed. The liver picks them out of the bloodstream, bends or breaks them, and lets the inactivated molecules float downstream like Ophelia, until they reach the kidney's waste disposal system. Ignominiously, most of them then end up in some urinary receptacle – a latrine or a pajama pants leg, depending on the brain's remaining degree of confusion. When all of them are gone from the brain receptors, the brain can think again, proper urinary habits return, and all is well.

In 1961, we understood how BZ delirium was "turned on", but none of us knew how to stop the flow. All we could do was sit and watch the fanciful drama just described, and take detailed notes.

This was very frustrating. Our drug investigations at Edgewood were supposed to be developing medical defenses against possible chemical attacks. Finding antidotes was a top priority. Pharmacology textbooks gave little encouragement. Supportive measures, such as maintaining hydration and sedation were about all they had to offer for belladonnoid toxicity.

Goodman and Gilman's 1965 edition of The Pharmacological Basis of Therapeutics (the most widely accepted source of such information throughout the last half-century) contained a skeptical assessment of the efficacy of theoretical antidotes such as physostigmine and other anticholinesterase agents. In fact, all the experts on atropine and other belladonna type drugs seemed to agree that physostigmine might be useful in reversing of the peripheral effects of atropine, but would not alter the associated delirium.

Surprisingly, it appeared that there had been hardly any therapeutic progress in the management of belladonna poisoning since the 19th century, when opium was the most commonly used treatment. The first six decades of the 20th century spawned many new drugs, but no one seemed to have reported anything good for atropine delirium in mainstream medical journals.

When patients came to emergency rooms after an atropine overdose, most physicians were unaware that physostigmine readily enters the brain and might be helpful. Nevertheless, in early 1961, Dr. Jerry Strong, a department colleague, decided to give physostigmine a trial as an antidote. He tested it against JB-329 (Ditran), a blend of two short acting atropine-like compounds. Unimpressed with the results, he put what he considered a couple of uninteresting volunteer charts in his filing cabinet.

Months later, the theoretical appeal of physostigmine stimulated us to give it some further thought. We retrieved the clinical records of the two volunteers Jerry had tested and reviewed their NF performance scores before and after physostigmine administration. Unexpectedly, it seemed clear to us that the scores had improved substantially after treatment – contrary to Jerry's assessment, that physostigmine had been ineffective. Perhaps Jerry simply discounted the results because he did not consider the improvement substantial enough to warrant further trials.

Encouraged, we decided to try physostigmine again. We were delighted when it dramatically restored NF scores of clearly incapacitated volunteers to near normal levels. The first time this happened, I could not help feeling a little

bit like Columbus. Of course (as Columbus himself was lucky enough never to realize), we were not the first to discover this "New World."

Just as we were patting ourselves on the back, a more extensive review of the literature made us aware that we had merely reinvented the wheel. Our only consolation was that the experts who wrote the "up-to-date" clinical pharmacology books also had not kept up with all the literature. However, as we soon came to realize, animal pharmacologists had known all along that physostigmine could antagonize the central toxicity of atropine in animals. But what self-respecting physician spends his spare time reading textbooks of animal pharmacology?

Since we were on the hunt, we did read a few such books, discovering that we were not the first, by a long shot, to observe the effectiveness of physostigmine as a belladonnoid antidote. We also found several relevant articles, published a decade earlier in the American Journal of Psychiatry and several other reputable journals. They came from a relatively little known group of psychiatrists who were investigating a new form of therapy in their hospital. The story is somewhat convoluted, but nonetheless interesting.

In 1950, antipsychotic drugs such as Thorazine had not yet appeared on the psychiatric scene. Physical treatments such as long soaks in hot tubs, cold showers, electric shock, psychosurgery and insulin coma therapy were still the latest thing. Recognizing that these treatments were not particularly pleasant (except perhaps the hot tubs), and that insulin coma treatments were definitely pretty nasty (producing what some patients described as a sense of impending death), Drs. Forrer, Miller, Goldner, Grisell, Schwartz and a few others decided to look for a more acceptable way to produce a therapeutic coma.

Atropine seemed an appealing choice for this purpose. Soon they began treating intractably depressed and psychotic patients with large doses of this familiar belladonna drug. An early morning injection could produce a comatose state, from which the patient would awake after a 4 mg injection of physostigmine. Within minutes, she would be quite alert again and with the help of a few supplemental oral doses, would be on the way to occupational therapy without missing any of the other scheduled activities. Amazing!

The doctors used huge doses – many times the largest amount we ever gave our volunteers – but safety did not seem to be a problem. Intramuscular doses of 30-100 mg of atropine became routine. They gave the coma treatments, (usually a dozen or so) every other day until there was clinical improvement. Sometimes they gave even larger doses. One patient received a dose of over 200 mg (considered twice the lethal dose by Drs. Goodman and Gilman).

To administer such large doses, the authors had to have the atropine solutions prepared in a more concentrated form. The new injectable ampoules contained 50 mg per cc instead of the usual 2 or 5mg. These megadoses of atropine, and the claim that the resulting coma and delirium could be reversed by 4 mg of a drug "known" to be ineffective in treating atropine toxicity, might have caused their reports to be regarded as balderdash by some readers.

I can almost hear some of the musings of the unbelievers: "After all, this study was done by psychiatrists. Who knows, maybe they absent-mindedly moved the decimal points." In any case, the new treatment method did not make it into mainstream American psychiatry, much less general medical practice. Nor did the good news that physostigmine was an effective antidote for atropine delirium. (Incidentally, I met Forrer's colleague, Dr. Miller, in 1981, 30 years after their first publications about atropine coma therapy. He was invited to

address the committee set up by the National Academy of Sciences to evaluate the long-term effects of BZ and seemed to be quite levelheaded.)

Meanwhile, the reports by Forrer et al. inspired doctors Toyoji Wada, Shoji Horigome and Takashi Sakurada to try it out on patients at the Hirosaki University School of Medicine, Hirosaki. Using a similar protocol, they treated 51 cases between 1957 and 1960. The doctors gave patients an average of 30-50 mg by injection (up to a maximum dose of 220 mg) every other day for "3-7 weeks without cessation." They published, "Clinical Experience of the So-Called 'Atropine Toxicity Therapy' (Forrer)" in 1960 in Toboku J. Exper. Med.

Intriguingly, the Japanese investigators apparently did not use physostigmine to terminate the atropine comas. For unexplained reasons, they eased recovery by giving nothing more than small doses of glucose, Vitamins B or C, Pereston-N and methionine, occasionally adding acetylcholine and methyl-neostigmine sulphate. Quite a therapeutic cocktail! Unless "Pereston-N" is a Japanese brand name for physostigmine, their only apparent use of the latter was in eye drops given to reverse pupillary dilatation. Perhaps as a reward, they chose to give ice cream for thirst, headache, and fatigue and particularly "for recovery from disturbed consciousness and so on (sic)."

It is baffling that the Japanese evidently carried out these treatments without the help of a true antidote. In our studies, doses of atropine no higher than 10 or 12 mg invariably produced delirium lasting 6-8 hours. By all accounts in the literature, larger doses produce commensurately longer periods of incapacitation. In 1945, for example, a health care worker apparently misread a container marked 1 gm" as "1 mg" and gave this enormous oral dose to a U.S. sailor. He was comatose for an unspecified period, and then delirious for most of the ensuing week, but he recovered fully.

Since it is hard to imagine anyone recovering rapidly from large doses of atropine without a dose of physostigmine or some similar centrally active anticholinesterase, I recently tried to find out more about Pereston-N. A Google search of the Internet indicated that it is not physostigmine, but its effects are unclear. (Unfortunately, most search engines have not yet begun to include much of the medical literature prior to 1970, which made it difficult to pursue the question further.)

In any event, the results of the Japanese treatment were only modest. Although the investigators reported substantial improvement in clinical status, they actually classified only about 35% as slightly or significantly improved. This suggests that the reported success of atropine coma therapy by Forrer et al. may also have been overly sanguine.

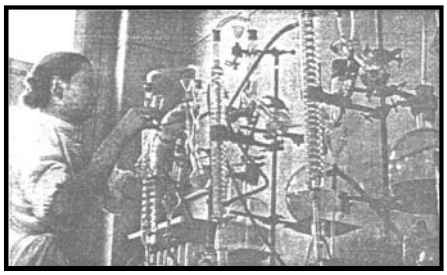
Goodman found still another series of atropine coma treatments for mental illness in the April 1963 issue of the Bulletin of Health Medical Science and History. Authors R. Dolmierski, M.D. and S. Smoczynski conducted their therapeutic studies in the Department of Psychic Diseases of the Medical School in Gdansk, Poland.

They gave twenty-one male and female patients suffering from various psychotic illnesses up to 12 doses of 30-100 mg of atropine. They injected physostigmine, in doses of 8-16 mg (!) 3-4 hours after the onset of coma, supplemented by 2 mg every half hour until the patient regained consciousness. They then used supplemental small oral doses of physostigmine as necessary to maintain a clear sensorium (awareness of time, place, and person).

This Polish study thus reports the use of doses of physostigmine up to four

times the highest dose we ever gave to any of our volunteers. Still, they reported no ill effects, and the patients improved significantly. Nor did the authors report any negative after effects. When one considers that most American clinicians have cautioned against giving delirious patients initial doses of more than 2 mg of physostigmine by injection, the apparently safe use of 8-16 mg is astonishing.

As an entertaining aside, the Polish system of psychiatric diagnostic nomenclature seems very different from the American Diagnostic and Statistical Manual (DSM). I found myself bemused by the diagnosis of "Diencephalosis, hydrocephalus internus, syndrome psychoorganicum incipiens, stratification anancastico-pithiatica." Nevertheless, the 60-year old patient suffering from these conditions supposedly recovered fully after eight comas and returned to professional life. Judging from the clinical description of his pre-treatment psychopathology, the diagnosis in the U.S. would probably have been "obsessive compulsive disorder."



The mysteries of scientific laboratories

In 1962, we had not yet read any of the above reports. They came to our attention much later, after physostigmine had become our standard treatment for BZ and other belladonnoid intoxications. They all remain puzzling in some respects.

First, according to all the authors, their patients recovered in time to engage in occupational therapy the same day, even after immense doses of atropine – up to 200 mg or more. This contradicts our own studies with such compounds. We always observed higher doses to have longer-lasting effects. Doubling the dose of BZ, for example, extends its duration by about 48 hours.

Second, as described by Forrer and colleagues, administration of only one or two doses of physostigmine sufficed to terminate delirium, no matter how high a dose of atropine they had given. In our lab, we found that higher doses of BZ-like drugs required larger doses of physostigmine to reverse their effects. If the authors were reporting correctly, one would have to speculate that there is also some kind of "ceiling effect" for atropine, causing higher doses to "spill over" into the urine. Case reports in the medical literature, however, do not support this idea. Poisoning with large doses of belladonna drugs was always associated with lengthy periods of delirium.

It was bad enough to learn that other psychiatrists had discovered the effectiveness of physostigmine more than a decade earlier. It was even more humbling to discover that even Forrer and his canny colleagues had not been the first to discover physostigmine's clinical usefulness. Dr. Kleinwachter had beaten everyone to the punch!

The indefatigable Sp5 Ephraim Goodman found the doctor's report in an Austrian journal published almost 100 years before both Forrer's group and our own. Fluent in German, Goodman was readily able to render a translation. It was a clinical account of the doctor's experience at the Royal Imperial Jail in Prague.

Professor Kleinwachter was an ophthalmologist, working in a nearby clinic, when the Royal Imperial Jail officials called upon him to help with an emergency. Three inmates had inadvertently poisoned themselves with tincture of belladonna.

Seeking alcohol, the victims had broken into the prison pharmacy, where they found a bottle of clear fluid that appeared to be just what they were seeking. Eagerly, they downed the contents. Unfortunately, the tincture was not merely alcohol, but contained a hefty dose of atropine. An hour later, two of them were

stuporous. The third man had been more abstemious, and was less incapacitated.

The good doctor hurried to the scene and immediately noticed the dilated pupils and other signs of belladonna toxicity in the two most affected inmates. He was accustomed to using tincture of belladonna to dilate the pupils of his own patients prior to a detailed eye examination. When finished, he would add a few drops of Calabar extract (!), knowing it would restore normal pupil size. His patient would then be able to see clearly again before leaving the clinic.

"Hmm…" presumably said Dr. K, after examining the prisoners. "I wonder if what works in the eye would work the same way in the body, and enable these poor wretches to regain their sanity." He decided it was worth a try.

Kleinwachter proceeded to give the most severely affected prisoner a small spoonful of the bitter extract, mixed with a spoonful of sugar (perhaps to "make the medicine go down"). To the second delirious but less severely affected inmate, he gave only plain sugar. Within twenty minutes, the first man became lucid, and was able to describe the theft and consumption of the belladonna extract. The man who had received sugar alone, on the other hand, remained disoriented and unable to communicate. Not only was this a stunning example of serendipity – it was a scientifically impressive demonstration of the doctor's awareness of the need for placebo controls in any good experiment!

Kleinwachter enthusiastically recommended that other physicians, if ever confronted by belladonna toxicity, use Calabar extract (physostigmine). His report, however, never made it into American textbooks of clinical pharmacology. A few late 19th century publications by other authors mentioned physostigmine's efficacy, but thereafter it faded into relative oblivion until the resourceful Sp-5 Goodman unearthed and translated the story.

Calabar extract actually served as a form of "nerve gas" in certain primitive tribes. They used it as an "ordeal" drug, based on the belief that a suspected criminal would die from its effects if guilty, but survive if innocent. Perhaps it really did facilitate the administration of justice. Superstitious belief in its uncanny powers may have induced so much anxiety in guilty suspects that, fearing a lethal consequence, they ironically did themselves in by releasing various stress chemicals. Combined with Calabar juice, naturally released substances might have caused their justified demise!

The "nerve agent" analogy is not so far-fetched. Physostigmine's only distinction from VX and other anticholinesterase poisons is that it is much less potent. Its relative lack of potency is the only thing that makes it impractical for use as a deadly chemical weapon. Like VX, physostigmine alone can be lethal if one administers excessive dosage.

By the same token, atropine could easily take the place of BZ as a "feared hallucinogen" if it were not for the fact that thirty times as much would be required to do the same job – again, a logistical rather than a pharmacological limitation. The bottom line is that nerve-agent type drugs are effective antidotes for BZ-like drugs, and vice versa!

Ditran, briefly promoted as an antidepressant by Drs. Ostfeld, Arguete and Abood in the late 1950s, was another glycolate we later examined with regard to its relative potency and reversibility. In a parallel approach to atropine coma, Ostfeld et al. had given delirium-producing doses of Ditran and reported therapeutic effects. As with atropine-coma therapy, however, "Ditran coma therapy" never caught on.

We also studied the belladonnoid drug scopolamine extensively. Like atropine, it had long been used in general practice, and resembles atropine, but with greater relative central potency. It is also relatively short-acting, making it convenient to work with. Like all the belladonnoid drugs, it too produces delirium and requires only about three times as much as the incapacitating dose of BZ to render a normal soldier unable to function.

After demonstrating the effectiveness of physostigmine in reversing scopolamine delirium, we were curious as to whether other centrally active anticholinesterase compounds would work as well (or possibly better). In the course of their Ditran studies, Ostfeld and colleagues had also discovered that tetrahydroaminoacridine (THA) was an effective antidote. In a small study of volunteers intoxicated with BZ, we likewise found that THA could reverse their incapacitation. Disturbingly, however, we noted minor abnormalities of liver function in follow-up lab tests of some of the THA-treated subjects. Fortunately, these changes were temporary and reverted to normal within a short period. Nevertheless, it seemed prudent to put THA aside.

Chemist Bill Groff – responsible for keeping tabs on treatment medications.

We explored some other possibilities. George Aghajanian tried Thorazine, often used to calm obstreperous patients brought to emergency rooms after a belladonnoid overdose. No doubt, it quieted such patients. In a controlled study of its effects on scopolamine delirium, however, George found not only that it didn't work, but it made things worse. It deepened the stupor and delayed recovery. Thorazine may have become popular, despite a lack of true antidotal effectiveness, because it provided a temporary respite to harried ER doctors.

Dr. Aghajanian also tried the nerve agent GB (sarin) as a possible antidote. It worked quite well, as did VX, another well-known lethal nerve agent. He and Dr. Sidell successfully used both drugs to reverse EA 3580 intoxication. If not for the general public fear of anything to do with "nerve gas," one might recommend sarin or VX as superior antidotes to use in the treatment of drug-induced delirium.

Other drugs that have anticholinergic side effects, such as tricyclic antidepressants and antihistamines, also respond well to physostigmine. I used it with excellent results to treat a young woman whom I saw as a patient in 1974 in the Martin Army Hospital emergency room at Fort Benning, Georgia. She was in a delirious state after overdosing with Benadryl, but her head cleared within a few minutes of receiving a 3 mg injection of physostigmine.

Some belladonnoids are readily available to anyone foolish enough to take them for recreational purposes. Asthmador, for example, is an over-the-counter powder rich in scopolamine and often used by physicians in years past to treat asthma. It also enjoyed a certain popularity among young risk-takers during the hippie years, creating some ludicrous scenes.

My brother (also a physician) witnessed an Asthmador-intoxicated youth in the early 1960s, attempting to crawl across a New York City street, clinging to the trouser cuff of a nearby police officer. Another friend told of similar adventures in Chicago, produced by combining Asthmador with mescaline (of all things). He was out of his mind for two days, and spent a good part of the time running naked from one hotel room to another, loudly banging on all the doors to warn the occupants of an impending atomic bomb. Delirium takes many forms.

Jimson Weed is a natural source of atropine, and is sometimes deliberately

used to produce intoxication, either as a way to get "high" (good luck!) or to induce a "trance" state for spiritual purposes. Witches frequently used it in the middle ages to initiate their wild orgies, and American cattle sometimes ate too much of it, prompting ranchers to refer to it as "loco weed." more often this was Astragalus honii, or Oxytropus, both legumes, while Jimson "loco" weed was more often a drug of abuse in adolescents).

Starting in the 1970s, many authors finally began to comment on the effectiveness of physostigmine in turning off drug-induced delirium. Unhappily, at least for Dr. Ed Crowell and me, they tended preferentially to cite a 1970 clinical report by Dr. Duvoisin. Three years earlier, in 1967, Ed and I had already published the first controlled study of physostigmine's ability to reverse scopolamine delirium in Clinical Pharmacology and Therapeutics. Alas, it seems that those who choose to publish in academically oriented journals rather than mainstream clinical publications such as the Journal of the American Medical Association are sometimes doomed to suffer relative anomie.

Never mind the publicity. We were happy to have found the "handle of the spigot" that turns on the effects of BZ and other incapacitating agents, and then learned how to turn it back the other way, shutting down the delirium that BZ and other belladonnoids can so readily produce.

* * * * *

12 ALTERED STATES IN FISH TANKS AND FIELD TESTS

"What do *I* know?"
Michel de Montaigne
(1533-1592)

Dr. Harold Abramson studied Siamese fighting fish and noted that infinitesimal doses of LSD in their watery environment made them rise to the surface, where they hung open-mouthed for long periods. He also gave it to his private psychiatric patients, and even to his secretary, and published their accounts of its effects. Although the public did not become aware of the fact until many years later, the CIA was actually paying for much of his work (as well as that of many other leading scientists). Back in 1950, Abramson was the nation's leading authority on the subject of LSD – his expertise ranged from its physical chemistry to its "psycho-chemistry."

Other researchers soon became intrigued with the unprecedented potency and exotic effects of the amazing new drug. Some saw a similarity between the symptoms it produced and those observed in psychotic patients. The term "psychotomimetic" entered the English language, becoming a popular addition to the psychiatric dictionary.

The U.S. military was not involved in any type of covert collaboration with the CIA in the early 1950s. Nevertheless, the CIA soon established cooperative relationships with the Army Intelligence Corps. Subsequently, enough crosstalk took place between the Intelligence Corps and the Chemical Corps to stimulate creative thinking as to how "psychochemicals" such as LSD might help the Chemical Corps develop a more humane weapon.

Volunteers enjoy lunch on the day before LSD or BZ

In theory, the notion had much to recommend it and when the Wolff Committee submitted its report in 1955, a research road map seemed clearly marked. Army Chemical Corps scientists were soon venturing into unexplored territory. Since Edgewood Arsenal had facilities for animal testing, an abundance of chemical expertise and a volunteer program that was nascent but capable of expansion, it was a natural choice as a location for LSD investigative work,

And expand it did, as the Wolff Committee report evolved into more concrete plans. Major General William Creasy played the role of fundraiser, mesmerizing Congress into believing that "war without death" might be more than a chemical pipedream. With funds and the go-ahead, volunteer studies began to proliferate.

In the years between 1956 and 1960, baby steps, and then bolder strides, took military testing of LSD from the fantasy stage all the way to field studies. This escalation was probably too rapid, mirroring the CIA's earlier precipitous eagerness to test LSD's operational value. Without a solid scientific base, CIA non-physicians had treated it a bit like a secret new toy in their bag of "dirty tricks." They thought it permissible to surreptitiously spike the bar drinks of unwitting citizens, believing that national defense interests trumped individual civil rights.

Safe to fire even after receiving a drug

Although the early Chemical Corps researchers approached the testing of LSD with more sophistication than their CIA predecessors, they also tended to get ahead of their own expertise. In the late 1950s, Dr. Van Sim and colleagues sometimes gave LSD covertly to Edgewood volunteers. Such studies could be, and eventually were, criticized as lacking in rigorous design, and particularly for their lack of sufficient regard for possible adverse psychological consequences, as well as trampling on the civil rights of the unknowing recipients. Nevertheless, Dr. Sim and his team at Edgewood did carry out some interesting and informative field tests of military skills.

Our own studies, starting in 1961, were likewise far from perfect in design, but we strictly avoided giving any drug covertly. We were, however, still going through a learning period with respect to experimental efficiency. As previously enumerated, there were still many "kinks" to work out. Accordingly, until we upgraded our test environment and completed dose-response studies of the effects of each drug in a controlled clinical setting, we felt it

best to hold back from trying to test military performance.

LSD can make laughter irresistible

By early 1962, we finally felt ready to undertake a small "military skills" study. Three volunteers participated in a three-day experiment. After they completed baseline practice, we gave fairly small doses of BZ, LSD or atropine placebo to each in random order on three successive days. The tasks included putting on gas masks, rifle assembly, and firing an electronic rifle at a target capable of scoring their accuracy. To see how these drugs would affect three soldiers working together, we had them set up a pup tent on the grassy area just outside the ward.

Doing a good job with tent assembly

We included the NF and SC paper and pencil tests to see how scores on these indoor tests would relate to performance on the military tasks. Between scheduled measurements, we let the men relax, play cards and, if not feeling either too confused (or too amused) by the drug effects, eat their meals in the conventional manner.

We found that 1.5 mcg/kg of LSD significantly impaired rifle accuracy. Although on the placebo day the men could easily put on a gas mask rapidly and correctly, they did poorly after LSD. Rifle assembly, a task well learned in basic and advanced training, suddenly became very difficult. Two of the men could not keep from laughing as they were asked to perform one seemingly meaningless task after another.

Volunteers practice putting on their gas masks as rapidly as possible

As expected, cooperating in the pup tent task was no problem during the placebo run, but under the influence of LSD, the group dramatically lost its ability to work together. While one soldier was pounding tent pegs into the ground, another would be removing them. Although eventually they succeeded in erecting the tent, it took them much longer than under placebo conditions. Their performance on the paper and pencil tests (NF and SC) showed similar impairments, paralleling their changing ability to carry out the military tasks.

When the effects of LSD wore off, some volunteers reported a letdown feeling. But the next day, following a good

night's rest, a sense of well-being almost invariably returned.

This small study provided useful "impressionistic" data in addition to objective measures of performance. Conducting more elaborate "field tests" with LSD did not seem feasible, however. It remained for the British, three years later, to carry out a realistic military exercise in which trained commandos attempted to defend their position against an enemy platoon. Details of that interesting study are described in a later chapter.

We found no shortage of literature describing LSD's effects on personal feelings and fantasies. Most of this information, however, came from its use within a therapeutic context. Our mission, on the other hand, required focusing on LSD's incapacitating effects, rather than spiritual insights, perceptual distortions, or transcendental experiences. Measuring the ability to perform as soldiers came first in our list of priorities; tabulation of subjective psychological phenomena, although clinically fascinating, was of secondary importance.

Daniel X. Freedman, MD

Because of increased funding, and expansion of the Clinical Research Department, a reorganization took place in early 1963. The reorganizers created a separate Psychopharmacology Branch and placed me in charge.

I was still the only psychiatrist in the lab, but this was about to change with the welcome arrival of George Aghajanian, who had just finished his psychiatry training at Yale. George was serious about research as a career, having studied LSD and published papers on the subject under the guidance of Daniel X. Freedman while he was still a medical student.

Danny Freedman was one of America's great psychopharmacologists. After writing a textbook of psychiatry with Fritz Redlich, he headed up the Department of Psychiatry at the University of Chicago for many years, later moving to join the UCLA faculty. He also served with distinction as editor of the Psychiatry until his premature death in 1993.

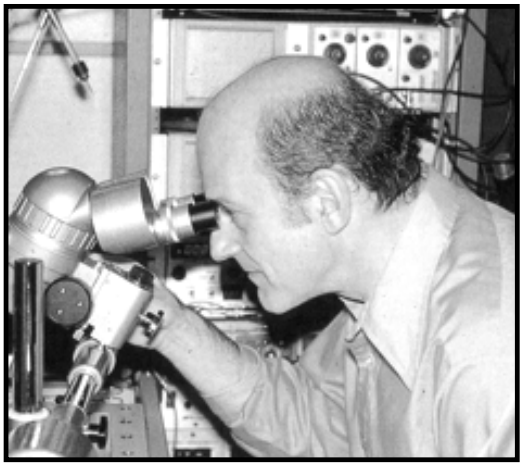
When George answered the draft, he chose to spend his obligatory two years in the Army doing drug research at Edgewood Arsenal. It was soon apparent that, in addition to a dry sense of humor, he had a superior background in brain chemistry. Indeed, I owe him a huge debt of gratitude for what he taught me about drug mechanisms and experimental design. Together, we completed several studies of LSD and BZ-type agents.

George cannot resist writing in a logical conclusion over the text of this ad for Librium

George and I also became close friends. I even persuaded him to take up golf. Although he got off to a slow start (hitting three other golfers with errant shots in a single week), he persisted and became quite addicted to the game. Some years ago, he told me he has many requests to be a guest speaker at conferences, but only accepts the ones that guarantee the availability of a golf course!

Always unassuming, George's profound knowledge of pharmacology and insistence on including rigorous controls in our designs helped raise our standards. Often he persuaded me to rethink an experimental idea. We spent a lot of time together brainstorming appropriate definitions for various drug parameters. Whenever I expressed my beliefs about a pharmacological mechanism, he would listen intently and then sometimes say quietly "Perhaps not." His mild manner of dissent was disarming. George did not hesitate, however, to back up soft comments with hard scientific facts. He once remarked offhandedly that psychopharmacology was "not something to dabble in." He was indisputably correct about that. After 40 years trying to understand drug actions, brain receptors and molecular pharmacology, I realize clearly just how right he was.

LSD proved to be an excellent drug to study in a clinical setting. Its duration of effects was usually only about 12 hours, so it was generally a single-day experiment. In contrast, BZ testing was a marathon procedure, requiring three or more days of round-the-clock close observation.



George Aghajanian, MD. A true scientist, George has become the nation's acknowledged expert on the mode of action of LSD in the brain. He has long been a good friend as well.

In our 1961 studies of LSD, although we carried out a few preliminary inhalation chamber studies, we generally used the oral route. The minimal effective oral dose (MED_{50}) and the average incapacitating dose (ID_{50}) proved to be about 1.0 mcg/kg and 2.4 mcg/kg respectively (i.e., total doses of about 75 and 180 mcg). The latter is less than 75% of the dose that Albert Hoffman consumed in 1943, which brought on his terrifying, but historically unforgettable, bicycle ride home from his Swiss laboratory at Sandoz. (Although this event is periodically celebrated by his admirers, prefacing great historic events with the consumption of 250 mcg of LSD would probably be a bad idea.)

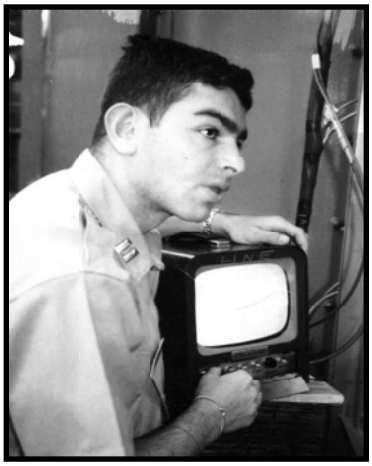
Our subjects spent the 24 hours prior to drug administration establishing physiological and performance baselines, even sleeping in the same rooms where they would be tested. They thus became acquainted with the nursing staff and the responsible doctor, a familiarization process we believed would help prevent "bad trips." If sullen reclusiveness or paranoia developed during the test, a trusted staff member, better than a stranger, could provide effective reassurance. Nevertheless, the behavioral effects of LSD proved to be less predictable than for BZ, at the high as well as the low end of the dose scale.

Because of erratic responses, it was difficult to determine precisely the incapacitating dose of LSD. Unlike BZ, relatively small doses of LSD could affect performance profoundly in a few individuals, while a few others managed to perform reasonably well after higher doses. Most LSD subjects remained alert and at least partially in touch with the environment, while those who received BZ did not, making unpredictability a predictable feature of LSD responses.

This was because LSD-drugged subjects usually retained some mental competence. Their attitude and mood, however, had major effects on their performance on simple tests such as NF and SC. They frequently developed an LSD-induced skepticism about the relevance of such trivial tasks and sometimes they would refuse or not try very hard to complete them. On the other hand, even the most cooperative and highly motivated LSD volunteer could never perform at his pre-drug skill levels while under its influence.

By 1963, we had done considerable testing of LSD by the oral route, but we knew the military was more interested in the effectiveness of the respiratory route. Our first study of aerosolized LSD made use of an ancient "Devilbiss nebulizer," a glass device relied on for decades by asthma sufferers. We partially filled its glass chamber with a very dilute solution of LSD in distilled water.

Our lack of familiarity with the Devilbiss apparatus was soon obvious. The first solution was so dilute that the volunteers had to huff and puff doggedly for almost half an hour to get it all into their lungs. Nevertheless, we observed that once they finally finished inhaling it, the magnitude of response turned out to be roughly one-third that of a similar dose given by the oral route.



Dr. "Bud" Bing tunes the oscilloscope

Oscar Bing, George Aghajanian and I then put our heads together and decided to design a more reliable test of LSD's inhalation effectiveness. We also wanted to ascertain whether different chemical forms of LSD were equally potent. A third objective was to compare the effects of two doses given two weeks apart.

Sixteen volunteers agreed to participate in this two-part experiment. They received various randomly assigned doses of aerosolized LSD, using the controlled breathing technique described in an earlier chapter. The results showed no significant difference in effects between the two forms of the drug. With both chemical forms of LSD, the inhalation route was only about a third as effective as the oral route, which was surprising. I did not expect the rough estimate derived from our crude preliminary test with the Devilbiss nebulizer to prove so accurate.

Strangely enough, three years later Dr. Harold Abramson told me how he had reached almost the same conclusion, using a more or less jerry-rigged method of administration while working for the CIA several years before our Edgewood testing. He estimated that aerosolized LSD was only a third as potent as when given by the oral route. He described his somewhat crude but ingenious technique in an unpublished report he wrote for the CIA sometime in the early 1950s. He entrusted the original typed draft to me in 1966 and it is included in the appendix of this book.

Repeating the same range of dosage with the same subjects after a two-week interval, we observed neither "tolerance" nor increased sensitivity. This was an interesting finding because others had shown that tolerance to LSD develops rapidly when consecutive doses are closely spaced. Probably it is not true tolerance, which generally occurs only after many exposures to a drug. It may be simply the result of temporary desensitization of certain LSD receptors, lasting only until they regain their original ability to respond.

In the early 1950s, for example, when psychotherapists sometimes gave LSD repeatedly to their patients (as in the case of Cary Grant, who published a vivid description of his hundred or more "LSD-assisted" therapy sessions), the effects did not diminish, provided that two or three days were allowed to elapse between doses. Harold Isbell observed this phenomenon at the Addiction Research Center in Lexington, Kentucky, where he did extensive classified drug research in the 1950s and 60s. He received support from government funding (including the CIA). In one study, Isbell gave LSD daily to a group of inmate addicts for up to two months – 70 days in one instance. As an incentive, he promised liberal doses of injectable morphine after the study was completed. In his reports, he mentioned how surprised he was to find that, with repeated daily administration, it took up to three or four times as large a dose of LSD to maintain the same level of effect.

Some critics have cited Isbell's seemingly cavalier experiments as an example of gross mistreatment of volunteers. They assume that daily dosage with LSD is equivalent to some kind of torture. The inmates, however, did not seem reluctant to taking the drug every day, apparently feeling that being given

generous doses of their beloved morphine after each test was sufficient compensation. Isbell found no evidence that his volunteers suffered any damage from their multiple-dose LSD experience. Of course, one might question the ethics of supporting a morphine addict's habit in a facility established to treat addiction.

The author discussing drugs with Dr. Harold Isbell

About fifteen years after our LSD research at Edgewood, Leo Hollister and I collaborated on a study for the California Department of Justice, comparing the effects of alcohol and marijuana on driving performance. In the process, I interviewed more than 200 young male volunteers. One of them, a prime specimen of physical fitness and lucid intellect, told me he had taken LSD virtually every day while he was in high school, simply for fun and stimulation (a surprisingly large number of individuals still use LSD frequently for recreational purposes.)

This volunteer, a picture of mental and physical health, estimated that he had "dropped acid" about 1,000 times – exact dosage not specified, but presumably low enough to allow him to stay in school and graduate. Sporting a crew cut and polite as a West Point cadet, he was also an enthusiastic skydiver, skin diver and competitive orienteer – challenging and potentially dangerous activities requiring peak physical fitness. These hobbies and his earlier frequent consumption of LSD suggested an inherent attraction to risk (as did his volunteering for our drug study).

I suspect that allegations of serious damage to the brain and personality from chronic use of LSD have been overblown. Daily self-administration of other abusable drugs has not usually been associated with demonstrable brain damage, especially after the user gives up his habitual use of the substance.

This does not mean, of course, that anyone would condone giving LSD daily for two months, even if the person were willing or actually wished to take it. There are still many unknowns that ought to give pause to anyone contemplating such a study, including possible adverse psychological consequences. The danger of triggering an underlying psychosis, for example, is real, as Dr. Thomas Ungerleider and others have documented. Furthermore, living in an altered state for extended periods might also alter the way one routinely perceives the real world, not necessarily an advantage to someone who must live in it.

In all our studies, we were concerned about possible "bad trips" as well as the more remote likelihood of uncovering a latent psychosis. When testing LSD, we took special pains to ensure a favorable "set and setting" and selected only volunteers who met the most stringent screening criteria for psychological stability. Nevertheless, some form of hostile behavior surfaced in 20% of subjects given doses above 2.0 mcg/kg (i.e., about 150 mcg). Most lower dose LSD tests, however, turned out to be relatively calm and uneventful.

On one occasion, however, I approached a normally cheerful and friendly volunteer who, despite receiving a fairly low dose of LSD, was clearly feeling its effects. With one hand, I was holding a cardboard cup full of coffee and with the other, a cigarette (concern about smoking was not very great in 1962 – many of us considered it a relatively inconsequential habit, even if we smoked while

working with volunteers). I made a friendly comment and was startled when this normally courteous volunteer assumed a confrontational stance.

"You're a coward," he said. "Your eyes are yellow." He glared at me without blinking.

I tried flashing my most disarming smile. Suddenly his hand flew past my face and my cup of coffee went flying across the room. I was startled, and reflecting that retreat was the prescribed behavior for cowards, I obligingly backed away. His aggressive mood soon subsided and he apologized profusely when the test was over. Perhaps he expected me to file court-martial charges against him for "assaulting" an officer. I hastened to reassure him that he was not a candidate for an "anger management" program, and that he should regard the drug and not himself as responsible for his outburst. Thankfully, such incidents were rare.

In addition to these experiments, George Aghajanian proceeded to see if Thorazine would reverse LSD-induced performance impairment. At the time, Thorazine was still the most widely accepted medication for controlling bad trips. George found that it raised NF scores only slightly and did not shorten the overall duration of impairment. Surprisingly, Thorazine sometimes even delayed the final return of performance scores to baseline.

With Oscar ("Bud") Bing as co-investigator, George also succeeded in devising the first reliable method for measuring LSD levels in the blood, working with a small group of volunteers. The method was based on a fluorometric assay – LSD at the time being among the most fluorescent substances known.

Before he began using his assay technique with volunteers, George was puzzled by the difficulty he was having in obtaining repeatable values using known solutions of LSD. He finally realized that the answer to this problem was to wash the glassware scrupulously and use lint-free diapers, of all things, to dry them. (Obsessive-compulsive patients may take some comfort from this discovery.) Unless the glassware was squeaky clean, LSD molecules tended to stick to its surface, leading to inconsistent readings. After eliminating this "kink," he was ready to begin measuring plasma levels in the volunteers. He and Bud then found that LSD had a consistent half-life of about three hours in the bloodstream. Furthermore, NF scores returned to normal in parallel with the fall in LSD level.

This demonstration of LSD's long half-life was particularly interesting. For years, most investigators assumed it was only about 20 minutes, based on measurements in rats. The (unwarranted) supposition that the elimination rate would be the same in man as in the rat led to some fanciful speculations.

One theory was that LSD produced its effects through a "trigger" mechanism of some sort, causing effects to continue long after the drug had left the body. That seemed quite mysterious, since the subjective effects of other drugs usually did not outlast their presence in the brain. The explanation, some argued, must be some semi-permanent change in the nervous system that remained after the drug was gone.

Margaret Filbert, PhD
After George Aghajanian left Edgewood Arsenal in 1965, Margaret assumed responsibility for assaying LSD, using the photofluorometric method he had developed with Bud Bing. Marge began work at Edgewood as a physiologist in 1950 and in 2007, after 57 years of continuous service she now coordinates Special Projects in the Office of the Post Commander.

Other people thought the opposite: that some of the LSD is "sequestered" in the brain for extended periods, possibly providing an explanation for "flashbacks." Some believed that these small amounts of residual LSD could also cause brain damage. Additional research has fairly well refuted both beliefs. The possibility remains, however, that subtle changes at the sub-microscopic level, perhaps involving specific enzymes within nerve cells, might result from

prolonged, repetitive LSD use. Recent dramatic advances in the field of molecular pharmacology may soon open the door to the resolution of such questions.

In 1969, Professor J. Thomas Ungerleider at UCLA published an article about LSD in the American Journal of Psychiatry. At that time, Dr. Ungerleider was studying LSD users who came, or were brought, to the emergency room because of bad trips. In his article, he stated that unfortunately there was no way to measure LSD in the blood, making it impossible to confirm the diagnosis or to know precisely how large a dose had been ingested.

I wrote a letter to the journal, pointing out that Drs. Aghajanian and Bing had already reported a method for measuring blood levels of LSD. After the editor published my letter, Tom responded, acknowledging that this might indeed be possible in a specially equipped laboratory but was hardly practical in a clinical setting. He was right about that, of course.

Tom was, and still is, a nationally respected expert on LSD and other abusable drugs. We were not personally well acquainted at the time we exchanged letters, but after my retirement from the Army in 1976, we became colleagues and close friends. We collaborated in the preparation of two chapters about substance abuse for academic books and in between, spent lots of time playing tennis together. Throughout my career, chance events have brought me into contact and collaboration with many well known LSD researchers.

While working on this book, I calculated the half-life of LSD by a different method, using data from several dozen Edgewood volunteers whose blood levels were still in my files. I came up with an estimate of 160 minutes, quite close to George's earlier estimate of 175 minutes (based on only five subjects).

In 1969, we recommended long-term reevaluation of our subjects. But it wasn't until 1980 that LTC David McFarling at the Walter Reed Army Institute of Research (WRAIR) published a comprehensive follow-up of Edgewood volunteers who had received LSD. The results, discussed in detail later in this book, failed to demonstrate any clear-cut, long-term adverse medical or psychiatric effects.

McFarling's findings were reassuring. In the mid 1960s, for example, a number of investigators had reported finding breaks in the chromosomes of individuals who had previously used LSD. The implication was that some DNA damage might have occurred.

Examining the chromosomes of some of our volunteers before and after LSD exposure turned up no significant changes. Nevertheless, reports both of chromosome breakage and non-breakage continued until an almost equal number of negative and positive findings had accumulated in about 40 scientific articles.

The argument was finally more or less put to rest by a comprehensive review published in Science in the late 1970's. The author concluded that neither believers nor non-believers in genetic damage had been able to prove their case. Several scientists noted that other drugs, such as caffeine, were also associated with occasional chromosome disruption. Accordingly, the reviewer's conclusion amounted to "no verdict" – a finding sometimes used by Scottish courts – and research on the subject subsequently dried up.

Once, while I was at Edgewood, a district attorney in Brooklyn, New York, called to ask what would happen if someone dumped a large amount of LSD in the local reservoir. I could not resist commenting (with tongue-in-cheek) that if something like that happened in Brooklyn it might go unnoticed. I felt entitled to

invoke the tired "Brooklyn stereotype" since, until age five, I had resided in that colorful borough.

I added, with greater seriousness, that mass intoxication resulting from LSD in the Brooklyn water supply was not a very realistic scenario, since it would require a very large quantity of the drug, and most of it would quickly be degraded by sunlight and chlorination. Nevertheless, now that domestic terrorism has become a dreaded possibility, an anxious public is once again voicing fears of a chemical apocalypse. It may well be that this fear is itself the thing we need to fear, as Franklin D. Roosevelt so wisely assured American citizens more than six decades ago.

* * * * *

13 NAME YOUR POISON: SAFETY FIRST AND ALWAYS

I know which side my bread is buttered.
John Heywood, Proverbs (1546)

It was Kermit's turn to serve. I leaned forward, ready to chip the ball back and storm the net. My competitive self was silently coaching me: "This guy is going down. He shouldn't be winning. He's playing over his head."

It was bad coaching. Emotion was taking over. A few seconds later Kermit hit a hard shot to my backhand. I was moving forward, planning to volley, and it looked like he was going to pass me again. Making an overly energetic effort to intercept the fast moving ball, I swung my body to the left, but my left foot failed to pivot. A snapping sound told me I had done something bad to my left knee.

I was lying on the court, my knee locked in a slightly flexed position. Sitting there, unable to get up right away, I knew a double dose of bad luck had struck. I surely wasn't going to play any more tennis for a while. Worse, the accident came just as I was preparing to conduct a major indoor field test with BZ.

Safety First, indeed!

I sank momentarily into self-pity, never a worthy emotion. Much worse things occasionally happened to the staff. Five years later, a young doctor, recently assigned to our department, would run his car into a steel beam protruding from the rear of a truck paused at a stop light. He never saw the red warning flag tied to the beam in time to stop. It plunged lethally through his windshield, almost taking his head off.

I was in California at the time, spending two years at Stanford as a post-doctoral student, courtesy of the Army. Dr. Fred Sidell, who had taken over as acting Department Chief, told me the horrible story in a letter. I imagined the shock that everyone in the Medical Laboratories must have experienced and felt very sad, but grateful not to have had to endure it all up close.

The moral? While medical research with potent chemical weapons is a dangerous game, it seems that the research staff was at greater risk just dealing with the exigencies of everyday life! Over a period of 20 years, more than 7,000 volunteers spent an estimated total of 14,000 months at Edgewood Arsenal. To my knowledge, not one of them died or suffered a serious illness or permanent injury. That adds up to 1,167 man-years of survival. Statistically, at least one out of a thousand young soldiers chosen at random might be expected to expire during any one-year period. By this logic, Edgewood was possibly the safest military place in the world to spend two months!

At that moment however, I was not really thinking about longevity. I was worried about the upcoming experiment. We were scheduled to launch a 72-hour test with four volunteers, three of whom would receive BZ and the fourth a placebo, in a simulated military setting. Everything had already gone quite well in a 36-hour non-drug practice trial the previous weekend. This would be the real thing.

The hypothesis was that four competent soldiers would have considerable difficulty carrying out assignments in a semi-realistic military environment if three of them were dosed with BZ. If four soldiers ran into a cloud of BZ smoke in a combat area, one of them might mask quickly enough, while the others would breathe it in, absorbing various amounts. What would happen then? Could one man carry the load while his buddies were partially or completely incapacitated?

To keep things simple, we deliberately left antidotes out of the design. We also thought it best to carry out the experiment indoors, in a secure environment. Less than a month earlier, we had tried an outdoor test with some worrisome results. These occurred when Colonel Frank Bauer, Doug Lindsey's replacement as Chief of the Medical Laboratories, approved our request to construct an obstacle course to test volunteer performance in a physically challenging outdoor environment.

The obstacle course included a row of double-layered rubber tires to step through, followed by a series of six wooden hurdles, a 24-inch diameter pipe to crawl through and a long 4 x 4-inch timber rail, elevated on blocks, to traverse. We also added some other outdoor tasks: a gas mask drill, pup tent assembly, dummy grenade tossing and a message to carry across a 90-foot clearing to a sentry guarding a hypothetical headquarters.

Two volunteers participated. One of them was L (who was to be the designated leader in the upcoming 3-day indoor exercise). He had been the least affected of 25 men we had tested at incapacitating doses of BZ. During the obstacle course experiment, he also held up surprisingly well, but was considerably slower and made numerous mistakes. His NF scores, however, never dropped below 60%.

On the same obstacle course, the second man responded more predictably. He needed constant assistance at four hours to keep from falling down and took more than three times as long to complete the course. He arrived exhausted at the finish. Unable to don his gas mask unaided, it took him a full minute to do

so, even with help, compared to ten seconds unassisted before BZ. Furthermore, he was unable to do any meaningful task, including simple addition, for almost 48 hours.

On day two, this volunteer was still mumbling incoherently. He was hardly able to throw dummy grenades, dropping several of them after pulling the pins. Although he managed to get his gas mask on after much fumbling, he took a deep breath of outside air just before sealing it, a fatal error in a nerve gas environment.

When told to carry a message to the "headquarters," he saluted smartly, ran halfway, but then made a 90-degree turn and trotted off into the woods. A corpsman chased him down after about 100 yards. The volunteer explained (in typical "alibi" fashion) that he thought he was told to run the obstacle course. Then, while trying to erect a tent, he again took off suddenly, running at full speed. In other words, he did everything wrong, and would have been a certain casualty if obliged to act alone after a BZ attack.

Given this erratic behavior, we decided outdoor testing carried a significant risk of injury, even with close supervision. As always, we believed that safety concerns should take precedence over outdoor realism.

So that was how we ended up with a specially constructed 16 x 20 foot enclosure in the Graphic Arts Department film studio. From an adjacent room we could watch the volunteers' behavior on closed circuit TV, planning to step in only if necessary to prevent injury. It was the most realistic military environment we could concoct without creating unacceptable risks.

It was, of course, impossible to script a 72-hour movie. Keeping four young volunteers fully occupied for three days with a variety of military tasks and challenges was not going to be easy. Also, as the responsible physician, I felt my uninterrupted on-site attention was required.

What to do? My afternoon had started with a tennis match. Thanks to my competitive reflexes, it appeared to be ending with the cancellation of the most ambitious BZ study we had ever attempted. This test had been my baby from the start. It had required a lot of convincing to get approval from skeptical superiors. Spending the weekend in an orthopedic ward was just not an option.

"Can you walk?" asked Kermit, solicitously helping me to my feet.

"Not without help," I said. "Well, I guess I can hop to the car."

"I'm really sorry," he said.

"Not your fault," I acknowledged grimly. "Pride goeth before a fall. Literally, in my case."

"Here, let me help you into the back seat of my car," Kermit said. "We'll get you to the dispensary."

This cloud of despair might have a silver lining, I thought. Kermit was a surgeon.

"Can't you be my doctor?" I implored. "I've got a big test scheduled and I can't afford an extensive work-up and possible shipment to a hospital in traction."

Kermit was not an orthopedist. Nevertheless, somewhat against his better judgment, he borrowed some traction equipment from the dispensary and skeptically drove me to the film production area. I sat in the car, while he rounded up a hospital bed.

He set me up with weights and pulleys, trying to coax my knee to straighten out. But it turned out to be the knee dislocation from Hell. Although I didn't know it, I would be stuck in traction in that same hospital bed for many days; long after the test was over.

Meanwhile, the Graphic Arts people were arranging their photographic equipment. Several 35 mm cameras stood just outside sliding panels in the walls. The camera operators would open them periodically to record a few minutes of Technicolor volunteer action. Lloyd Matter was making last-minute adjustments of his TV cameras and the monitors that would help us keep track of what the men were doing. My bed and traction equipment were in place. Aspirin, codeine and faithful nurses would get me through the weekend.

The sturdy 16 x 20 foot "communication outpost" was set up inside the much larger film area. For added safety, the floor was covered with inch-thick foam rubber. The furnishings included two bunk beds, walkie-talkie, telephone and switchboard, radio-telephone, an event log, a small desk, a worktable, chairs and a draped-off chemical toilet.

The experiment must go on. Fortunately the clinical staff could handle anything.

On the walls: a medicine cabinet stocked with first aid items, a large situation map, a list of radio words for letters of the alphabet, a gas alarm and a conspicuous "switch" labeled "DANGER – DO NOT TOUCH." A Lister bag full of water hung in one corner, alongside several dozen pre-packaged meals. The room had good lighting, but the camera crew had placed additional high-wattage camera floods above the open ceiling, which they turned on only while filming.

At 0800, the nurses got out their injection needles and cameras rolled. Subject L, the one who had been through the obstacle course test two weeks earlier, was the nominal group leader. He was not as well educated as the others, but since he got the placebo, he would be the most compos mentis. We relied on him to ensure the well-being of the other three men, particularly subject Z, who got the highest dose (about half a milligram). It quickly took effect. Within two hours, he needed L's help to stay upright. Nevertheless, he angrily shook off attempts to assist him. Like most incapacitated subjects, he resented being "treated like a little kid." At that point, of course, almost any "little kid" would have been

better coordinated than he was, but like the chess champion in an earlier chapter, he had already lost awareness of his incompetence.

The other two men received only moderate doses – predictably, they were less affected. Volunteer H, an athletic type, tried to stave off the effects of the drug by repeatedly doing push-ups. C, more lethargic, simply lay on a cot and went to sleep. Both were essentially useless for 24 hours, although they did not become fully delirious.

At five hours, the gas alarm sounded and everyone was supposed to mask. Z, however, didn't respond and wouldn't accept help. For the next two days, he remained disoriented and hyperactive, constantly trying to find a way out of the small "outpost" where he and his fellow volunteers were supposed to work together as a communication team.

Mrs. Brenneman prepares the injection

By the second day, H and C were performing reasonably well. They managed to fulfill most of their assignments, but lacked enthusiasm. L had stayed up all through the first night, protecting Z from his own irrational behavior and other hazards.

At 36 hours, H had recovered sufficiently to take over Z's supervision and L was able to get a little rest. By this time, Z was becoming more active, trying to leave the room through the medicine cabinet, or saluting the drapes that screened the latrine.

"My God, get an ambulance quick – this dumb broad just tried to kill herself," he suddenly screamed, as he tried to revive a canvas gas mask container.

Meanwhile, back at Walter Reed, Dr. Rioch had asked Dr. Ed Weinstein to look in on the proceedings. As a senior investigator in Rioch's lab, Ed had studied language changes in brain-damaged patients. He arrived on Saturday afternoon. Like medical sportscasters, we spent several hours watching and interpreting whatever appeared on the closed circuit TV screen.

By the end of the second day, we were almost out of messages and assignments to relay to the volunteers. I suddenly understood how tough it must be for soap opera writers to keep coming up with new ideas for one episode after another. In an urgent brainstorming session, we put our heads together and came up with an agonizingly improvised scenario.

We told the military communicators to start sending new intelligence to the group inside the room – in a simple code. The messages informed the men that enemy forces were planning to move a train loaded with chemical weapons along a certain route. Observers in the field would continue to send more information as it came in. The volunteers' job was to keep track of incoming messages from various locations, put the facts together, and send their analysis by secure phone line to "forces in the rear."

As a military "scriptwriter," I had no idea what I was talking about, but the communicators, using more authentic lingo, managed to stimulate H's imagination. Soon he was "totally twisted up in the game" (as Queen Latifah humorously put it to Steve Martin in a recent movie).

After awhile, we started believing our own nonsense. Inside the room, L was likewise becoming increasingly engrossed in the fictional scenario. We used poker lingo in the messages, and soon L was energetically trying to puzzle out who "The Dealer" was and what a "full house" meant. It got increasingly complicated. L struggled to formulate appropriate replies, marked locations on the map, and wrinkled his brow as he tried to decipher riddle after riddle.

It was soon time for another film session and the plywood panels slid open. Z didn't understand this camera business and was anxious to explore the new technological threat. Gazing apprehensively through widely dilated pupils and thick glasses, he brought his face to within inches of the lens and stared quizzically into the giant eye of the alien creature.

Nurses review data in the days when smoking was considered normal

Z was unable to unravel the mystery. Whoever or whatever the large-eyed alien object was, it was not speaking. He shrugged, shook his head and decided it was probably a good time to leave. Taking his cap from a hook by the locked door, he put it on and bidding a casual "See you later" to the other members of his team, tried to turn the door handle (it was a ritual he repeated for several hours, always without success.)

On and on went the action while Alan Morrow, one of our psychologists, went on and on taking notes. When the study ended, he would have about 150 sheets of legal-sized yellow paper – a running narrative with dozens of verbatim examples of delirious speech.

Psychologist Alan Morrow times a test

Z remained the center of attention. When he found the door locked, he again attempted to escape through the medicine cabinet. As he contorted his body into various alarming positions, H finally pulled him back from taking a header.

Again and again, Z toured the room, seeking an exit in every corner. And each time, after some offhand remark like "Well, I'll see you later tonight, probably," Z would put on his cap and field jacket and start toward the door. And each time he found it locked, he would become upset. Finally, he turned to the others and announced his conclusion: "We're trapped!"

H glanced up briefly from his reading. "He's getting better," he said to no one in particular, as he went back to browsing through a magazine.

* * * * *

The non-medical "communicators" were still feeding information into the room by walkie-talkie and telephone, and L was still doing most of the work, logging the messages and marking the situation map with a wax crayon.

By this time, H and C were improving and able to be more helpful. Both showed remarkable presence of mind. While affecting lack of concern, sometimes pretending to read, they kept a vigilant eye on Z to be sure he did not panic and create a crisis. L, in particular, went to great pains to make sure Z drank adequate amounts of water, and fed him rations when he seemed too confused to feed himself. Z, of course, did not appreciate this patronizing behavior, and continued to resent everyone treating him as if he were helpless.

There was an audible sigh of relief when the 72-hour experiment finally ended. The cinematographers had lots of good footage and we had lots of vivid examples of delirious military behavior as summarized in Alan Morrow's 150 pages of notes. Later, the Graphic Arts editors produced a 20-minute film entitled "The Longest Weekend" (which probably applied more to the staff than to the subjects). It was widely shown as an illustration of the effects of BZ in a military setting.

After the test, the men expressed the view that Z would not only have been a complete loss to the unit, but an additional burden. They felt his helplessness would have created a great hazard in the field, where uneven terrain, roots, sharp rocks and other environmental dangers would make accidental injury almost inevitable. C suggested that Z would actually be safer tied to a tree but H objected, characterizing this idea as inhumane and likely to worsen Z's condition.

Z, on the other hand, thought it would be a very good idea. He argued that the restraints wouldn't have bothered him, since he wouldn't have known what was happening anyway and wouldn't remember it later. The men all agreed, however, that the mistakes they made in attempting to fulfill their assignments would seriously impair their usefulness in an authentic combat situation. They were also emphatic that if two, instead of one, had received Z's dose, the unit would have been completely disabled in the absence of medical assistance.

We had made it easy for the volunteers by providing for all their basic needs, and scheduling their tasks in an orderly manner within a clearly demarcated "life space." It was clear that greater realism would have shown even more plainly how completely disabled a similar team would be in an actual combat environment. In a more realistic situation, stimulus overload would undoubtedly cripple their capacity to function.

What would they have done? Without an exit barrier, many would probably have behaved like the soldiers Dr. Gaultier had described in 1813. Delirious from the ingestion of belladonnoid-containing berries, many of them wandered into the French bog. Some threw themselves into the flames of their own bonfires. A smaller number of those berries, on the other hand, might paradoxically have robbed them of a desire to do much of anything, without eliciting as much grossly irrational behavior. Low doses could seriously reduce the military competence of an organized force, with considerably less chance of a lethal overdose. A sluggish enemy, in fact, might also be easier to deal with than a totally disoriented, panicky and unpredictable one. The logical conclusion: less might be more, in the use of an incapacitating agent against an adversary.

I advanced this idea at a conference a few years later, but it fell on deaf ears. It seemed impossible to convince commanders that mild impairment of the enemy would make it possible to prevail militarily while limiting enemy casualties. I was sometimes discouraged about the seeming frequency of such disconnects between medical and military thinking.

The lethal potential of each of the drugs we studied was always a concern. In general, we had to rely on animal studies when estimating the lethal dose in man. It was necessary to test several species to be sure that they were similarly susceptible. And even if animal studies suggested a large safety margin for humans, additional factors had to be considered.

Larger animals, for example, are generally more sensitive to drugs. Relative central potency is another factor that varies from animal to animal. Dr. Theodore Stanley, Chairman of Anesthesiology at the University of Utah, recently pointed out to me that rats, for example, are able to survive per kilo doses of morphine that would quickly kill a mouse. The large heart of the rat can push out and draw back in enough oxygen from the lungs with each beat creating, in effect, an internal form of "artificial respiration."

Theodore Stanley, MD – Expert on opioid pharmacology

Most textbooks in the 1960s suggested that deaths from belladonnoid drugs were likewise due to central respiratory failure, even though there were insufficient empirical data to confirm this conclusion. To the contrary, a review of lethal studies of BZ in rats indicated that cardiac, rather than respiratory, failure caused death. Unlike morphine, BZ disturbs the heartbeat, not the ability to breathe. The ability of the rat (or human) beating heart to mechanically ventilate the lungs, therefore, does not apply to BZ.

The loss of heat-dissipating mechanisms (blockade of sweat gland function) may also have lethal consequences, even after normally safe doses of drugs like atropine. If ambient temperature is low, overheating is not likely to cause a fatal outcome. In a clinical situation, therefore, the first concern should be behavioral management. But close attention to temperature elevation remains important. One of our BZ volunteers was overwhelmed by heat even though the ambient temperature was only about 80 degrees. When his body temperature reached 104 degrees, we immediately administered physostigmine. It brought the thermometer back to normal within 20 minutes. As with heat stroke, cold baths or even ice water enemas (!) must be employed if no chemical antidotes are available.

As mentioned earlier, EA 3580, EA 3443 and EA 3167 are belladonnoids that all have a higher margin of safety than BZ, since they do not tend to block sweating at the incapacitating dose. Nevertheless, overheating can occur with high doses of any of the glycolate agents; estimates of the safety margin would therefore be unrealistically optimistic in a hot environment. But in cool climates, we estimated that the lethal dose of BZ would be at least 30-40 times the dose required for incapacitation. Is that a sufficient safety margin?

Lynn Klotz, Martin Furmanski, and Mark Wheelis don't think so. In an article on the Internet, titled "Beware the Siren's Song: Non-Lethal Agents are not Non-Lethal," they draw some conclusions that I contest. For example, they assert that to be conservative, we should compare the dose of a drug required to incapacitate 99% of the target population with the dose that would cause death in 1%. They present a mathematical model that assumes the likelihood of incapacitation to be equal to the percentage of nerve cell receptors occupied by the chemical agent.

The model fails to consider the difference between potency and efficacy. As Dr. Floyd Bloom (among many others) has pointed out, some drugs can produce a maximal effect by attaching to a minority of the cell receptors while others may occupy a majority of the receptors but produce little or no effect. Such drugs may be classified as partial agonists or even inverse agonists. Second, as argued earlier, it may be militarily more useful to incapacitate a small fraction of a target population rather than 99%. The lower doses required for this objective would of course be less likely to fall within the lethal range.

Delayed toxicity is another legitimate concern. Subtle adverse effects are

sometimes difficult to detect after the use of a psychoactive drug. We interviewed subjects and did thorough laboratory testing to screen for worrisome metabolic changes. Psychologist Jim Hart administered comprehensive pre- and post- intellectual tests to 22 belladonnoid subjects to check for possible delayed cognitive deficits. The results showed no significant differences.

What about long-term adverse effects, including disabilities, resulting from participation in a psychochemical test? We know that no serious short-term after effects occurred in the immediate post-test period. However, in isolated cases, subjects reported delayed symptoms. One volunteer described a brief recurrence of the hallucinations he had experienced during BZ delirium two weeks earlier. While drinking beer in a bar, he saw imaginary spiders. It only happened once, however. One LSD subject had paranoid thoughts that outlasted the clinical exposure to LSD by several days, but they cleared spontaneously.

Years later, when outside organizations began to probe for possible long-term effects, news articles carried a number of complaints about flashbacks, depression, headaches, epilepsy, and feelings of unreality. Investigational vigor and media interest were probably instrumental in eliciting many of these complaints. On the other hand, in all fairness, long-term follow-up should have been a routine part of our program.

Some of us did successfully argue for a small follow-up program in 1970, later carried out by Dr. Jack Klapper. It provided for evaluation of 50 volunteers, chosen randomly with respect to drug, but this was too small a number to permit meaningful conclusions. It would be another ten years before the Army would initiate a more searching review of adverse effects attributable to our experiments.

LSD: The first major follow-up study

The Army didn't act to shield itself from further criticism until the mid-1970s, when Congress began to feel increasing pressure from critics. Only then, did its members request a systematic search for possible after effects in former LSD volunteers. Lieutenant Colonel David A. McFarling, MD, a psychiatrist assigned to the Walter Reed Army Institute of Research (WRAIR) in DC, accepted the task. He designed a comprehensive follow-up study of all volunteers who had received LSD under Chemical Corps auspices. In October 1980, the US Army Medical Department, US Army Health Services Command, published his report.

Although McFarling attempted to contact all LSD subjects tested with LSD from 1955 through 1967, it was impossible for him to reach clear-cut conclusions. There were several reasons. Finding a matched group of control subjects, for example, proved to be "a major and ultimately insurmountable" problem. Former volunteers were a mixed group with varied origins and motivations.

A few were officers who had been encouraged to participate as part of their career training. The others were almost all well-screened enlisted volunteers. McFarling noted that most of them were above average in intelligence and health.

Then, too, their reasons for volunteering varied. Since they knew they would possibly receive potent psychoactive drugs, it is likely that most were "risk-takers" who might also be more likely to suffer future disabling or fatal consequences from other adventurous activities. In particular, risk takers are more inclined to abuse alcohol and other drugs, increasing the probability of

accidents and physical illness.

Some of those who welcomed follow-up examinations may have had their own agendas, including claims for compensation. Finally, bias among the findings of the approximately 100 examining physicians was almost certainly present. Some would be more (or less) likely to emphasize the significance of certain complaints. When the results of examinations at three different medical centers were submitted, their statistical summaries differed, which was somewhat troubling.

Despite a thorough computer search, McFarling could come up with names of only 686 individuals who received LSD between 1955 and 1967 (when LSD testing ended). This figure casts doubt on Van Sim's 1961 estimate that he and various contractors had given roughly 3,000 doses to 1500 individuals. It clearly discredits statements by some civilian writers that "2,000" volunteers were given LSD at Edgewood after 1960 "in order to test their response to interrogation by intelligence agents." I know that, after 1960, our lab at Edgewood tested LSD in approximately 100 volunteers. None was subjected to "interrogation by intelligence agents."

From McFarling's list of 686 men, 220 received full examinations and an additional 100 (making a total of 47% of those on the list) returned completed medical history questionnaires. This is a commendable percentage for a long-term follow-up study.

An effort to match the subjects with respect to age, education, AFQT intelligence scores and marital status proved unsuccessful. Only three of thirty men who were suitable matches agreed to spend a week undergoing examination (understandable, since they would receive only minimal compensation). Ultimately, the best McFarling could do was to draw tentative conclusions by comparing the frequency of post-LSD problems with corresponding national averages.

From a statistical standpoint, there was no significant difference between disorder rates in the LSD subjects and national rates for such disorders. Specific medical disorders that suggested a difference occurred in too small in number to be meaningful.

McFarling points out that at the time the report was being prepared, an estimated one to two million individuals in the United States had tried LSD. Many had used it numerous times. Since its publication in 1980, millions more have taken it. (Recent surveys indicate that the number is at least 20 million.) Additional studies by others have failed to identify clearly any adverse medical consequence from this use.

In 1960, Dr. Sidney Cohen's meta-analysis of 25,000 LSD exposures (derived from a large number of published reports) indicated a surprisingly low incidence of flashbacks and a very low rate of suicide. Almost all of them occurred soon after LSD use; suicides thereafter tended to reflect the incidence in the general population.

McFarling's 220 subjects all received a detailed psychiatric interview and a thorough psychological evaluation, as well as an electroencephalogram (EEG). The research team found no consistent abnormalities.

McFarling also failed to find any evidence of chromosome damage or congenital defects. There were no cases of leukemia – a commonly used indicator of toxicity. Subjects who claimed LSD-related infirmities listed a great

variety of symptoms and medical problems common within their age group. Depression, anxiety, nightmares, memory loss, phobias, psychosis, paranoia and personality changes were some of the more prevalent complaints. When considered on a case-by-case basis, these symptoms did not seem linked to Army LSD, given once or twice, many years previously.

The researchers "leaned over backwards" not to "whitewash" the evidence. When it was difficult to make an objective judgment, detailed case histories were included in the report. After reading all of them, I personally found it impossible to draw any firm conclusions.

BZ: Morbidity and Lethality Follow-up

Public and congressional concern about BZ-like incapacitating agents did not attain critical mass until 1979, when the Army decided that a comprehensive review of all subjects who had received "glycolates" would be prudent. It wanted a similar review of anticholinesterase nerve agents and called upon the National Academy of Sciences (NAS) for assistance.

The Board on Toxicology and Environmental Health Hazards of the National Research Council (Assembly of Life Sciences) took on the job. Dr. Frank N. Marzulli set up "blue ribbon" panels to carry out these two formidable analyses. Most members were respected professors of pharmacology, toxicology, and related specialties; others were qualified statisticians and experts in experimental design.

At first, I was included in the Anticholinergic Panel. Later, my role was changed to "consultant," to avoid any appearance of bias or conflict of interest. Between June 1980 and January 1982, I took four round-trip "red-eye" flights from Los Angeles to Washington, D.C. to attend the scheduled panel meetings. In April 1982, the committee published a draft of its report. It noted that between 1958 and 1975, 6,720 soldiers had taken part in the Edgewood program as test subjects. The review panel was able to account for almost 99% of them.

Anticholinergic Agents Mortality Findings

The panel reported on tests of 24 belladonnoid glycolates and related compounds given to 1,800 subjects. (For most of these compounds there were too few subjects to permit statistical analysis.) The charge of the panel was to identify whether:

1. Based on the data and information available, it is possible to provide an answer regarding long-term health effects and/or delayed sequellae, and/or
2. As tested, the involved chemicals are likely to produce long-term adverse health effects or delayed sequellae in the test subjects.

After considering all available data and performing additional lab testing for possible chromosomal and other genetic alterations, the panel concluded as follows:

1. The test compounds surveyed do not appear to have created a direct long-range hazard to human health or normal function, in the doses used at Edgewood. However, a more extensive study would add greater certainty to this conclusion. The high frequency of uncontrolled variables makes it difficult to evaluate possible behavioral effects.

2. Available data suggest that long-term toxic effects and/or delayed sequellae are unlikely.

Ironically, the data showed that fewer deaths occurred among those who received belladonnoids than in those who did not. Furthermore, those who received both a belladonnoid and another agent (unspecified) had an even lower death rate, compared to the expected rate for the general military population. This, of course, is not necessarily an endorsement of any of these chemicals as elixirs of longer life! (The rigorous selection process for volunteers is a more likely explanation.)

A second analysis considered lethality rates in volunteers who received only drugs other than glycolates. The results were similar.

As a whimsical aside, those who want ammunition to support the legalization of marijuana and LSD (or other psychedelic drugs) may draw comfort from the extremely low death rate in volunteers who received LSD only: 1.0 death instead of the expected 7.1. If one combines cannabis, LSD and "other drugs" subjects, there were only 5 deaths among 516 volunteers. The expected number is 21.1. (This might even be statistically significant!)

Equally ironic, atropine and scopolamine were the only belladonnoids associated with a higher than expected death rate – these medications, used for centuries, evidently were "grandfathered" into the list of FDA approved pharmaceuticals. There were 8 deaths among 147 volunteers who received only atropine or scopolamine, noticeably more than the actuarially expected 3.7.

Overall, it appears that volunteers who received psychoactive agents did not suffer premature deaths. The matter of morbidity is less clear-cut. As with LTC McFarling's study, it was almost impossible to reach firm conclusions. No major category of illness was overrepresented in the experimental group. The panel noted that illnesses related to chromosomal or DNA damage, such as the leukemias, had actually occurred less often than expected in those who had received a drug. Additional studies of the effects of experimental drugs on DNA material were also negative or inconclusive.

In their final report, the NAS panel gave the Edgewood volunteer program a provisional clean bill of health, noting the limitations of their investigation. I would add a common sense observation: drugs that produce no toxic effects within days or weeks of single use would seem unlikely to affect one's health 10-20 years later.

Safety among Edgewood Workers

Although none occurred with the volunteers, there were a few incidents in which employees were accidentally exposed to the drugs we tested. One worrisome incident occurred when T, a laboratory pharmacologist, accidentally ingested an unknown dose of long-acting EA 3167. He made this mistake on a Friday, slipping into delirium over the weekend. Somehow, he managed to show up at work on the following Monday and the diagnosis quickly became obvious.

T's accident occurred before we had fully established the effectiveness of physostigmine as an antidote, but we did have tetrahydroaminoacridine (THA) and used it over several days to minimize his delirious behavior. We housed him in our newly constructed padded ward, and watched him closely for two weeks as he gradually returned to an ostensibly normal mental state. I discussed the problem with Dr. Rioch at Walter Reed, who advised me to provide supportive counseling for as long as necessary to ensure full recovery.

T's motivation and efficiency were suboptimal for almost a year. We had no idea what dose he had absorbed. For several weeks, he was somewhat

depressed about not being able to function at full capacity. Eventually, to our relief, he regained his pre-exposure competence and thereafter continued his work as a productive pharmacologist, free of residual symptoms.

Another inadvertent exposure also occurred on a Friday, but not at Edgewood. The daughter of the Commander at Deseret Station, a small post in Utah, was working as a lab technician for the summer. Shortly before quitting time, while transferring solutions, she accidentally drew in a small amount of BZ solution from a glass pipette.

Unaware of the error, she returned to the women's residence, dressed for a date and went to the Officer's Club with her boyfriend. She ate normally, drank a little and even danced. But then she complained that she felt "tired," and her escort took her back to her "dorm." He didn't think she was excessively intoxicated when he left, but in the morning, the "housemother" found her lying across her bed – totally disoriented and incoherent.

At Edgewood, we got a call for help. Major Claude McClure (our acting Department Chief) and I were soon on a plane to Utah equipped with a supply of THA. We found our patient sitting quietly in the equivalent of a large pediatric crib. She was strikingly calm, playing with her fingers as though plucking flower petals, pleasantly mumbling nonsense. She, too, reminded me of Shakespeare's Ophelia, floating downstream in an altered state, blissfully detached from the world.

We decided there was no crisis and simply stayed by her "crib" until the BZ wore off. By Monday, she had almost fully recovered. The Commander thanked us and we flew back to Edgewood. His daughter reported no after effects.

Minor exposures also occurred at Dugway Proving Grounds, where remnants of BZ munitions remained in the soil. Workers sometimes came to the dispensary with "Big Eye" – one dilated pupil – probably caused by a small BZ particle kicked up while walking on the test grid. Physostigmine eye drops were usually sufficient to correct the problem.

There were also a few cases involving accidental contact with nerve agents. One case was particularly educational: a chemist's exposure to the nerve agent GD (soman, a long-acting irreversible anticholinesterase). Fred Sidell handled most of the therapy, using atropine and PAM chloride – the usual treatment for nerve agent poisoning.

The chemist continued to have symptoms for several weeks, while new red blood cells gradually replaced those containing GD. We tracked his cognitive recovery with regular NF tests. Like BZ, nerve agents cause a dose-related impairment in cognitive function, demonstrating that too much as well as too little functioning acetylcholine can impair thinking.

For more than a week, he complained of poor sleep, anxiety and nightmares. We decided to try scopolamine instead of atropine on alternate days, because of its greater relative central potency. The scopolamine produced more improvement in both his subjective symptoms and his NF scores. This suggests that scopolamine might conceivably be preferable to atropine in some cases of nerve agent poisoning. Regrettably, no one undertook to test this idea systematically. Consequently, atropine remains the Army's primary treatment for anticholinesterase poisoning.

One more interesting report should be mentioned in relationship to long-term follow-ups of former volunteers. An article by William F. Page, PhD (Military Medicine, 168, 3:239, 2003) provides an important addition to the

literature on possible adverse effects among Edgewood Volunteers exposed to various chemical agents during the period 1955-1975. 4,022 former volunteers were contacted by telephone and questioned in detail about their health. Those exposed at Edgewood were compared to those who were also exposed to chemicals elsewhere.

No significant differences were found between the health of subjects exposed only to chemical agents and those who were not exposed to any agents or only to other agents. Ther were two minor but statistically significant exceptions (less difficulty with "attention" and more difficulty with "sleeping" among those who were exposed to anticholinesterase agents). Many adverse neurological and psychological effects, however, were reported by those who had exposure to civilian or military chemical agents *outside* of their participation in the Edgewood program. These who reported non-Edgewood exposure to agents (for which no records other than personal recall were available) may have been influenced by recall bias.

Among workers, accidental exposures to toxic chemicals were surprisingly rare at Edgewood, despite spending five days a week close to these powerful substances. This leads one to doubt that brief or limited proximity to nerve gas storage containers during Desert Storm caused nervous system damage in the troops (although some may have been exposed to excessive quantities of depleted uranium). The low casualty rate among Arsenal workers, who for years worked directly with such nerve agents, lends support to this opinion. In any case, the rarity of ill effects was a blessing for which we all were thankful!

* * * * *

14 PROJECT DORK: SOLDIERING ON BZ IN THE DESERT

A small man can be just as exhausted as a great man.
Arthur Miller

November 1964: a month to remember. It began with a major arriving from Washington, DC, bearing a request from a four-star general – not something to take lightly. Soviet trawlers, lurking off the coast of Alaska, were making the Department of Defense extremely nervous. Direct military action was out of the question, of course, but General Dick had other ideas.

From briefings, he knew about the potency of BZ and its long duration of action. He visualized floating a BZ aerosol downwind to a trawler, incapacitating its crew. More amazingly, his idea had backing from the Department of the Army.

It would be an understatement to call General Dick's notion rather strange. On the other hand, what did I know? I thought of Tennyson's description of the brave troops in "The Charge of the Light Brigade," riding fearlessly into the Valley of Death: "Theirs not to question why? Theirs but to do and die!"

I eagerly welcomed yet another bizarre challenge, although it inspired skepticism. The plan didn't make a whole lot of sense, and it offended me on a rational level. On the other hand, the challenge ruthlessly tickled my imagination. As soon as the major left my office (where I had impulsively assured him that this bold operation could be accomplished), I immediately typed out a 15-page task plan, making up the details as I went along.

Meanwhile, the Chief of the Clinical Research Division, the Chief of the Medical Laboratories and the Scientific Director of the Chemical Research and Development Laboratory (CRDL) were all saying "No, most assuredly no!" to the young major. Since he apparently could only take "yes" for an answer, he relayed my lone positive response to a higher level. There, he found his sought-

for approval. The three echelons of bosses above me must have gritted their teeth when they decided not to countermand this "go-ahead" from an unseen higher power! Major Ketchum's future is on the line and he is dumb enough not to care!

Within a week, I put together a more detailed plan, including a list of the personnel I would need for two weeks of testing at Dugway Proving Grounds in Utah. Dugway was about the only place where specialists could test munitions on a seemingly endless desert range, easily large enough to prevent contamination of an inhabited area.

First, however, I felt the need to make a preliminary trip, to consult with the Dugway Post Commander and work out the details with key members of his staff. I was eager to present my plan, discuss the best way to make it happen, and agree on the special preparations we would need. I was, in the words of Whittier's poem, "Well pleased, for when did farmer boy count such a summons less than joy?" – describing the New England challenge of shoveling through a snow bank higher than one's head.

CRDL assigned CPT Keller, a young Chemical Corps officer, to accompany me on the trip to Utah. He was to observe the meeting and lend help where needed. Our enjoyment of the flight, however, was marred by a small glitch that couldn't be ignored without a smile. In accordance with Murphy's Law, as Keller opened the little container of cream that comes with courtesy coffee, it spurted all over the front of his uniform.

Once we landed, we spent more than an hour in our rental car, cruising around town looking for a one-hour dry cleaner, which turned out to be an impossible task at 8 P.M. In despair, we finally stopped at a 7-11, where Captain Keller loaded up on cleaning formulas and sponges. Back at the motel, I slept peacefully while he spent most of the night scrubbing the spots, pausing periodically to dry his official blouse on the radiator.

Project DORK volunteers on flatbed truck breathing with oscilloscopic feedback guidance

The following morning, uniforms acceptably clean; we met with the Post Commander, the Chief Scientist, and half a dozen staff officers. There was some sotto voce jesting about the operation's name – Project Dork – no doubt mischievously chosen by some wag. The implication of this not-so-subtle reference to General Dick, originator of the brainstorm we were about to implement, was clear.

We reviewed the specifications. General Dick wanted an experiment that would indicate whether sufficient BZ could float downwind to incapacitate volunteers 500 yards away. If that worked, he wanted a similar trial to take place at 1000 yards – a distance of over half a mile. I thought it difficult, but possible, and outlined a plan to make it work.

First, I proposed the construction of a special airtight booth on top of a flatbed trailer. The booth would contain instruments capable of measuring the dose inhaled through each volunteer's mask in real time. To insure reliability of the measurement, we would need two identical spectrophotometers. These devices already existed, but hadn't yet been field-tested. The Aerosol Branch at Edgewood had assured us, however, that they could modify and set them up as required without much difficulty.

I sketched the trailer truck, with its airtight booth, moving back and forth on a circular dirt road, either 500 or 1000 yards in radius. In front of the booth's picture window, the volunteers would each be watching individual oscilloscopes, facing the distant BZ source. Full protective clothing would permit exposure only to the aerosolized BZ they would inhale through their open-ended gas masks.

There was more. A strain gauge on each mask would indicate the airflow, and a small tube would divert a sample of the aerosol to the spectrophotometers, designed to calculate cumulative dosage in real time. Airtight Plexiglas windows would provide visual access to the volunteers. Auditory input would feed into each soldier's earpiece from a microphone in the booth.

Standing behind their separately mounted oscilloscopes, the men would receive individual guidance from a crayon curve drawn on the glass. As at Edgewood, this curve was their breathing guide: the scope beam would sweet across the screen every four seconds and would rise and fall as increasing and decreasing amounts of BZ-containing air passed through their individual intake tubes. The task was to control one's respiration so that the airflow would deflect the scope beam precisely along the target line.

A second microphone would allow communication with personnel back at the base station, more than two miles away. This link would keep observers informed of progress or problems, with frequent updates on dosage from the chemists monitoring the two spectrophotometers in the booth.

A helicopter provides rapid evacuation from the test grid to the MUST clinical ward

On and on I droned. Three so-called "Mars" generators (modified Venturi aircraft jets) would disseminate streams of BZ in the general direction of the trailer truck. To deal with vagaries in the wind patterns, the truck would move forward or backward along the circle as required to "track" the cloud. Upon reaching the desired dose the volunteers and booth occupants, all still wearing full protective clothing, would jump into a pickup truck and race across the sandy terrain back to where we had started.

Specialists equipped with decontamination hoses would wash us down and help us strip away our rubbery suits and masks. We would race to a waiting helicopter and be whisked to the clinical area, about 12 miles from the grid. There, doctors, nurses and technicians would be waiting to begin examinations. As I envisioned it, the whole idea was complex but workable.

No doubt slightly stunned to hear what might pass for a Steven Spielberg film pitch, the Chief Scientist and senior officers nevertheless gave their blessings to the proposal. Next, we were introduced to a colonel from the Medical Service Corps (MSC), who told us she had just the thing to house the volunteers and staff. She had just acquired two recently designed, inflatable hospital "wards" that had never been field-tested. She was eager to give them a real-life trial.

Since a plain desert would hardly do for realistic military skill testing, the Infantry colonel who headed the Dugway support battalion offered to create an artificial landscape. No problem. He'd just have his troops transplant real trees, and set up the accoutrements of a real battlefield – a guard station with a crossing barrier, foxholes in the sand and helicopters ready to drop exploding bomblets containing make-believe chemical smoke. He would recruit an imaginative subordinate to write the action sequences needed to test each volunteer's response to unexpected situations.

MUST units, ideal for safe clinical testing

Heady stuff! I examined pictures of the large and futuristic inflatable "MUST" units. Their design was both ingenious and functional. Each unit consisted of a series of semi-circular, air-filled cylinders, creating a structure that looked like an enormous green barrel, half buried in the sand. Each had an airtight airlock entrance. The colonel told us that these rubberized high-tech enclosures could be on site and ready to occupy within ten days.

Flexible tubing would bring filtered air into the MUST units, providing heat or cooling, as required. Designed to protect against chemical and biological agents, the units also served our purposes admirably. An additional floor covering, consisting of inch-thick foam rubber padding, would be added to cushion any falls.

Post carpenters would install interior partitions – one to set apart the nursing staff and another to provide a quiet cubicle for the NF and VITA cognitive testing. An "in-house" bathroom, complete with chemical toilet and sink would be placed in one corner, leaving ample space for the volunteers, their beds and accompanying hassocks for staff. Nothing less than a veritable Holiday Inn, modified to accommodate chemical warfare volunteers.

It was all wonder of wonders! I previously had doubts that I could persuade a no-nonsense Proving Ground commander to put practically the entire Post at the disposal of a lowly psychiatrist. A Hollywood producer might have had trouble throwing together all the features I wanted in less than a fortnight.

Back at Edgewood, it wasn't hard to recruit a first string team. I selected four of my favorite nurses (including, of course, the one with long red hair who had cornered me in the linen closet on the first day she arrived on the job – maybe I'll tell that story later and maybe I won't). Four physicians, six technicians, two administrators, the TV crew, and ten of the "best of the best" volunteers

The entire TV truck was tied down in the bay of the DC-3 all the way to Utah

completed the roster. Early on a Saturday evening, just twelve days before Thanksgiving, we all climbed aboard a military bus. Two hours later we were seated in a DC-3 that stood waiting expectantly on a New Jersey military airstrip.

So what did I feel, as we sat in the sling seats that lined the sides of a giant fuselage, gazing at the mammoth TV truck tied down in the center bay? Maybe just the way I felt in the 4th grade, sitting in a bus headed for the Wonder Bread Factory, where we would get to see fabulous machines, loading endless streams of fresh-baked bread onto conveyor belts. At the end of the tour, workers would give each of us a miniature loaf of bread in tiny, authentic Wonder Bread wrappers, to slice carefully and toast at home. Then and now, I was excited and bedazzled!

We had to make an unscheduled stop in Kansas City, due to ice on the wings and radar malfunction. The next morning, inclement weather prevented take-off and alternate transportation seemed necessary. I discovered that a scenic train was scheduled to leave for Salt Lake in a few hours, and decided to go for it. A call to Edgewood elicited some hemming and hawing, but finally someone in Washington approved the move from plane to train. The TV truck would continue by air when the weather cleared. The whole thing was a totally non-Army-like exception to normal travel regulations.

We made up for the lost day by completing the volunteer performance and physiological baselines en route. Upon arrival in Salt Lake City, a waiting bus took us 80 miles north to desert-surrounded Dugway Proving Grounds.

Meanwhile, preliminary tests with dogs positioned at various distances confirmed that the BZ smoke concentrations would be in the right range. Heart rate changes in dogs provided a reliable estimate of the aerosol concentrations that would reach the volunteers on the truck. The numbers were reassuringly close to what we had hoped for. Everything was set to go as soon as meteorological conditions were favorable. We needed a 5-7 mile per hour breeze, and an "inversion" condition that would keep the smoke close to the ground; fortunately, both wind and weather cooperated.

An Army chopper carried us out to the test grid. Never having ridden in a helicopter I sat, electrified, next to the pilot. The first four volunteers and I suited up in protective clothing and masks, as did the chemists. A pickup truck took us out to the flatbed trailer, where we took our positions and reported in to "headquarters." A minute or two later, a cloud of BZ began to spew forth from the generators.

Eerily lit by searchlights, the cloud was easy to see. It took several minutes to reach us. White, like steam from a kettle, its puffs roiled, growing in size to

the height of a tsunami as it broke silently across the volunteers. While they breathed, we prayed that the calculations were correct. The dosing challenge was akin to floating at least one but not more than three aspirin tablets to a headache sufferer – from more than a quarter of a mile away.

Fifteen minutes elapsed before both spectrophotometers showed that we had reached the target dose. The Mars generators stopped and almost immediately we could see the approaching lights of the pickup truck, racing to hustle us back to the decon station. A thorough hosing and some help in removing our protective gear left us free to high-tail it to the helicopter. As I again sat up front with the pilot, everything seemed like a war movie! Thankfully, the volunteers did not develop symptoms during the 20-minute flight, and as soon as we reached the MUST units, the medical team rapidly swarmed over them, rushing them inside to start their examinations.

Early BZ effects appeared within a few minutes, but the full extent of impairment took several hours to develop. In a solemn dance, the scheduled events cycled eight times, through one-hour, four-segment blocks. First came a medical check during which Subject A was examined by doctor and nurse; they checked reflexes, took vital signs and recorded symptoms and behavior on a checklist.

Back from the test grid, rapid decontamination, and a fast trot to the helicopter

Subject B simultaneously began segment two in the NF/VITA test cubicle, adding numbers and estimating time intervals. Outside, Subject C was engaged in segment three, attempting the first of eight military tasks, such as reporting a vehicle approaching the simulated barrier gate, or masking when a nearby bomblet issued smoke. Segment four reserved fifteen minutes for subjects to eat, drink, use the portable latrine and rest. Rest was obviously desired, but restlessness intervened and by two hours, simple walking was difficult. As the men became drowsy their heads sometimes drooped onto their NF test sheets. They rubbed their eyes to no avail as the VITA scoring lights became increasingly blurred.

When the repetitive cycle of measurements ended at eight hours, two of the volunteers were no longer testable. The other two were impaired, but still able to score above the cut-off that defined incapacitation. By reviewing dots and lines on the poster-sized graphs maintained on the nursing area desks, one could easily keep track of their scores and ratings.

Second MUST unit – reserved for observers

As this complex caravan of procedures moved along without complications, euphoric vibes were detectable in the MUST unit. Members of the clinical staff rotated in 12-hour shifts. Two physicians, two nurses and two technicians were in the clinical area at all times. I was happy to be a seventh wheel, watching the action on the monitors in the other MUST unit.

Lloyd Matter had placed remotely controllable cameras in the clinical area. He also mounted one on a tall, specially constructed TV tower just outside. It provided excellent telephoto views of the guard gate, foxhole, approaching helicopter or smoke grenade, depending on the focus of interest. Two monitors in the second MUST unit provided audio and video coverage of both indoor and outdoor activities for the observers.

Four hours into the schedule, I became aware of a well-dressed civilian from Washington standing beside me. He was studying the monitors intently, asking an occasional question. After a while, he commented pleasantly, "You seem to have this thing pretty well organized." But the next time I looked, he was gone. I still don't know who he was.

The task is to report presence of smoke

The final tally for phase one: two men were incapacitated and two were moderately impaired although still partially functional. Two out of four was the statistically optimal fraction. We had precisely bracketed the target dose. The generators had indeed floated the equivalent of "slightly more than two aspirin" to half the group, and "slightly less than two aspirin" to the other half. A betting man would have considered such a result a long shot at best.

By 72 hours, all four volunteers had recovered. From the graphs, one could estimate that the doses fell between 0.25 and 0.60 milligrams of BZ. I had a silly

fantasy of dozens of Soviet naval personnel sprawled or staggering on the deck of a trawler while their befuddled commander attempted to get things under control. I wondered how General Dick expected the American Navy to know if they had succeeded in incapacitating a Soviet trawler. We had no dose estimates for trawler incapacitation.

Nurses gave physostigmine intermittently to the two most affected volunteers. Whenever they withheld the antidote for more than two hours, scores predictably fell to the untreated level. These observations furthered our knowledge about the effectiveness and duration of physostigmine's actions. We had reached all our goals for the first field test without a glitch and on Saturday, we could release both the volunteers and the medical staff for the weekend. But on Monday, we had to be ready try the test at a 1,000 yards test with a second group of volunteers.

I went over the test results in a review session with the Post Commander, Chief Scientist and engineers. They expressed concern that we might not have enough BZ to reach target levels at 1,000 yards. The first test had used more BZ than expected, and only about 50 pounds remained.

For those who like large numbers, 50 pounds would be enough, theoretically, for 50,000,000 doses, if divided into equal portions and distributed like individual M & M's to a line of people long enough to encircle the earth. But would that be enough to incapacitate even a small town when released in the air? Without getting into complex calculations, I can assure you it would not.

On Saturday, I ruminated some more about the feasibility of achieving satisfactory results at 1,000 yards, where it would theoretically take four times as much BZ to reach the same target dose. However, if the volunteers increased their breathing volume sufficiently, we could cut the exposure time by half, maybe even more.

I rushed over to General Stone's quarters with this idea, hoping he would not be too upset by the weekend intrusion. He was not and, after careful discussion, gave the idea his blessing. Once again, tennis may have played a role. We had played together often when he was a colonel at Edgewood Arsenal. Funny thing about tennis friendships!

At morning staff meeting, the Chief Scientist and other experts finally agreed to go ahead with this proposal. A conference call that included both Edgewood and Washington resulted in another lengthy discussion. Everyone knew that despite our initial success, we were playing for high stakes. But suppressing their initial skepticism, the final decision-makers gave us the approval to proceed

Monday came and new obstacles loomed. Meteorological conditions at the test grid were unfavorable and remained so into the evening. At 4:00 A.M. the following morning, wind speed and atmospheric inversion finally became satisfactory. It was time to wriggle into the elaborate protective gear one more time.

With the new group of four volunteers aboard the pickup truck we solemnly rode across the test grid, bouncing heavily over a moonscape of rocks and ruts. Once in position, we checked out the equipment and radioed that we were ready. Once more, BZ issued from the Mars generators in an expanding stream as the volunteers began tracking their respirations on the oscilloscopes. As feared, the initial dosage build-up was disturbingly slow. Headquarters radioed gloomily that the supply of BZ was dwindling fast and might be insufficient to deliver the required dose.

"Okay, guys" I said, over the mike set up to address only the volunteers. "You'll need to jog in place. If you start panting, so much the better. Just keep breathing as deeply and rapidly as you can without getting lightheaded." Soon, the spectrophotometer dose readings began to rise more rapidly and I thought, "It's like one of those sinking submarine movies." In my fantasy the screen script reads: "camera shows depth gauge hovering in the red danger zone – switches dramatically to show the crew scurrying to throw out everything movable. They have already dumped the ballast. Suddenly the depth gauge shows that the submarine is rising…" I visualized the formulaic happy ending where the sub, against all odds, miraculously reaches the surface.

The 5-mile runs the men had hated back at their home installations seemed to be paying off. They jogged for almost 40 minutes, gulping large volumes of air through their masks. Almost at the instant the BZ supply ran out, the chemists announced that we had reached our target. We were soon back in the pickup, bouncing toward the decontamination site, ready for the wash-down and the helicopter ride to the MUST units. This time, because we had been so long on the grid, the men were already showing a slight rise in heart rate. Fortunately, there were no accompanying behavioral changes.

When the helicopter landed at the MUST unit, the men could still walk, talk and (had we thought of it) chew some gum – to keep their saliva flowing. The rest of the protocol went as smoothly as the first time. Remarkably, just as with the other group of volunteers, BZ again incapacitated two of the four men, and only moderately affected the other two. Providence must have decided to smile on our endeavors. By Thursday, Thanksgiving Day, we declared the test a success and released the volunteers and most of the staff.

There was still one day left before our flight home on Saturday morning. On Thursday night, one of the senior Dugway officers threw an open house celebratory party. Everyone was sky high. We danced with the nurses and congratulated ourselves. When the party broke up, my adrenaline was still flowing. As an impulsive final flourish, I decided that we should write our summary report the next day and have it in finished form before our plane departed on Saturday morning.

Although short of sleep, the other team physicians were willing to make this final effort. Around midnight, I called General Stone at his home, told him what we intended to do and requested some clerical and artwork assistance. He hastened to call in two secretaries and four graphic arts specialists and provided us a suite of offices to work in.

At six in the morning, the other doctors and I were dressed and ready to start writing. We already had the large composite graphs showing performance scores, physiologic measurements and the effects of treatment with physostigmine. The artists took over and immediately started re-drawing each graph in a more professional format. It took them all day to finish the eight composites.

Sitting around a large table, each doctor took on a portion of the manuscript. I edited the segments as soon as they were drafted and passed them to the secretaries. Both were typing furiously, virtually nonstop. We worked continuously, pausing only briefly for sandwiches, until four o'clock the following morning. The seemingly tireless secretaries continued to pound the keys like crazy, somehow managing to keep up with us.

When we finished, we had roughly 100 pages of typing and graphic illustrations, covering all aspects of the testing. There were still a few hours to

sleep and prepare for our flight. When we awoke, a clerk had made ten Xerox copies, neatly stapled. I casually handed one to Colonel Stone. He almost forgot to wish us good-bye, seemingly bewildered by the hundred-page report in his hand, completed in less than 24 hours, only two days after two of what must have been the most other-worldly field tests ever carried out at Dugway Proving Grounds.

"I think we should all be promoted to colonel," commented Dr. Barry Tharp. "And you" he jested, "should get at least a star."

Back at Edgewood, I left a copy of the report at the quarters of Medical Lab Chief, Colonel Joe Blair, and went home to crash. Project Dork had been completed almost exactly one month from the day that a persistent major from Washington had come to Edgewood with a bizarre request from a four-star general!

While dozing off, I pictured myself standing on a hillside, looking out over the Utah desert, imagining that Russian spies were watching. Perhaps they were drinking vodka and joking among themselves about the very idea that the US military was contemplating neutralizing one of their trawlers with a cloud of BZ. How could they have been so skeptical?

A last look back at the Utah desert.

Project DORK: The Movie

After two weeks of sky-high unreality at the "Utah Desert Olympics," it was hard to return to the realities of daily life. Like mighty mite Mary Lou Retton, who finished her last vault at the 1984 Olympics with a perfect 10.0, we felt we had "stuck it" on the sands of Dugway. The TV "rushes" – 15 hours of documentation – included a great variety of technically excellent close-ups and cover shots. More important, they provided an audio-visual record of volunteers struggling with realistically designed military tasks. They graphically showed how BZ could usurp the ability to stay upright, check an ID at a barrier gate, or detect and report a smoking bomblet or a low-flying helicopter.

A few days later, the infantry colonel's scoring of the military tasks arrived in the mail. He had been required to rate them "blind," because there were deliberately no time stamps on them and Lloyd had re-recorded them in random sequence. Nevertheless, the colonel's judgment of military competence in each scene conformed closely to the corresponding NF score. The Edgewood cognitive tests once again proved to be good predictors of performance in the field.

I wrote letters of commendation for everyone who had helped in the project. Perhaps it was no surprise that the CRDL commander was in no hurry to pass them along. He waited six weeks and needed several reminders before he finally signed them – another signal that the "management" was not exactly thrilled. Clearly, there were still some residual fumes about my getting a go-ahead from some "dream-weaving" four-star general who had overruled their vocal opposition.

Complying with the wishes of a four-star general without support from one's immediate superiors does little to increase one's popularity. General Dick allegedly wrote a letter of commendation for me personally, but somehow I never received it. My new boss, COL Nick Bottiglieri, however, wrote me a nice letter of appreciation.

I should point out that Nick had a great sense of humor. He was also

supportive and easy to work for. One day, Fred Sidell and I dropped by his office at lunchtime. He was studying some notes, and enthusiastically told us about his newfound ability to remember the details of any medical journal article by reading it two days in a row! As he spoke, he casually took a Dexedrine pill with a sip of coffee. Nick was sure a fun, hard working guy!

Although we'd completed our report of the on-site test results, the data continued to come in, providing information about aerosol concentrations, breathing volumes, and other numbers needed to make estimates of the incapacitating dose under field conditions. Calculating the aerosol incapacitating dose (ICt_{50}) was one of the major objectives of the exercise. Happily, the effects at 500 and 1,000 yards were consistent with predictions, and almost identical to the indoor aerosol results at Edgewood.

One task remained. I was eager to make a film to preserve the drama of the Dork project experiment, but wanted to avoid excessive braggadocio. I recalled James Joyce's advice in his 1916 novel, Portrait of the Artist as a Young Man, that a creator should remain "within or behind or above his handiwork, invisible, refined out of existence, indifferent, paring his fingernails." I decided to clip mine a bit shorter.

Assembling "Cloud of Confusion" from video clips. From left: Phil Kysor, Dr. Dave Sawhill, the author, and Dr. Barry Tharp

With Nick's support, the film was funded. Cloud of Confusion seemed like a good title. I spent about a week creating the storyboard and script, deliberately trying to imbue it with an aura of mystery.

To set the tone, the film opens on a dark screen. There is a lengthy silence. Slowly, eerie music swells up and an Orson Welles type voice mechanically intones: "On this very desert…" etc. Gradually, a white wisp of smoke becomes visible on the left, growing larger as it spreads across the screen.

Next comes a series of rapidly changing scenes, accompanied by increasingly agitated music: a volunteer staggering at the barrier gate, another reeling with ataxia in the MUST unit, a third slumped over an NF test, struggling against overwhelming drowsiness. Then, an accelerating crescendo of stumbling, confusion, incoherent speech, the dropping of uncooperative gas masks and the eventual surrender to stupor. The music hits an abrupt climax and falls silent. Once again, the screen fades to black.

We recorded the middle segment live in the studio, with the studio director playing the role of field commander. He begins by calmly reviewing the test procedure, with Dr. Barry Tharp wearing his professional white coat. As Barry describes each test, the director inquires about the significance of various details. He wants to know everything about the experimental design; how the dose was calculated and how it was regulated on the test grid; how physostigmine manages to reverse incapacitation. Barry carefully answers all his questions with the help of colorful analogies, simple graphs and hastily penciled notations on a desk pad.

The third "movement" in this symphonic pastiche shows the effectiveness of physostigmine as treatment, followed by a post-test discussion – four volunteers and

a doctor seated around a table The volunteers, in turn, try to estimate the probable effects of the drug they'd received, if they were in an actual combat situation. All agree they would have been totally ineffective for at least 24 hours.

Their thoughtful and articulate comments reassure the viewer that these intelligent soldiers have fully recovered. A closing scene echoes a quiet passage from Bartok's The Miraculous Mandarin and ends with a wide-angle view of two relaxed volunteers, casually tossing a football back and forth in the deepening twilight of the Utah desert.

I couldn't wait to show the final kinescope of Cloud of Confusion to everyone who had been with me in Utah and, particularly, Nick Bottiglieri. He was visibly bemused by the melodramatic content, particularly the mysterious music and War of the Worlds styled narrative. When it ended, and the lights came on, he hesitated. "It was good, but a little... (he searched for the word)… psychiatric." I ruefully had to smile. What did he expect from a psychiatrist?

It was my purpose to create a contemplative, suspenseful mood in order to heighten interest, hoping to distinguish this movie from the usual dry Army documentary. In retrospect, perhaps I was overly optimistic about the cinematic sensibilities of the intended audience. Alternatively, I may have been overly impressed by my own artistic brilliance.

Despite all, officers in the Munitions and Army Materiel commands, as well as representatives from Great Britain, Canada, and the European NATO nations subsequently viewed Cloud of Confusion. I didn't hear much feedback except a rumor that "the French liked it" (not surprising, somehow). The film probably lies buried deep in a vault somewhere. I sometimes wonder wistfully if anyone will ever see it again.

An intriguing postscript to the Dork operation was a telegram from a civilian in Utah who wanted to share his expertise with our laboratories. Its wording raised the suspicion that his roof might have been missing a shingle or two (as they say). As far as I know, no one responded to this well-intended communication, but it seemed like an interesting piece of memorabilia, and I tucked it into the project folder.

The tab for the week of film production by Logos Studios came to about $13,500. Hardly an extravagant expenditure, considering that the actual adventure in the desert at Dugway Proving Grounds had allegedly cost more than a million dollars! In the upbeat opinion of the medical team, the Army got full value for its money.

* * * * *

I HOMESTEADED NORTH OF LUND UTAH YEARS AGO AND WAS TURNED DOWN ON A RESEARCH PATENT IN 1939 BECAUSE I WANTED A RESEARCH PATENT, BUT THE PATENT LAWS WOULD HAVE HAD TO BE CHANGED I HAVE THE DRAWINGS OF A DEVICE WHICH WILL NEUTRALIZE THE GAS OR IT CAN BE MADE ON THE BATTLEFIELD BY ALL MEANS DO NOT DESTROY IT OR SHIP IT TO SEA TO SINK, BEFORE YOU FLY A MECHANICAL ENGINEER A CHEMIST AND A SCHIENTIST (sic) TO LOUISVILLE KENTUCKY. EVERYTHING IS READY TO SHOW YOU.

Unsolicited but interesting idea

15 RUMMAGING THROUGH THE CLOSET

To travel hopefully is better than to arrive.

Sir James Jeans

Like forgotten shoes and seldom-worn sweaters, dusty memories come tumbling down as I run my hands along the closet shelf marked "First Six Years at Edgewood". Each is a story, too short to fill a chapter, but keenly bright in my recollection. Here are a few I remember most vividly.

Computational Drifting

Working on experimental data at Edgewood drew me relentlessly into a deepening vortex of mathematics and other abstract domains, such as electronic circuits. I would often visit the Biostatistics Office and talk to John Atkinson about his LGP-30 computer, and how I could learn to use it. It was a monstrous device, one end taking in long ribbons of paper punched with holes that told it what to do and the other end typing answers without fingers on another role of paper, like the tapes that activate a player piano.

By 1962, I was bombarding John with more and more questions, at times slowing his productive work to a crawl. He decided to persuade Medical Lab Chief Colonel Frank Bauer to send me to Philadelphia. There, Elizabeth Schoff, professor of computer sciences at the University of Pennsylvania, was asked to set aside a week to tutor me.

Since Dr. Schoff was under contract, I suppose it behooved her to drop everything and oblige her Edgewood contract officer. I don't think she was particularly happy about this, but she responded graciously. Nice as she was, however, I began to feel I was reliving initiation week at my fraternity house. Suddenly, I was grasping a ping-pong ball with my naked butt and doing the face-up lobster relay at top speed across the dayroom and back. Well, maybe it wasn't quite that bad!

"This is called the accumulator," she said, making movements in the empty air like a delirious patient on BZ. "It has space for eight bits, and is really the heart of all the action."

I nodded soberly, thinking I would no doubt understand this eventually.

"In order to get numbers into the accumulator, you must use only eight bits for each command."

I contracted the special facial muscles acquired during eons of human evolution to signal comprehension.

"Unfortunately, four bits are needed to show the address of the memory location you are referring to." She paused to evaluate how much dismay this might be causing. "This leaves only four bits with which to express your command." Another pause. "That's not very many, is it?"

"Seems like enough," I said, affecting deep understanding.

"Don't forget the single parity bit," said Dr. Schoff, reminding me that I didn't know everything.

The lessons were starting to form an endless loop. "…Add one to the accumulator… Subtract one from the accumulator…If the accumulator is greater than one, jump to location xxyy, where there is an additional instruction…After the right series of commands, the accumulator will type the letter "A."

This, it seemed, was what was meant by "machine language." A cave dweller could out-talk this apparatus just by grunting, I thought. But there was no room for a cynical attitude; I had only five days to absorb two weeks of computer wisdom. By day three, I began to feel the need to seek treatment for a bad case of ones and zeros. Unfortunately, there was no crash cart available for this affliction.

Dr. Schoff kept saying I was doing really well. But compressing a two-week course into five days was like packing five quarts of ice cream into a one-pint container. When I got back home, I decided that the next time I felt like being a programmer, I should take a nap and review my opportunities more cautiously.

John continued to overestimate my mathematical skills by persuading me to take an extension course with him. It was enticingly listed as "Functions of a Complex Variable" and required the purchase of a textbook entitled Conformal Mapping. The syllabus warned that students should not undertake this course without having worked through three years of calculus – John convinced me that in my case one semester of elementary calculus, more than a decade ago, would suffice.

I was soon trapped in the world of imaginary numbers and gradually acquired a startle response whenever I heard a sonic boom. I recalled how Mark

Twain once described his life as that of a blind man groping along in a tunnel, periodically bursting into roars of laughter. This somehow prompted me to ask Professor Metzer how a blind man could tell, "Conformal Mapping-wise," which way he was going in a tunnel. I thought it was a good question, but his eyes appeared to dim with sympathy. And at the end of the course, he also gave me a sympathy grade of "D." He was indeed a compassionate professor.

Math mysteries continued to plague me. If I crammed too many statistics into my head, I ran the risk of trespassing on the psychologists' sacred stomping grounds. I became afraid of using non-parametric tests of significance. I had previously devised a quixotic Total Response Index (TRI), and the purist psychologists had revolted! Despite all, my lifelong fondness for mathematics persisted.

Well, I might forget calculus, but a trip to England was going to be much easier to remember…

Dandelion and Mead

T.S. Eliot may have been wrong when he wrote that, "April is the cruelest month."

I am walking in Hyde Park and here in London, April is being surprisingly kind. I am jet-lagged, but the London sun on the daffodils and forsythia in Hyde Park seems to sweep away the mental fog. No matter that a chain of mix-ups has preceded my arrival…

Toward the end of 1964, British scientist Dr. Bill Ladell invited me to visit Porton Down, where the secret Chemical Defence Experimental Establishment was located. Bill thought I would find it useful to observe an LSD field test, which was designed to test the ability of highly trained LSD-dosed commandos to defend their position against undrugged "attackers."

Porton Down – British Chemical Testing Laboratories

Because I didn't know enough to send it by airmail, my letter of acceptance took almost two months to arrive, and by then the field test was history. Nevertheless, Bill said I was still welcome to visit. Meanwhile, the bureaucracy had added its own internal screw-up so that when I arrived, no one was expecting me. "You've picked the worst possible week to come," said Dr. Ladell, when I called him at Porton. "We're going through an inspection – maybe you could come next week." He now had two good reasons to be annoyed.

In addition, MI-5 itself had not been told I was coming and I narrowly escaped immediate deportation. More charitable heads prevailed, however, and I was allowed to stay in London for a week while awaiting clearance at Porton. I had no choice but to check into the nearby Officer's Club, where cigarettes cost a dollar a carton and a friendly maid brought tea right to your bed every morning. I wrote long letters home, visited museums, and listened to self-styled orators debating Leninism in Hyde Park. And of course in the evening there was always a bevy of English girls hanging around "Terry," who was nattily dressed in his tuxedo, singing bawdy songs at the grand piano and laughing at his own jokes. It was surprisingly easy to talk with the young women, and speculate with them about adventurous things to do.

The next week, at Porton, I was assigned a VIP room and treated like a dignitary. I attentively viewed the film of the LSD exercise. On day one, having taken placebos, the commandos showed their advanced training to advantage and easily overwhelmed the attackers. On day two, after 150 mcg of LSD, their performance deteriorated rapidly. The radio operator soon became uncooperative and paid little attention to orders. Others ignored their assignments. One climbed a tree. By the end of the first hour, the officer-in-charge said he could no longer control his troops and declared himself a casualty. No doubt about it – LSD could disrupt even the most elite troops. On the third day, back on placebos, the commandos once again functioned like well-oiled fighting machines.

Curiously, the research staff was willing to stage a realistic military exercise with LSD, but seemed timid about trying it with BZ. Their tests with the latter involved only low-to-medium doses. Lacking any padded rooms, they were reluctant to work with delirious subjects.

One of the women on the research team was in the process of testing a slightly woozy volunteer. He was having difficulty solving more than a few of the simple addition problems on a Number Facility form.

Side trip to mysterious Stonehenge

"It's interesting that you're using the same performance measures as we do," I whispered.

"Didn't you know?" she said. "We got them from your protocols at Edgewood."

"Really?" I replied.

"Yes, indeed," she smiled. "I believe the Canadians are also copying your methods."

After touring the lab, we proceeded to lunch in the richly paneled dining room, its tables covered with fresh linen and elegant silverware. As was the custom, staff officers were casually helping themselves to lunchtime cocktails. Eschewing ice in their drinks, the Brits simply added a bit of soda to a finger or two of whiskey, using a pressurized silver soda dispenser. When I tried to do the same, I squeezed too hard and produced a firehose effect, soda water splashing everywhere. English propriety took over – most smiles were stifled, but many of the officers could not resist chortling. My guide Roger Brimblecombe was howling with laughter and my ineptitude won me instantaneous acceptance. I even overheard someone describe me as a "splendid chap."

After lunch, Roger, widely known for his own work with drugs, led me through his lab. It was not his lucky day. Roger had planned to test an antidote agent in an anesthetized cat but embarrassingly, the poor animal unexpectedly expired before he could complete the experiment. Equally bad luck interrupted his planned cardiac study with another cat, which succumbed for unknown reasons on the operating table. Undaunted, we discussed his earlier research and decided to meet later for a game of squash. Next came tub baths (in separate tubs) – the British seem to prefer them to showers.

At the Silver Plough, a quaint country pub, an astonishing variety of local

alcoholic beverages was available, most of them unfamiliar. Roger persuaded me to sample a glass of dandelion wine. When I commented tactfully that it was "interesting," he insisted I also try something called "mead." After I managed to ingest that one, my interest in alcohol subsided for the rest of the evening.

Earlier, I had spent considerable time with psychiatrist Max Hollyhock. He had just published his views on mescaline and LSD in The New Scientist, a slim but widely read opinion magazine. In his article, he advanced cogent arguments for the use of psychochemicals as humane weapons; it seemed, however, that few readers had found this proposal particularly appealing.

Along with other statistics, Max had calculated the amount of aerosolized LSD that would be needed to incapacitate everyone in an area roughly equal to a third of a square mile. It turned out to be an enormous amount.

I later learned that, in spite of his maverick opinions, Max was subsequently appointed as a senior official in the British equivalent of the FDA. Before leaving the UK, I visited his home at the southern tip of England. In the course of two weeks, I had managed to see quite a bit of English life, and left the British Isles reluctantly. But it was important to get home and back in step with our own fast-moving program and our new team of high-energy doctors…

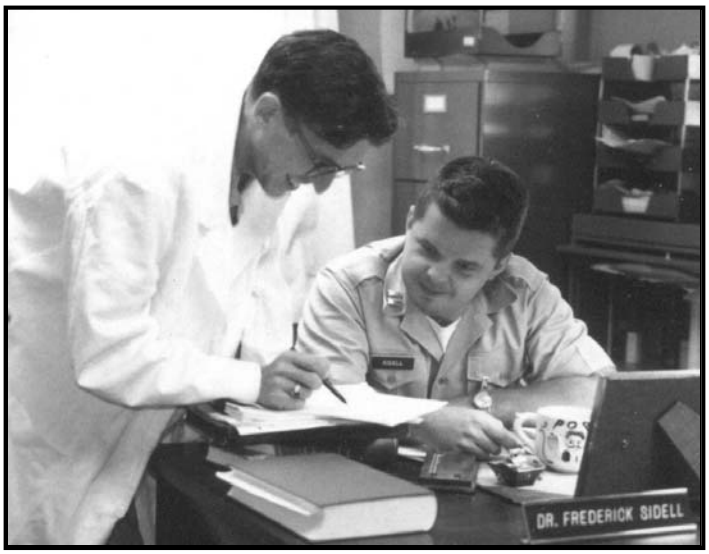
1963-65 - Working Out With the "A Team"

Reminiscent of the trajectory of a launch into near orbit, the Edgewood volunteer program rose to an apogee between 1963 and 1965. The powers-that-be liked the results of BZ testing enough to provide more money, a bigger staff and many new drugs for us to test. Our momentum increased in 1964, when Dr. Fred Sidell joined the Department. He was strong as a tokamak (a massive mechanical pressing device), eager to work, and blessed with a head full of ideas. Although he had just finished his residency in internal medicine, it was clear that he knew what he was doing. Within a year, he was running the Clinical Investigation Branch, where research focused mostly on the treatment of nerve agents.

Dr. Frederick Sidell – Leader of the "A-Team"

Fred also played a little tennis. His motto on the tennis court was the same as in the lab: "Invictus!" In one game, I fed him a drop shot and he tried so hard to get it that his feet slid under the net. Not only would Captain Sidell prove to be a fireball of energy on and off the tennis court, but he also did Edgewood Arsenal a

big favor by continuing to serve as a civilian for an additional thirty years. He became the acknowledged national expert on nerve agents, working as teacher, editor, and government consultant. When he retired in the late 1990s, the Sidell Learning Center was built at Edgewood Arsenal in recognition of his exemplary career.



Dr. Arthur Hayes discussing results with Fred Sidell

The years from 1963 to 1966 were filled with exploding creativity. Depending on when and where you looked, you could find Fred injecting mice with nerve agent antidotes at 4:30 A.M. or George Aghajanian refining the world's first reliable method for measuring LSD blood levels. Not far away, you might see future ophthalmologist Dave Harper trying out chemical eye drops that could restore visual acuity in BZ subjects, or veterinarian Millard Mershon using a micro-syringe to apply precise doses of a belladonnoid drug to the skin of a volunteer.

The "A-team" was always in motion. Art Hayes, internist and former Rhodes' Scholar, precisely measured the effect of atropine on the EKG. Barry Tharp, future professor of neurology at Stanford, studied EEG tracings, looking for the elusive "14 and 6" wave patterns thought to be markers of psychopathic traits. Engineers in the aerosol lab busily fabricated inhalation devices that could produce LSD in various particle sizes. And I…well, I was here and there, devising incapacitating agent studies, taking LSD, briefing visitors, and inventing reasons to make movies.

We worked hard, but we also found time for fun. We had picnics and barbecues where our families ate hot dogs, played softball, and hurled Frisbees. Phil Kysor made a home movie of one of these gatherings, proving statistically, to a high level of significance, that chemical warfare research did not inhibit playfulness. Rather, it significantly elevated the "esprit de corps" index.

All soldiers, including officers, were obliged to pass a physical proficiency test every year. Among other torments, this included push-ups, ladder traversal, grenade tossing and a one mile run against the clock. Many of the physicians resented this requirement, often not bothering to show up as scheduled. Predictably, we received a Disposition Form (DF) sternly criticizing this mutinous behavior

Although a mere major, as Chief of the Psychopharmacology Branch I felt obligated to refute the insinuation that we were unfit. Most of us were active in sports, and some had been outstanding athletes in college. Dick Fencel, for example, had earned varsity letters as captain of the VMI baseball team, quarterback on the freshman football team, starting guard on the basketball varsity, and a javelin thrower on the track team. Barry Tharp had come close to equaling the national record in the half-mile. I was captain of the Post tennis team, Bud Bing was on the Post pistol team, and Dave Sawhill (the violinist and music major) had made it to the state finals as a heavyweight wrestler. Surely, this proved that although we were doctors, we were physically fit.

Since I generally seem to take to troublemaking as readily as Tigger took to Roo's medicine in Winnie the Pooh, I composed a stinging critique of the proficiency test and sent it off to the CRDL commander. It included a challenge to "any and all pusillanimous non-medical officers at the main labs to a game of basketball, volleyball, or sport of their choice at a time and place of their choosing." My boss, "Fiery Nick" Bottiglieri, was entertained by my impudent DF and recklessly added his own pugnacious endorsement (medical doctors, you see, instinctively sense that they are above the law).

A scathing rebuke came back from the CRDL commander noting that the "ability of a bunch of muscle-bound doctors" to defeat less athletic officers in such a contest proved nothing. In any event, it would in no way be an acceptable substitute for the official fitness test. The tone of his reply contained no hint of humor.

It dawned on me that perhaps I had been overreaching. Obediently, I rounded up the reluctant docs and we all went out to take the prescribed tests. Not surprisingly, some of us could not even meet the minimal standards of fitness. Once again, an act of hubris predictably came before a fall from grace!

This humiliation did not cure my learning disability in the area of proper behavior. In 1964, with Christmas Holidays fast approaching, I persuaded the padded ward staff to help create a parody of our own scientific craziness. TV engineer Lloyd Matter agreed to record an action-filled episode of a commercial hospital soap opera, removing the sound track. After viewing it once or twice, a few doctors and nurses joined me in dubbing improvised dialogue over the silent video. On the screen, handsome doctors and beautiful nurses silently scrambled to deal with the restless antics of a bed-ridden patient.

Our superimposed dialogue converted the patient in the soap opera into a never-before-seen BZ case. While he thrashed about in a foment of excitement, the on-screen doctors and nurses frantically suggested, debated, accepted and rejected NF testing and treatment with physostigmine. Background laughter further compounded the dubbed-in confusion. Pleased with our perversity, we contentedly watched the playback as we munched ice cream and cake.

Best little lunchroom in the whole town of Edgewood

A week later, fun and games with the TV recorder ended abruptly when photos from Playboy appeared on the closed circuit monitors. Lloyd found himself on the Post Commander's carpet, receiving a cautionary reprimand, after which sobriety and propriety promptly returned.

We were not as out of control as it might seem. Most of the time, we were actually quite serious and disciplined. We maintained high research standards and kept good records. Just to be sure, however, the Surgeon General established an outside panel to review our plans and activities. The members were blue-ribbon types, respected academicians from the civilian community.

The panel spent a full day listening to summaries of our findings, and ambling thoughtfully through our facilities. Their verdict was highly favorable and their written report to the Post Commander resulted in letters of appreciation

to those who had made presentations. It was reassuring to learn that what we were doing measured up to prevailing ethical and safety standards.

Although I was not practicing clinical psychiatry, some MP's, at their wits' end, called upon my services one afternoon. A young enlisted man, for reasons unknown, had insisted on getting in their way all day. When asked what his problem was, he simply remained mute. "Would I see him?" They brought him to my office, where I hustled to resurrect my therapeutic skills.

"Hi," I said. "I'm Dr. Ketchum. What seems to be the problem?"

The young man looked at me suspiciously and remained silent.

"I'm a psychiatrist," I said, "and I'd like to help you if I can. But you need to talk to me so I can understand your problem."

That didn't work either. I tried a few other compassionate ploys but silence seemed to be the gold standard for this young man.

"Okay," I said. "It looks like maybe you should be in the hospital for a bit, until things get sorted out." I picked up the phone, called one of the Walter Reed residents, told him I was sending him a patient for evaluation, and advised the delighted MP's to whisk the recalcitrant trooper to the hospital.

When he heard this, the young soldier suddenly started talking, and, once he got going, seemed unable to stop. He was floridly paranoid and clearly delusional.

"I appreciate your situation," I said. "But it's a little too late to go into all that right now. Besides, you need to be in the hospital."

"Can I call a lawyer?" he asked, as the MP's gently guided him toward the door."

"No," I said, and went back to whatever I had been doing.

News of this intervention spread around the Post. The next day, I started getting requests from several other individuals for therapeutic advice. One colonel reported that his cat had vomited that morning and viewing this had made him vomit in turn. I declined to schedule him for evaluation, suggesting that he go to the Post Dispensary.

The demand for my services eventually evaporated, as I continued to make it clear that I was not open for psychotherapeutic services. Overnight stardom was not hard to attain, but it was also not so easy to extinguish. In the offing, however, was a chance to mingle with some real LSD research stars, unlikely to dim any time soon…

The Man from Amityville

I'm not sure how it started, but in early 1965, I began exchanging letters with Dr. Harold Abramson, one of the most well known LSD pioneers in the United States. Aware of our studies with LSD, he asked if I would like to attend a conference he was organizing. Many illustrious LSD experts from all over the world would be there for a three-day exchange of data and opinions.

I said I'd like very much to attend, and added that I had videotaped a fascinating post-test discussion among four LSD volunteers (presented fully in an earlier chapter). Although the test had no therapeutic intent, one member of the group, had, with coaxing, been persuaded by the others to admit his feelings of

shame whenever he had fantasies about the nurses. I cited one dramatic moment when he described how the effects of LSD made him feel like he was inside "a little acorn," with the whole world suddenly coming "PLOP" down on top of him.

Dr. A. was intrigued. After he reviewed the entire transcript, he immediately invited me to show and discuss the videotape at his conference. Regrettably, the Edgewood security people were unwilling to allow this degree of publicity, but otherwise approved my attendance. At the meeting, 30-40 researchers whose names I had previously seen only in journals, met in a luxurious conference room. I gravitated almost immediately to Dr. Daniel Freedman (George Aghajanian's mentor) and our long discussions at mealtimes marked the beginning of a valued friendship.

Sometimes I impulsively spoke out of turn. After one prestigious speaker's presentation, I took issue with the lack of a control group in his study. He seemed a bit irritated. At intermission, I drifted uneasily over to the conference chairman, Dr. Frank Fremont-Smith, who was chatting with Dr. Abramson.

"I hope I wasn't out of line with my comment," I said, aware that I was probably again speaking out of turn.

"Not at all," said Abramson.

"Youth is a wonderful thing," said Fremont-Smith. "You shouldn't worry about speaking up."

I was relieved. ("Age can also be a wonderful thing," I thought to myself later).

The meeting transactions subsequently appeared in a volume titled "The Use of LSD in Psychotherapy and Alcoholism." It was published just after tighter government restrictions had essentially ended LSD's previously permissible therapeutic use.

Abramson continued to be quite friendly. He invited me to visit him at his home later in the year, to converse further. When I arrived at his house in Syosset, Long Island, he gave me an unpublished draft of a report prepared for the CIA fifteen years earlier. He also talked about his involvement in the treatment of Frank Olson, the CIA biologist who had been slipped an LSD mickey in 1953 by MK-ULTRA chief Dr. Sidney Gottlieb. He became paranoid and two weeks later ended up dead on the sidewalk ten stories below his hotel room – allegedly a suicide.

As we chatted in the back yard, Abramson told me not only about his former work with the CIA and other educational and research experiences, but even the secrets of growing the Zoysia grass that provided a lush green footing beneath our feet as we walked and talked. I left carrying a folder of his unpublished research and permission to use it as I wished.

A hand-typed manuscript (mentioned earlier) detailed the ingenious method he had used to estimate the effectiveness of aerosolized LSD. Using a small breathing chamber, and washing down what was left after the subject had inhaled it for a minute, he was able to calculate the amount retained in the lungs. Then, estimating the intensity of the response, he concluded that the inhalation route was about one-third as effective as the oral route. Fifteen years later, with the benefit of much more sophisticated technology, we reached the identical

conclusion!

I told him I wanted to try LSD myself, since it appeared that all the other researchers had, and asked him how much to take. He said that 50 mcg would probably have an aphrodisiac effect, while 100 mcg would probably produce some anxiety. I resolved this Hobson's choice (professionally speaking) by taking an intermediate dose, as described in a previous chapter.

Later I invited Abramson to give a lecture to our research group at Edgewood. Strangely, he limited his talk to his work with Siamese fighting fish in an LSD-spiked fish tank. I had expected more than a fish lecture and afterwards he made a request that took me aback.

"Do you suppose you could get me about ten kilos of Army LSD?" he asked, in what appeared to be total innocence.

"What do you have in mind?" I said.

"I have this tremendous curiosity about what fish in a reservoir would do if I dumped a large amount into the water."

This was the nuttiest idea I had ever heard, especially coming from the mouth of such an internationally renowned expert. I was not even sure the Army even had that much LSD. Nevertheless, I put his question to our lab chief. The answer took about ten milliseconds to come back quite loudly in the negative.

That was my last significant encounter with the good doctor. But my mind was already headed elsewhere, thinking of a way to talk the Army into sending me back to school…

Prospecting for Pribram

In mid-1964, while the pace and complexity of work and the number of experiments were growing exponentially, my fantasies were also quietly multiplying. I was concerned about the absence of any systematic linking of brain function to drug activity. It would be wonderful to be able to establish such connections between the drugs I was studying and corresponding pathways in the brain, but my knowledge of brain function was limited. Both electronic circuitry and neural nets were still beyond my comprehension.

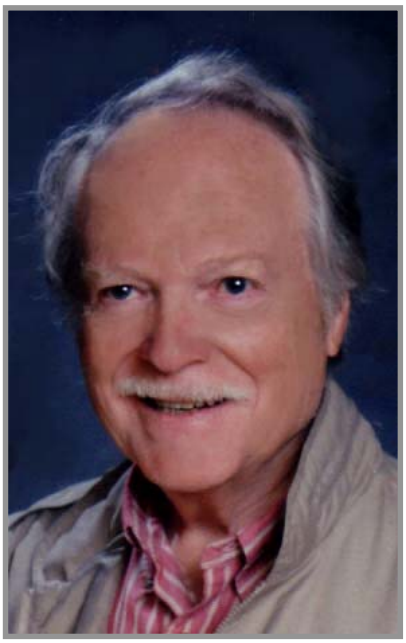
Ignoring a chronic tendency to become overly fond of my own ideas, I decided that it wouldn't hurt to try for a post-doctoral fellowship. I wrote to Colonel Bill Tiffany, Consultant in Psychiatry to the Surgeon General, laying out a vision of what I could do for the Army, and perhaps for science itself. I re-read that letter recently, and had to smile at the lofty verbiage I had strung together to support my case. Here I was, unashamedly asking for a two-year "sabbatical" while still on active duty.

Any competent neuroscientist should have recognized the arguments I presented as sophomoric fantasy. But I had somehow developed a reputation for being gifted within the military's higher psychiatric echelons. My request actually received serious consideration. Perhaps it was because I had emphasized that I was likely to return to Edgewood with a completely new set of neuropharmacological tools – cutting-edge methods that would allow me to make meaningful inroads into the underlying mechanisms of psychochemical drugs – for the benefit of all.

I was amazed to receive this preliminary encouragement. It did not take

long for me to make appointments at Stanford and UCLA. I wanted first to talk with professors whom I considered to be at the frontiers of brain-behavior relationships. Although I failed to evoke much enthusiasm at UCLA, Karl Pribram at Stanford was quite receptive. He said he would be happy to sponsor me if the Army agreed. I was welcome to spend two years in his neuropsychology lab, assuming he would not be obliged to provide a stipend. (Karl was always acutely concerned about cash flow.)

I continued to keep my hopes alive through 1965, writing follow-up letters to all those who would be involved in the final decision. Amazingly, everyone seemed willing to buy into my academic dream. I passed unhindered through all the doors. It was almost as if I were doing the Army a favor. By the start of 1966, my orders had all but been stamped "Approved." I would spend two years in Pribram's lab at Stanford, pursuing nothing but my intellectual curiosity, in "civvies," drawing full pay and allowances. My only military duties would be to submit quarterly progress summaries.



Dr. Theodore McBride Badgley, my psychiatry mentor and good friend

Only in the Army, it seems, do such idealistic dreams fail to end with a rude awakening. As my old mentor, Mack Badgley remarked later with a headshake and a smile, "I don't know, Jim – the things you get away with!" Which reminds me of still another unconventional undertaking that began as a game of bridge…

Game Boys

Chuck Wickstrom came into my life sometime in 1964. He was a physicist who ran the Radiological Physics branch across the "campus" from our laboratory. There was nothing in our respective professional assignments to connect us. We just happened to meet at a weekly duplicate bridge event at the Officer's Club.

Right away, I found Chuck intriguing. For one thing, he had too much energy, a fascinating trait. Not satisfied with his responsibilities as Branch Chief, for example, he traveled to Baltimore three evenings a week to teach college classes in astronomy.

His primary passion, however, was games: card games, board games, chess games – you name it. He had a tall Sears' storage cabinet filled with box upon box of games, and he had played them all. He even wrote to the game inventors, suggesting improvements. Modestly, he mentioned that he had played over 90 games of "International Geographical Politics" (or something like that) with his wife and written down every move in every game.

Chuck seemed almost like a humanoid computer without enough "batch-processing" tasks in his queue and available for additional programming. It was not difficult to interest Chuck in our volunteer testing program.

"Tell you what, Chuck," I said. "If you would teach a group of volunteers to

play lightning chess, we could see how drugs would affect such a high level skill."

"Tremendous!" he said. "When do we start?"

Chuck found time to teach 12 volunteers the essentials of the game, and had them play each other at the rate of 10 seconds per move, until he could rank them in a win-loss probability table. We then gave six of them 35 micrograms of LSD and had them play against the other six, to whom we gave placebo. Two weeks later, we repeated the procedure, giving LSD to the opponents. Still later, we used a similar crossover design with 1.0 milligram of oral scopolamine instead of LSD. In each study, these relatively low doses of drug produced substantial performance changes.

When the next group of volunteers arrived, Chuck suggested using "D-Day," a less structured board game that required the strategic use of military assets. Once again, the drugged individuals were relatively ineffective. Scoring, however, was a knotty problem. Chuck devised a "blunder index" which clearly identified the drugged teams, but before he could finish his analysis, he received orders to Viet Nam. Sic transit gloria Wickstromi (Thus passeth the glory of Wickstrom!).

I still have his unpublished experimental data in my filing cabinet. Years later, I came across a journal article reporting the effect of LSD when given to chess masters. The results were very similar, suggesting again that even the best brains lose some of their analytical powers in the presence of relatively small doses of LSD.

Poor judgment, of course, does not require an intoxicating drug. I observed this phenomenon in a distinguished professor who managed to behave foolishly, even while in full possession of his faculties.

The Kligman Capers

Our program was running hot by mid-1964 – lots of volunteers were testing lots of drugs. We were, in fact, pushing the envelope of our capacity to provide padded environments, which were necessary for those who sometimes needed watching for as long as a week or ten days. Although we were working in an annex, our annex needed an annex.

Professor Albert Kligman

A ready-to-utilize testing site was available at Holmesburg Prison in Philadelphia. Dr. Albert Kligman, Chairman of the Department of Dermatology at the University of Pennsylvania, had been using the prison inmates to test various skin lotions, for which he was receiving generous stipends from various pharmaceutical companies. It turned out later that this arrangement was somewhat lacking in professional accountability (as documented in Alan Hornblum's carefully researched Acres of Skin). At the time, however, Edgewood scientists considered

Kligman to be an illustrious researcher – he had even published a widely used textbook of dermatology. Nick Bottiglieri sent Dick Fencel and me to Philadelphia to meet Professor Kligman and assess the lay of the land.

Holmesburg is a large, maximal security prison. When first I passed through its massive gates and entered its gray interior, I felt a moment of apprehension. I had never been in an OZ-like prison before, where men who had committed serious crimes were allowed to wander around outside their cells. Some were physically close enough to throw a punch, which kept me on high alert. I was surprised to find, however, that we were never harassed with catcalls, funny looks or hostile gestures, much less physical assault.

I soon learned why these dangerous men moved aside respectfully as we passed among them. Although Kligman paid only small sums for skin testing, the prisoners considered him to be a walking ATM. (Not surprising, considering that prisons pay almost nothing for a days work.) It was understandable that when "the Man" walked by, he and his guests were granted friendly deference.

Sol McBride was Kligman's administrator. He was slick and canny and empowered to select volunteer inmates for skin tests, giving him considerable status among the prison populace. As we proceeded to the two mobile homes he had modified to accommodate his experiments, Kligman commented, "We've done lots of productive research here, Jim. Thank goodness, we have Sol here, who really knows how to make sure the tests run smoothly. I'm sure we can do some good work for your group as well." He seemed like a sincere, idealistic man.

"That's great," I said. "Can you modify one of your trailers for us? We need two padded cubicles and a place for staff to keep medications and record observations of the men we test. They're not the sort of drugs you have been dealing with. Men can get temporarily delirious on some of them, and need a special environment to prevent injuries."

"Whatever you say, Jim, we can do. Just give us the word and we'll get right on it. We don't have any problem with the men we test. A little money can buy a lot of cooperation."

Back at Edgewood, Dick and I reported that the lay of the land at Holmesburg was attractive and neatly maintained. It looked like a good place to do quality testing. As promised, Kligman and Sol McBride soon had one trailer refurbished just as we wanted it, with padded rooms and padded floors. Inside, across from the cubicles, was a nursing station. It had large unbreakable windows through which doctors and technicians could unobtrusively observe the subjects.

The initial testing was cautious, mainly establishing the minimal effective doses for each of a series of new belladonnoids. Sometimes, however, the quality and quantity of on-site staffing was not what it should have been. On one visit, I became quite upset with the prison staff's lack of expertise regarding psychoactive drug effects. Dr. Kligman came down to Edgewood to meet with some of us and discuss this problem.

As we sat down to talk, Kligman became the model of obsequious cooperation. At 33, I felt like a brash youngster alongside the illustrious

professor, textbook author and experienced researcher. But I did not hesitate to criticize frankly the deficiencies I had observed.

Kligman was immediately penitent. "Jim, we can do a lot better. I promise you. Whatever needs doing, we'll do."

"You need a properly qualified psychopharmacologist on the staff," I said. "The quality control and completeness of the data you are providing is unsatisfactory." Here I was, lecturing an esteemed professor, and he was being remorseful. Clearly, he knew how to hang on to lucrative contracts. He agreed to hire a drug-savvy research-oriented physician to supervise the studies whenever there was no Edgewood physician on-site.

That sounded good but what he did was to hire Dr. Herb Copelan, a private practice, non-research-oriented internist, on a part-time basis. This was less than optimal, but it was easy to understand how difficult it was to find a fully trained psychopharmacologist willing to take on a temporary prison job (with no retirement benefits). Since Kligman had corrected most of the remaining deficiencies, I had no further complaints.

Around this time, a euphoric but occasionally absent-minded young doctor from Brooklyn named Dave Kitzes answered the draft and joined our team. At 26, he was very bright and already a life master in bridge. His shrewdness at the bridge table, however, did not always carry over to the experimental ward.

I asked Dave to accompany me to Holmesburg when we began work with EA 3167, a particularly long acting belladonnoid. The first doses were very low, causing only minor changes that cleared overnight. We upped the dose slowly, and when the effects did not increase appreciably, raised it another 20%. By this time, I was leaving Dave at the prison after the first few hours, to continue supervising. He returned one Friday afternoon in an expansive mood. The latest increase in dosage had unexpectedly produced delirium.

"It's working great," Dave said. "Both of the inmates were actively hallucinating when I left." He smiled, expecting me to share his enthusiasm.

"Are you kidding?" I said. "Get back in the car. We're not going to leave anyone in a state of delirium without providing treatment. They should both be getting physostigmine. Who knows how long their delirium will last if untreated?" I was more than mildly pissed off. Our goal was limited to producing only mild to moderate effects. Fortunately, with repeated doses of physostigmine, both of the Holmesburg men were kept in a relatively lucid state and follow-up psychological testing six months later showed no residual cognitive effects.

Another thing I was interested in was the incapacitating dose of atropine itself, historically the "natural mother of all belladonnoids." We did not have sufficient data on atropine to make precise comparisons with the synthetic belladonnoids. We therefore put on the schedule several volunteers who met all the screening criteria.

The inmates referred to one of them as "Snooks." He was a very large, very powerfully built man with a history of drug-related problems, but none of them were recent. Actually, it was almost impossible to find inmates who had never been addicted to one street drug or another. Although drugs were always obtainable in the prison, few inmates could afford to maintain a heavy habit. Just to be sure, however,

we routinely checked their urines before giving them any experimental drugs.

Although imposingly muscular, Snooks had a mild disposition. I felt he would be a satisfactory subject. His partner on the test, a slightly built former heroin addict with a placid temperament, also seemed unlikely to be a problem. Nevertheless, I always felt more secure when physical backup was nearby.

An inmate who had murdered his wife in a fit of domestic rage some years ago had agreed to assist me and, in particular, to provide security. A skilled wrestler who had earned a college degree, he was a model prisoner. He certainly seemed qualified to deal with disoriented or unruly subjects.

In the morning, I injected atropine into each subject's deltoid muscle and waited for the onset of the usual symptoms. Nothing happened for about ten minutes. Then, a loud yell came from Snooks' cubicle, temporarily bolted to keep him from wandering while disoriented.

"I want the antidote, I want the antidote!" he shouted.

"It's okay, Snooks," I calmly replied. "It's common to have some brief discomfort with this drug. It'll pass in a few minutes."

There was a brief period of silence.

"Everything okay, Snooks?" I inquired a bit nervously from outside. There was still no answer.

Suddenly, the solid, heavily padded door of his cubicle flew off its hinges and landed flat in the open area. Two seconds later, there was Snooks, standing about four feet in front of me. It would be fraudulent for me to claim I was unmoved by this demonstration.

"Doc, I'd like the antidote now," he stated calmly, in a measured voice. I noted that his body language seemed non-threatening but paradoxically this made him appear even more dangerous. I tried not to contemplate what he would do if I refused his request.

"Sure, sure, Snooks – that's just fine, we'll get it for you now, right away. It'll just take a minute, only a minute," I said in as cheery a voice as I could muster.

While Snooks quietly seethed, barely an arm's length away, my assistant the wife-killer remained in his booth. At this point, I doubted that even a heavyweight college wrestler could handle a man of such massive proportions. If Snooks were so inclined, he could probably convert me into an interesting teaching case on an orthopedic ward.

Fortunately, Snooks was also a surprisingly patient man. He waited calmly while my assistant drew physostigmine into a syringe and handed it to me to inject. Even before it could take effect, Snooks quietly returned to his bed and made no further trouble. The thick, unhinged door, however, continued to lie flat on the floor – a poignant tribute to his door-busting ability.

Throughout this crisis, Snooks' partner in the adjacent cubicle remained half-asleep and in no apparent discomfort. He later said that he had enjoyed the atropine very much, and wouldn't mind doing it again. He said it reminded him of the pleasant effects of heroin. By this time, I was thoroughly confused, but at

least my heart rate had worked its way back to normal.

As a postscript to our efforts at Holmesburg, the "eager-to-please" Professor Albert M. Kligman eventually found himself in considerable hot water about some of his dermatological studies. To quote from the August 5, 1966 issue of Time, "[Dr. Kligman] was noted to be investigating new drugs for no fewer than 33 manufacturers and the FDA's Dr. Frances O. Kelsey (of thalidomide fame) began to wonder how thoroughly and carefully Kligman & Co. could do all that work."

Further investigation revealed that Kligman had reported tests on three groups of prisoners, but he could only find the records for two. In addition, he had reported blood tests on "patients" who were not even in his "hospital." For only the second time in its history, the FDA struck a doctor's name from its approved list of researchers. My earlier criticism of the quality of the work he was doing may not have been so outrageous after all.

Bringing out the Artillery

My first tour at Edgewood Arsenal was ending. On my desk were orders to spend the next two years at Stanford. Adding to the good news was my promotion to Lieutenant Colonel on 29 June 1966.

Fred Sidell arranged a farewell party and asked the medical officers in the department to bring poems relevant to my departure. The one by former Rhodes Scholar Art Hayes best captures the gemütlich ambience of the lab where I had spent almost six years. I take the liberty of quoting a few stanzas here:

ELEGY WRITTEN AT EDGEWOOD ARSENAL

The siren wails the end of work today;
All office lights are out; the wards are still;
The volunteers have left to sleep or play;
The safe's been locked and doubly checked by Bill.

No one remains behind for all is done,
Save those with special duty to derive;
The aidmen 'til the light of morning sun
Are ever vigilant, at two one two six five.

And in the awesome office of the chief,
The Major seeks new ways to data process,
Resolutely armed with the belief
That calculators bring us all great happiness.

And in a padded room across the way
A wand'ring volunteer remains on test,
His NF scores will hopefully display
Which of the agents tried is truly best.

Their crisp and starchy uniforms of white,
The nurses plan to wear another time,
When called upon to help from morn to night,
And play their role so faithful and sublime.

The laboratory benches now are quiet,
No samples in the autotechnicon,
A respite short, before the next day's diet
Of cholinesterase and on and on.

The psychologists have all departed too,
Their MMPI's mark their bailiwick,
Those tests whose cryptic answers tell them who
Is really quite OK and who is sick.

* * *

A copper plaque will one day mark this site
Beside the waters of the Chesapeake,
And throngs will read with unabashed delight:
"'Tis here stood Clinical Research" – signed "Nick."

Arthur H. Hayes, Jr.

"A-Team members" – Back row, from left: Drs. Sussman, Safer, Hayes, Crowell, 1Lt Hart, Drs. Gipstein, Gottlieb
Front row, from left: Drs. Simmonds, Pless, Sidell, Ketchum, Goldstein, Needle

Although almost all our home furniture was already in the moving van, there were enough mattresses, boxes and candles to accommodate an afterthought party for the department staff. Thumbing through a booklet of traditional Army party drinks, I chose Artillery Punch. It was an ill-advised combination of rum, gin, coffee, orange and prune juice and what-all else I can't recall. I filled a brand-new 20-gallon plastic garbage can with this supposedly traditional concoction, and the obliging guests innocently consumed it to excess. It was not my finest moment, but it was one of my very last before loading the car and driving off to meet the Western horizon.

* * * * *

16 POST-DOC WITH PRIBRAM

Instead of feeling complimented when we are called an ass, we are left in doubt

Mark Twain: ***Pudd'nhead Wilson's Calendar***

As we drove westward through green hills, fresh meadows, great mountains and featureless deserts, the trappings of military life were as forgotten as outdated pages on a calendar. All that I had been and done in the tiny ramshackle complex of clapboard workshops on the Chesapeake Bay became a book whose covers I had closed and placed on a high shelf. Provincial life at Edgewood, exciting in many ways for almost six years, had lost its luster. We were now speeding to a new world. Each time the sunset glowed through our windshield I could feel its pull, promising, like a beacon on the sea, the nearness of a harbor.

Black-brimmed cap, golden brass and forest green uniform were deep inside a suitcase that would remain closed and out of sight for weeks and months to come. In Palo Alto, we found a cozy cottage, half-hidden from the street by leaves and blossoms all around and above. It was far more inviting than our old row house, with its bare patch of lawn and a view that featured an Army supermarket across the street and glimpses of chemical smokestacks in the background.

The new workplace was a suite of rooms in the Medical Center. About 15 researchers and students worked and studied in a total area of no more than 1800 square feet, apportioned among five or six rooms. Dr. Pribram had a small office and the only secretary. A larger room was reserved for a small PDP-8 computer and accompanying files and furniture. There were three other doors behind which laboratory space ranged in size from very small to moderately spacious. As a new post-doc student, dressed in slacks and sweater, I felt like a visitor, rather than a staff member.

I had hoped for a room, but instead was lucky to have a four-foot section of an L-shaped desk that lined the area just outside of Pribram's office, shared by several other post-doc students who lacked any particular status or seniority. Secretarial assistance was almost non-existent, limited to having a short official letter typed by Pribram's secretary when she was not otherwise occupied – time slots that seemed as rare as eclipses of the sun.

Dr. Karl Pribram – early in his research career

I was not really unhappy about being suddenly transported from department chief to something approaching non-personhood. It was a form of freedom. I could come and go as I pleased, and in fact accomplished more outside the laboratory area than I did within it. I found intellectual stimulation in classes and the library. In the lab, conversation seemed to be the main activity. Much of it went nowhere and sometimes it degenerated into silliness and parody. When it did, it provided temporary sanctuary from the nagging suspicion that my work was lacking in direction.

Despite my own motivational problems, I enjoyed being around Karl Pribram. The son of a European physician and a Polynesian princess, he had grown up to be both a man of science and a romantic. He had become attracted to psychology, after which he became obsessed with the brain and its ability to communicate both within itself and with other sentient beings. He had little regard for psychiatrists, however, whom he (rightly) considered to lack much knowledge of the structure – much less the mechanisms – of brain function.

To me, he occasionally seemed to have become entangled in contradictions. Although he certainly did not wish to be regarded as a modern version of Freud, he wrote a lengthy paper intended to update Freud's notion of the "psychic apparatus." He hoped to apply the newly developed tools of neurophysiology and computer technology to modernize Freud's insights. Freud was originally a neurologist but like Karl, found "mental" exploration more challenging than the mechanistic mapping of the nervous system that preoccupied neurologists. Yet Freud's concepts about the mind dealt mainly with the individual and his personal inner conflicts. Only later in his life did "interpersonal" communication and interest in "the beyond within" (as Sidney Cohen described certain ineffable LSD-induced states of consciousness) begin to shift his focus to a different realm.

The almost total absence of psychedelic chemistry no doubt made it easier for Freud to deny the "oceanic feeling" that others claimed to experience – a sense of existing in a larger, more inclusive universe, one that transcends words and objectifiable phenomena. Freud hoped that chemistry would eventually lead the way to an understanding of thoughts and feelings.

Ironically, it was not just the kind of chemistry taught in laboratories that would help attain such understanding. The paradigm of psychedelic energy as a possible source of enlightenment had not yet been fully formulated and would have seemed like witchcraft to most scientists. Even now, only a few have chosen to follow that path.

Dr. Sandra Blehert, post-doc fellow, examines slides

Nevertheless, Freud's non-material constructs such as id, ego, superego, repression, and the unconscious mind were bizarre enough to offend conventional thinkers. Obviously, he sensed dimensions of awareness that no one could measure with electrodes or microscopes. I think Pribram admired this aspect of Freud's search for meaning and wanted to carry it further.

I worked in Pribram's lab as much as possible but outside problems, the overhang of papers I needed to write about my Edgewood studies, and a general lack of focus compromised my energies. I audited classes in calculus and electrical engineering. I attended courses in computer programming and neuropsychology. Nevertheless, the liberating ambience of the Stanford environment itself often stole my attention.

Our house, four miles away, wrapped in the shade of a willow tree and swathed in bougainvillea, brought back golden memories of an internship in San Francisco, a decade earlier. I still recall driving through the Palo Alto streets on a sunny afternoon in October, listening to Bobby Darin singing "If I Were a Carpenter." It was a natural high, a warm floating feeling, the kind that seems so rare, perhaps a glimpse of what Albert Hofmann described as awareness of the "transpersonal transmitter and receiver" in his slim volume "Insight/Outlook."

In the lab, I tried to involve myself with monkeys, since they were the animals that Pribram used almost exclusively to explore the effects of brain structures on learning and memory. He liked to recount the event that triggered his attempt to bring psychology and neurosurgery together.

A woman whose brain tumor he had removed displayed a curious mental deficit. If asked whether she was hungry she would say "not at all" but if food were visible, she would devour it voraciously. Integration between state of mind and behavior was obviously not working as it should. Perhaps creating other surgical discontinuities would shed light on poorly understood control mechanisms in the brain.

On two occasions, as I recall, Karl let me take a turn as his surgical assistant. To exercise this coveted privilege, I first had to procure the monkeys from their cages in the animal room. Not a routine task! Monkeys in cages are not friendly by nature. Even the Crocodile Hunter would probably have had a moment of doubt before intruding on their space. Definitely not something to try at home.

Nevertheless, our first operation together went smoothly enough. The second, a more ambitious and delicate maneuver, required Karl to reach the optic nerve, deep within the center of the brain. As I held the clamps that exposed the desired site, Karl, although blessed with tiny hands, made a false move with his scalpel and nicked the nerve. I thought it was because I had not held the retractor steady, but I checked with him recently and he actually remembered the incident

and told me it was only because I said something like "You can't do…" which hit a chord. He says he could never stand hearing those words, which had often come from administrators. In any case it looked like I might not pass my "neurosurgery boards."

I had been warned beforehand about Pribram's fury, usually hidden behind a cordial exterior, whenever things went wrong. So I didn't stay discouraged very long. Instead, I transferred my energies to the PDP-8 computer, which was state-of the-art for small laboratories.

The main computer on campus was housed in a special building, and virtually inaccessible to students. In my course in ALGOL (an intimidating programming language using nested commands surrounded by parentheses within other parentheses) students had a total of six seconds of computing time per semester to squander on their homework assignments. They would first have to leave the data in the form of a stack of Hollerith punch cards and then come back the next day to find out the results.

A student's life – almost forgotten

The PDP-8 was a $25,000 box containing eight kilobytes of working memory, roughly 100,000 times less than a good $2,000 computer has today. But it was superior to the Edgewood LGP-30, and accepted magnetic instead of paper tape. Memory, however, was lost if not recorded back onto the same tape at the end of the session. This required instructions in "assembly language," another complex programming skill that took much time to learn.

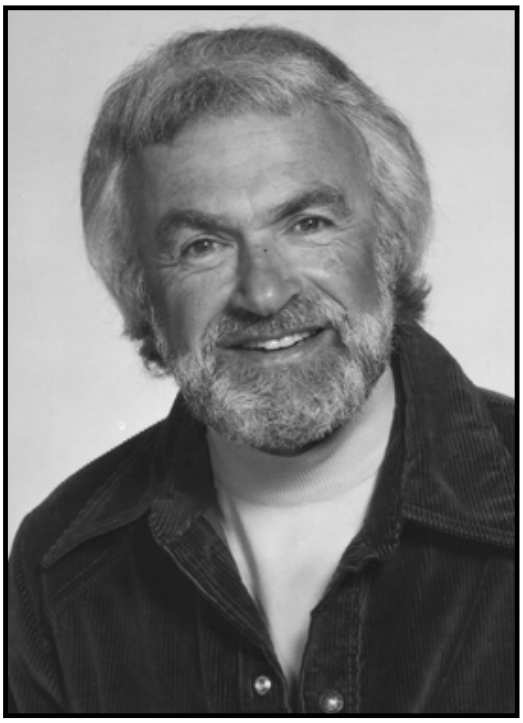
Ironically, a blind student, Walt Grueninger, who had lost his sight to a rare eye infection after two years of medical school, helped me quite a bit. It was soon obvious, however, that computer programming was not going to be a major tool in my educational kit – at least not for another 15 years.

I turned to bookish pursuits. I made hundreds of flashcards from a textbook on physiological psychology. I soon found that the underlying neurological networks that lay inside B. F. Skinner's "black box" encompassed too wide a vista to explore in less than a lifetime. Although I was making only minor headway epistemologically, I succeeded in evoking some laughter in one of Pribram's weekly seminars. While reviewing gender differences, I learned that the vigilance of female chickens was inferior to that of males. I remarked that "obviously, female chickens would make very poor soldiers." It amused some of the 1960s students, of course, that an Army officer would notice only the military implications of a scientific study. And it amused me that the students' liberal anti-military biases would find confirmation in my narrow mind-set, even though my tongue was obviously firmly in my cheek.

"Sleeping with the enemy" at Stanford was very pleasurable. I have always considered intelligence and wit more important than political persuasion. I didn't know much about Viet Nam, and it was hardly ever mentioned at Edgewood. But I figured if our government thought it was justified, it must be righteous. Only much later was I finally convinced that the war had been ill-advised, reflecting an inability to relate to the values of different cultures (as well as less noble territorial ambitions). Cultural incongruence is an even more obvious part of our problems in Iraq today. We believe we are being helpful, and are bewildered when the recipients consider us intrusive and coercive. I say this without judging the larger

controversy about our occupation of Iraq – opinions clearly differ sharply on that question.

But politics were not an obstacle to friendship at Stanford. Thank goodness, science was the main interest and we were all "on the same page" in that regard. None of us really knew what to make of the vast ocean of experimental findings. Nevertheless, we hoped we would live to see the day when the significance of our work would become clear. Such clarity, unfortunately, is one of those ever-receding horizons.



Karl Pribram did not receive his most significant recognition and awards until the 1980s

Karl Pribram was no prosaic scientist. He was a visionary who hungered for a unified theory of behavior, just as Einstein struggled in vain to create a unified field theory. Today, equally obsessed physicists and mathematicians strive for a "theory of everything." If someone succeeds, I suspect that it will defy, rather than enhance comprehension for most of us.

Karl sometimes seized on relatively simplistic models of behavior and devised colorful ways to promote them. One was the "TOTE" model – Test-Operate-Test-Exit – which he diagrammed as a simple feedback loop. It was just another way of saying the brain dictated an action and then looked to see if it produced the intended result. Well, anyone who has practiced a golf swing could agree with that concept!

Karl was a complex, driven scientist, and I would not wish to trivialize his work or his writings. Like other major figures in the brain research world, he added many new and thoughtful ideas to the never-ending discourse about the nature of the mind-brain relationship. I liked and admired his tenacity and fervor. It's just that his fervor sometimes occasionally led him to create theories that outdistanced the available facts. His conviction that the brain worked like a hologram, for example, while appealing to the imagination, was more intuitive than deductive. To his credit, however, the same idea continues to intrigue many brain theorists and may someday be confirmed.

When it became clear that I was not going to the head of the class in neurosurgery, I shifted to another project I had begun at Edgewood – constructing a transparent brain from multiple layers of Plexiglas. Tracing illustrations of brain sections and piling them up didn't work as well visually as I had hoped, however. I eventually decided to give it up and direct my energies elsewhere. Perhaps someday someone will stumble on my unfinished brain model lodged in the San Andreas Fault amongst the rubble of a great earthquake. But I doubt it.

There were other distractions. Although lacking some of the intensity of the Berkeley confrontations, social upheaval was becoming conspicuous at Stanford. At Edgewood, the "counterinsurgency" operations of the United States in Viet Nam had been a relatively infrequent topic of conversation. Here, it was difficult to maintain my relatively apolitical views in the face of student demonstrations.

Most of the students either were in favor of the developing war or opposed to it, but the most counter-culturally-inclined students mocked the entire scenario. On a day when anti-war activists decided to wear black armbands, the

war supporters responded with white armbands. The nihilistic third group donned cereal boxes on their arms, signifying that signifying anything was ridiculous.

When Dean Rusk delivered an unannounced address in the university auditorium, word spread like wildfire. Students by the hundreds came streaming across the grassy quadrangle. Their plan was to cut off his escape. I saw them running and found myself running alongside them, hopping over obstacles and low fences in a state of frenzied, ignorant excitement. Rusk, however, had an escape strategy. He successfully sneaked away to his limousine through a little used back exit.

Despite my being a US Army lieutenant colonel, and inclined, at that time, to support whatever the government was doing, my laboratory comrades never treated me disdainfully. I even organized two weekend outings, issuing instructions in the precise format of a military directive. The other post-doc students sometimes teasingly referred to me as "the Colonel."

"Happenings" were springing up everywhere. The Warren Commission report was a major point of contention among the students. Most of them were skeptical. Professor John Kaplan and attorney Mark Lane, a dedicated detractor of the Commission's integrity, engaged in an exciting debate. (Kaplan was an enigmatic intellectual who later wrote a powerfully persuasive but ultimately futile book in favor of marijuana decriminalization.)

Post-Docs Bob Douglas and Lauren Gerbrandt discuss various possible explanations for the consolidation of memory in the hippocampus

On the day of the debate, Kaplan brought all 23 huge volumes of the Commission Findings with him and stood them on a table between heavy bookends. Whenever Lane made a controversial statement, Kaplan dashed like Charlie Chaplin to the row of books, hauled out the exactly right volume and unerringly found the right page to read, theatrically denouncing Lane's claim. The polarized audience was vastly entertained by this battle between two such sharp-tongued adversaries.

Meanwhile, back at the lab, I joined forces with Professor Norman Mackworth, who was at Stanford on a distinguished fellowship from England, and Dr. Muriel Bagshaw, a senior fellow. We were trying to develop a method for tracking a monkey's eye movements when various scenes were presented within its visual field. I offered to fabricate a mask that would hold the monkey's head steady, and limit his field of vision to the area of interest. It was made of fiberglass – a nasty material to work with. The study was still in its infancy when my time at Stanford ended.

Letters from Fred Sidell kept me fully informed of doings at Edgewood. He was clearly doing an excellent job as Acting Chief in my absence, although he was frustrated that the program was being progressively diverted away from research and toward a variety of mundane tasks.

By good luck, my stay at Stanford coincided with the emergence of the hippie Revolution. I was fascinated with this spectacular development. One bright day, I stood in a brown business suit and tie, taking movies of the

Dr. David Smith, founder of the Haight-Ashbury Free Clinic

exotically dressed-up kids as they strolled in exhibitionistic delight along Haight Street. It was a day of love. They didn't even seem to notice my cinematic activity.

Dr. David Smith had just established the Haight-Ashbury Free Clinic, first of its kind in the country. For about ten months, I spent every Thursday evening working as a volunteer doctor, interviewing and treating young people who had taken too much LSD, PCP or STP. No one was sure just what STP was at first. Some were sure it stood for "serenity, tranquility and peace." Actually, it turned out to be DOM, a psychedelic amphetamine derivative created by Dr. Alexander Shulgin.

The Clinic was (and still is) a converted old 3-story residence, with the second floor serving as the intake area. At all hours, disheveled or lavishly costumed individuals would appear. It was often a challenge to figure out what drug they had taken. One man in his 30's was brought in by his "group." He was their revered guru and teacher. He was also very paranoid and wanted to leave, but his group managed to reassure him that he needed help from the doctor.

"The doctor" (me in this instance) was less than confident about his ability to help the distracted patient. A walk-in closet contained row after row of medications, provided pro bono by various drug houses. But which one to prescribe? Thorazine was a favorite choice for difficult to manage patients, but as I knew from our Edgewood studies of Thorazine and butyrophenones such as Haldol that the result would probably be what was sometimes described by patients as "Thorazine on the outside and LSD on the inside" – not exactly what psychedelic "tripping" was supposed to feel like.

I thought Valium might be better to help anxious psychedelic casualties come down a bit more pleasantly. I hadn't seen or heard of others using it, although I have to assume that some physicians, and no doubt some LSD users, had the sense to try it. (Today, Ativan would probably be the treatment of choice – it resembles Valium in its mode of action but has the advantage of being short acting and injectable.) Anyway, Valium seemed to soften the effects of LSD.

No one was paid for his or her services at the Clinic. Nevertheless, there was no shortage of volunteer staff. Those were heady days in San Francisco, and the self-proclaimed right to run away from affluent middle class homes during one's crisis of teenage alienation was evidently a compelling notion. It was a reason to break with the "establishment," defined by one flower child as consisting of "anyone over 30."

1967 seemed like the most magical year. The hippie movement (which started in 1965) spread rapidly, taking over a rather conservative mid-San Francisco community soon to be known as "The Haight." I have footage of an elderly local resident eyeing me with undisguised hostility as I filmed him walking past my camera. He probably thought I was some Hollywood type, trying to get material that would advance my creative career at one of the movie studios.

He was one of the few senior citizens visible on the street. I saw a few girls sitting on the sidewalk in their Goodwill-derived get-ups, scanning the passing parade of trippers from beneath demurely sagging eyelids. Fur coats and Army fatigues walked arm in arm. One shop, renamed "The Diggers," advertised free food for anyone who wanted some. A cardboard sign in its window quoted Matthew 15: "Beware of false prophets, which come to you in sheep's clothing,

but inwardly they are ravening wolves." I was not sure which prophets they were referring to.

On the street, as I watched fresh-complexioned 15 year-old girls extending free flowers to anyone who noticed them, I was once again reminded of Ophelia.

Speaking of Peace and Love, one day a young man came in, quite disorganized but verbally profuse. He said he had taken a drug called "the Peace Pill." None of us knew what it was, but the effects were obviously not caused by just a few tabs of LSD. We persuaded him to lie down in a quiet area and eventually he regained his sanity.

Later we learned that "peace pill" was a clever play on PCP. Someone had introduced it at a nearby rock concert. Several serious injuries resulted from its disorienting, and at the same time energizing, effects. I believe I was the first doctor at the clinic to deal with a PCP bummer. We had no true antidote, and to my knowledge, no one has yet developed one that reverses all the undesirable actions of PCP in the central nervous system. PCP receptors have since been identified in the brain, but many other neurochemical systems are also directly or indirectly involved.

I remember a married couple who were trying to survive without doing anything much, and not enjoying it. I met them weekly for several months, mostly just listening, since I had no answers to their existential problems. Another memorable female patient was a telephone operator. One young man came in shirtless, having hitchhiked 150 miles from a commune in the desert just to get some penicillin to treat a friend's ear infection. I gave him some and he promptly left, planning to hitchhike back to the commune – at night. That was quite an errand to run for a friend!

A distinctly non-Army home for two years on Ivy Lane, in Palo Alto

By the time I left Stanford and the clinic in September 1968, the golden days of the Haight were fading and speed freaks had pretty much taken over the neighborhood. With speed, came crime and violence. But before that happened, I got to see the best of the Hippie scene, even attending a "Be-In" on a vast lawn where Tim Leary held forth before a thousand or more enthralled young people sitting on the grass (and smoking some as well).

He suggested everyone make paper airplanes and launch them over the crowd. Soon the air was filled with folded, crisscrossing, winged symbols of love. Each plane was caught by someone and released again, maintaining a swirl of folded white paper gliders for quite a long time. I experienced the love energy and wondered if the world could ever be that way. But the shared hopes and fantasies of the unique group of psychedelic pioneers who had made the pilgrimage to San Francisco were ultimately dashed, along with the optimism of their admirers.

When it was time to return to my chemical warfare research, I decided it

was only fair to tell my "therapy" patients that I was really a lieutenant colonel in the Army Medical Corps, and would be going back to Maryland to continue the chemical warfare research that had paved the way for my two years at Stanford. Steeped as they were in anti-war sentiment, this naturally "blew their minds." Nevertheless, they forgave me.

A few years later, I returned to the Haight and conducted a televised interview with Dr. David Smith. He had started the Free Clinic, but I never really got to know him while I was working there. The 1973 interview was for a course on drug and alcohol abuse I was preparing for the Academy of Health Sciences at Fort Sam Houston. David and I did not become truly acquainted at that time, however, and did not meet again until another five years had passed. Then we quickly became good friends.

And meanwhile, though I was not there to see it, the old clinical research annex was burning.

1967: Immolation of the old barracks style clinical research annex to make room for the long predicted new building

Once, while still at Stanford, I visited Edgewood Arsenal for a week, to write up the results of my studies with EA 3167, the ultra-long acting glycolate previously described. Later, back at Stanford, I also helped with a few other research projects in Dr. Pribram's lab. Beyond these activities, however, my stay at Stanford fell short of fulfilling my initial grand agenda. I must admit, though, that I did appreciate the privilege of roaming around the Stanford campus for two years, unfettered and in student garb, even though it all ended with little to show in the way of solid accomplishment.

As my time at Stanford was approaching an end, my old boss Joe Blair at Edgewood and my mentor David Rioch at the Walter Reed Army Institute of Research (WRAIR) simultaneously requested my assignment to their installations. Both apparently believed (incorrectly) that my competence had somehow been enhanced by my 24-month sojourn in the magic halls of academe.

I was particularly flattered by Dr. Rioch's efforts to have me assigned as his deputy chief of the Neuropsychiatry Division at WRAIR, since I knew he was retiring soon and seeking a successor. This would have placed me at the head of a prestigious research laboratory that had already produced a Nobel Prize winner (David Hubel) as well as numerous distinguished experts in neuroanatomy, neurophysiology and experimental psychology. The thought of having a world famous neuroanatomist such as Wallé Nauta or a widely influential theoretical

and experimental psychologist such as Joe Brady under my "super-vision" was enthralling. But it was also terrifying. To tell the truth, I felt unworthy of even trying to fill the shoes of such a distinguished neuroscientist as David Rioch.

The old clinical building bids farewell as it is reduced to ashes

Accordingly, I elected to go back to Edgewood. I figured that at least I knew my way around that laboratory and could continue the kind of work I had enjoyed for almost six years before my two-year "sabbatical" at Stanford. Alas, although that decision may have been the logical one, I soon found that the research situation at Edgewood had changed in ways that clearly heralded "the decline and fall of the psychochemical empire."

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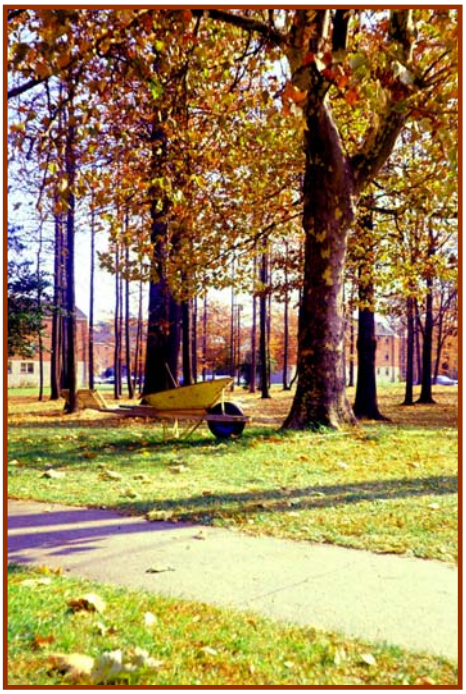
17 EDGEWOOD AGAIN: HOPING FOR DÉJÀ VU

To business that we love we rise betime,
And go to't with delight.
Shakespeare



Autumn afternoon at Edgewood

I somehow felt that moving from West to East ran counter to the pioneer spirit. Returning from the crepe myrtle and warm days of winter to the bleak peninsula that is Edgewood Arsenal was not too bad in September, but I knew that frosty Maryland days would not be long in coming.

Lots of changes. The old Clinical Research annex, with its echoing corridors, had been replaced by a 1.5 million dollar new structure named after James Woods, an early charismatic chief of the Medical Research Laboratories. In place of two-by-fours, sheetrock and the long ancient hallway with its well-worn rubber mat that I had trod so often at night – with a stir of excitement – there was now steel and concrete, forming a rectangular shell and housing a large courtyard. Smooth-walled, wide corridors now coursed through the interior and paralleled the outer walls.

It was okay, but it was different; somehow I felt that things in general would also be different – and I was right. Oh, it was grand! A broad set of steps led to thick-glassed front doors. A large new parking lot was close to the building, separated from it by an expanse of manicured grass, divided in the center by a fifty-foot walkway leading to the entrance. Inside was a spacious lobby, with corridors leading to the right and left as well as straight ahead. An impressive sign-in desk and a security guard now ensured that only employees and approved guests could travel to the interior.

Gone were the familiar friendly clinical wards where we had done such fascinating research. Gone was the padded room with its see-through mirror and hinged opening, through which nurse and technician could watch the occupant and administer his periodic Number Facility and Speed of Closure tests or give him

a clipboard and pencil with which to Draw-a-Man. Gone, and missed the most, was the large padded ward, with its six individual cubicles, enclosed nursing booth and open area where the volunteers could play cards, take their meals or watch TV.

The new Clinical Research Building

Many would say it was wonderful to have a real emergency room, fully equipped with the latest stainless steel autoclave, glass cabinets and modern medical devices – all the things a physician might need to manage potential chemical casualties brought to a loading platform from anywhere on the Post by the new ambulance. It all sparkled brightly.

Charlie Krause and the new ambulance

No longer Acting Chief, I was now the real Chief of the Clinical Research Department. A re-organization had expanded the department into five branches and was home to more than ninety personnel. The Clinical Investigation Branch had absorbed the Psychopharmacology Branch, an ominous indication that much of incapacitating agent research was already obsolescent. There was a new Clinical Chemistry Branch, a Toxicology Branch and a separate Administrative Branch. I had a newly painted office to the right of the main entrance. My former secretary, Regina Van Valkenburgh, and former administrator Carl Stearn were still there, and seemed unchanged, but now worked in an adjacent and larger well-furnished work area. I was happy that they, at least, were just the way I remembered them.

Fred Sidell had done an heroic job during my absence. Under his leadership, Clinical Research was publishing more research papers than any of the other three Medical Laboratory departments. Most reports were classified, but it was encouraging that some had been approved for open publication in mainstream

journals.

Lots of new equipment

The new Clinical Research building, whose construction had not even been started when I left in 1966, was now awaiting a splashy dedication. I missed the old clapboard annex that had gone up in smoke, with only photographs to remember it. Meanwhile there was this brand new building, waiting for a formal baptism. Inevitably, it would include at least one too many speeches and many more VIPs than could be comfortably accommodated. Nevertheless, the impressive, multi-million dollar, state-of-the-art structure warranted a ceremony. Forget nostalgia for the shabby old annex; for better or worse, this is where I would be spending the next three years.

One of my first assignments was to arrange a tour for the VIPs on dedication day. It was impossible to crowd them all into a single laboratory area, but it was also unreasonable to make them wait in line. We decided to divide them into groups and use walkie-talkie signals to move them along every ten minutes and keep the transitions on schedule. The plan worked well. My new chief, Colonel Henry Uhrig, was duly impressed.

Time to dedicate the new Clinical Research Building (1969)

For a few months, I enjoyed a smooth relationship with Hank. But thunderclouds were slowly gathering. The smoldering problems that Fred had noted in his letters were becoming increasingly obvious.

The magnitude of Fred Sidell's administrative accomplishments also became more apparent as I struggled through the first few months as Department Chief. I inherited the executive tasks he had handled well without any real help. It did not take me long to realize what he had been contending with.

Since none of his superiors had seen fit to recognize Fred's remarkable performance in any official way, I felt I should try to offset this egregious oversight. Consequently, in February 1969, I submitted and received (after an unreasonable delay) approval of a narrative award. Limitations of space permit only a much-abridged version:

"This Decoration for Exceptional Civilian Service is awarded to Dr. Frederick R. Sidell of the Clinical Investigation Branch, Clinical Research Department, Medical Research Laboratory, Research Laboratories, Edgewood Arsenal, Maryland, for exemplary performance of duty during the period from August 1966 to February 1969.

"….During this two and one-half years, he somehow managed to design and carry out more research task plans than any other member of the department, wrote and published a total of 11 original research reports as senior author (and two as co-author), served as project officer and alternate contract officer for two major research contracts, supervised and wrote ratings for fourteen medical officers and six other professional level employees, wrote and put into effect seven detailed Standard Operation Procedures (SOP's) for department use, a volunteer handbook and innumerable memoranda for record, and represented the department in staff meetings, Review and Analysis meetings and the many other administrative and technical conferences required in the laboratory.

…"He led his professional colleagues not only by directive, but example. During a one-month period in 1968, he repeatedly came to work at 4 A.M. to administer injections to subjects so that they might be tested during normal duty hours by scientists from another department.

...."He did not forget his basic commitment to the ideals of the good physician. He was never absent when a serious emergency required the best available medical care…Of greatest significance…was the fact that he was obliged to work under circumstances that could only be described as adverse… With limited resources, and little encouragement, he persisted in his attempts to stimulate research initiative, often in the face of discouraging apathy, and even cynicism, from his colleagues.

…."Thanks largely to his own prodigious output, his department published more scientific reports during the last two years than any within the Medical Research Laboratory. In both age and experience, he was unusually young to be given administrative and technical supervisory responsibility of the magnitude of department chief.

…."During a difficult period, he not only sustained the department but improved it; he set an outstanding example to the entire laboratory by his selfless and devoted conduct. Not only was he loyal to his inner standards of excellence, but to his chief and his colleagues. It would be remiss not to recognize and commend to the highest degree the quiet, but unfaltering dedication he has shown. Dr. Sidell's performance brings more than credit to his organization and to the Government Service. It brings high honor and rare distinction."

Fred was actually uncomfortable about receiving this recognition. He was much more interested in his work than in awards. But at least it placed on record a chronicle of his accomplishments. He did a much better job than I could have done – better even than I ever aspired to do. The Chief's job was no longer fun. Morale in the department was far lower than in the early 1960s when there was eagerness and motivation to take on challenging projects.

The new physicians were a different breed. They were older and not very happy. Most of them had completed residency training under the recently enacted Berry Plan, which postponed their military obligations. Many had already established lucrative practices. Now that they had to pay the piper, they preferred a research assignment at Edgewood Arsenal to treating casualties as battalion surgeons in Viet Nam. One could hardly blame them. An expanding legion of young protestors had changed national sentiment. The majority no longer supported the war as a patriotic cause.

Where I once had a cadre of young doctors, fresh from one-year internships or just out of residency training, I now had a team of overqualified specialists. Some even had subspecialty training. One was an expert on renal disease. Another was a cardiologist. A third was a neurologist, with a résumé that included several published papers. Most of them had little real interest in the laboratory mission. They managed to make themselves scarce whenever possible. Already in their mid-thirties, they resented the Army for uprooting them from private practice and higher incomes. Who could blame them?

Bill McShane (with pipe) and two of the new doctors

There were other frustrations. Security clearances now often took six months to complete. This meant that the new doctors could only do classified research during the remaining eighteen months. Budgets were on the decline, and there seemed to be a built-in delay in getting replacements for departing technicians and physicians. A Regular Army major now served as our administrative officer, controlling expenditures and volunteer scheduling. He took his job too seriously. There were frequent arguments about the allocation of office space and supplies. I missed the days when a friendly and generous sergeant ran the supply room.

After a few months, the administrator finally left for another assignment (possibly at his own request). In his place, we acquired a young lieutenant who seemed cooperative enough, but unable to get the hang of long-established procedures. We were now getting up to eighty volunteers every two months from a pool of up to four hundred eager applicants. Scheduling examinations and drug tests for such a large cohort was becoming a minor nightmare.

Brand New Autoclave

The content of the testing program itself was increasingly boring, adding to the overall unease. Several untested agents required minimal dose evaluations, but nothing else really new had come along for quite a while. The previously enthusiastic support and interest shown by the higher-ups was progressively morphing. As Fred put it in one memo, the Clinical Research Department was becoming a "glorified assay mill." There was little tolerance for imaginative new projects. One could only undertake research when it had immediate relevance to "the mission" – and "the mission" seemed to be limited to measuring the basic features of a few compounds.

Meanwhile, a Regular Army lieutenant colonel was now chief of the recently established Psychology Department. He boldly competed for turf with our Clinical Research Department. Some psychologists even tried to preempt occupancy of newly installed padded rooms by simply moving into them, like prospectors staking claims.

One psychologist was a particular irritant. Anxious to add to his personal list of open literature publications, he teamed up with our newest psychiatrist. They started removing clinical records and extracting data from studies compiled by doctors who were no longer in the Army. Some were volunteer charts from my own experiments. This was not a big problem until they decided to write the papers under their own names. They argued that the data had been "abandoned and were fair game."

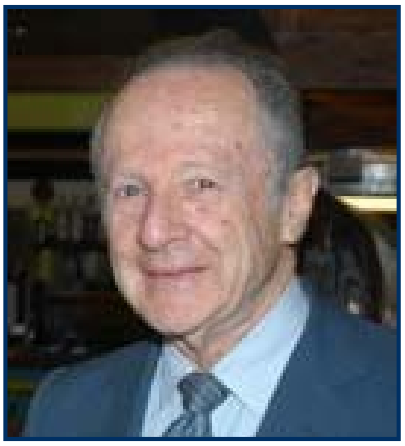
For the first time in my experience, the issue of intellectual property had become a bone of contention, as had the security of the records themselves. Fred discovered that these two young researchers had commandeered 150 volunteer charts. He recovered them by raiding their offices, and drew up a memo setting limits on such activity. Even so, when the Inspector General later reviewed the program, some 300 charts could not be located.

My time was taken up with settling petty disputes, dealing with a lack of

motivation among the older physicians and attending pro forma committee meetings. There was little time left for research. This was not the sort of work I had anticipated, and I did not like it.

One newly assigned doctor took a firm ethical stance against the volunteer testing program. I tried, without success, to persuade him that there were good ethical reasons for our work. I verbally wrestled with him at length on four occasions. He appreciated my efforts, but remained unconvinced. He was happy to receive an alternate assignment elsewhere.

It was not the first time I had tried to explore and, if possible, find a way to reconcile opposing views with my own. In the mid-1960s, Dr. Matthew Meselson had published a news article taking a moral stance against research on chemical warfare agents. Meselson later became the Thomas Dudley Cabot Professor of the Natural Sciences, Department of Molecular and Cellular Biology, Harvard University. He also served as a member of the NAS Committee on International Security and Arms Control and the Working Group on Biological Weapons Control.



Mathew Meselson, distinguished Harvard professor

In addition, Meselson was a member of the NAE Committee on Alternative Chemical Demilitarization Technologies and the Advisory Panel on the Chemical Research, Development and Engineering Center. I decided to write to him, and composed a two-page letter pointing out that he and I were approximately the same age, and had similar Ivy League educations. I wondered why we had reached such different views on the topic of chemical warfare, especially about incapacitating agents, which were intended to reduce wartime casualties.

I no longer have copies of the correspondence, but Dr. Meselson wrote a cordial reply, in which he stated that his main objection to incapacitating agents was that they introduced a new modality of warfare and he was afraid they might open the door to other more destructive weapons. I wrote another longer, somewhat rambling letter expressing further ideas and arguments on the subject, but he did not reply. I think he may have regarded me as a hopeless ideologue. On the other hand, since he also took an oath of matrimony that summer, I would not be surprised if he felt he had more interesting things to do.

Dr. Meselson remains a prominent leader in the cause of arms control, especially biological and chemical weapons, and has been the recipient of many deserved awards. It was nice that, despite our ideological differences, we were able to have a frank and friendly (although brief) exchange of opinions.

* * * * *

Sentiments were changing. Our work was becoming increasingly politicized. The media and the public were beginning to look disapprovingly on the testing of volunteers and, as mentioned previously, news articles were taking on a more negative tone.

Anti-war activists were starting to focus on chemical weapons. Military authorities were nervously holding their fingers to the wind. The news media found out we were again interested in the incapacitating potential of marijuana derivatives and they proceeded to have a field day. Reporters wrote articles derisively making fun of the Army's seeming intention to make the enemy lay down their arms by "turning them on"

In response, our medical director canceled further work on marijuana-

related compounds. I felt this was a rather craven act. Fred and I protested that no one had systematically studied the psychopharmacology of THC. (Dr. Sidney Cohen had made the same observation during a much earlier visit.) Many university researchers were eager to study the "killer weed," which was then (and is now) the most widely used prohibited drug in America. We had excellent facilities and a well-developed methodology for doing precise work on THC, but political correctness – or perhaps "military correctness" – stood in the way.

As Fred expressed in a memo, if the labs had any pride in their work, they would not only admit doing such research, but would point out the relative void in pharmacological knowledge about marijuana and let the world know that we were perfectly positioned to help fill it. We had sophisticated equipment, an excellent testing environment and a ready supply of volunteers. But Fred's arguments came to naught.

Although not motivated to become investigators of classified chemical agents, many of the specialist physicians hoped for an opportunity to do studies related to their own area of expertise. Generally, this was not possible. Our Medical Laboratory chief, Colonel Hank Uhrig, saw no reason to do research that did not advance the Chemical Corps agenda. And what was that agenda, really? Was it not to learn as much as possible about all drugs of possible military relevance?

Our loss of status in the laboratories was ominously symbolized by the next round of promotion for secretaries. Regina's name was not on the list. It should have been near the top. She went home from work early in great distress, leaving a poignant note on my desk expressing her pain about being passed over. It was painful to me as well, since Regina almost never complained, and always worked far beyond the requirements of her job description.

Regina Van Valkenburgh, most loyal secretary

Physicians also got short shrift. When our group paper on atropine, scopolamine and Ditran won first prize at a pharmacology conference sponsored by the Army Munitions Command, Hank Uhrig didn't even acknowledge the accomplishment. He seemed more interested in the fact that I was not wearing the correct uniform.

One day, he called me into his office and pointed out that I was still wearing the shoulder patches I had acquired at Stanford. Out came the long knives! Hank told his administrative assistant to find a couple of razor blades. Standing on each side, they unceremoniously cut the patches off, while I stood at attention.

During the first few months of my return, I had made extra efforts to establish a friendly relationship with Hank. I knew he was an inveterate jogger. One morning I surprised him by getting up at six A.M. to join him in his daily three-mile run. Having done no jogging previously, it took a supreme effort to finish. You should try it sometime.

Those were the halcyon days. Our relationship slowly deteriorated. Two years later, he told me he had originally thought of me as his future replacement as chief of the Medical Lab, but had recently changed his mind.

This was understandable. After an enthusiastic beginning, I had indeed begun to lose interest, mostly for the reasons I have enumerated. During the first year, I worked hard, and had high hopes that the program would regain its momentum. It didn't work out that way, however, and, in the end, I felt I should take much of the blame.

On the funny side, the enlisted volunteers were a great group, but you had to keep your eye on them! A few of them had a rebellious attitude that was sometimes cleverly disguised. When I received the customary picture of one volunteer group at the end of their assignment, I noted, on close inspection of the photograph, that one of them had contrived to nonchalantly give the program "the finger." Naturally, this act of gross insubordination could not be allowed to go unpunished!

Courageous Volunteer Serves in Spite of Physical Handicap

Edgewood Arsenal, Md. 11 Feb 70. PFC medical volunteer assigned to the Medical Research Labs, Edgewood Arsenal, Maryland, was officially commended today for courageous performance of duty in the face of a painful physical disability. (extreme right, second row in photo above) sustained a twisting injury to his middle finger, right hand, while engaged in a vigorous game of squash in the Arsenal gymnasium with another volunteer whose name was not disclosed. When asked to report for a group photograph the next day, ignored his personal discomfort and was present in full uniform. Were it not for the fact that his middle finger was stiffly extended and resting on his hat (to reduce strain on the tender knuckle) 's bravery would have gone undetected. Prompt medical evaluation revealed that the injury had spontaneously healed soon after the picture was taken and no treatment was required. According to LTC Ketchum, chief of the Clinical Medical Sciences Department: "Words in themselves are not sufficient to describe this man's attitude toward the program!"

I posted the photo on the volunteer bulletin board accompanied by the above tongue-in-cheek commentary, singling out the maverick soldier for special commendation. I think he got the point, but I never heard anything more about it.

Another touching, but unrelated occurrence was having the following lyrics bestowed upon me by two young physicians, Drs. Dean Beason and Paul Omelsku who were assigned to us for only six weeks. Not knowing quite what to do with them when they first arrived, I had asked them to extract data from a large number of clinical records as a necessary prelude to writing a report. They did a great job and, before they departed, left a thoughtful reflection on my desk.

THE MILKERS FOR THE COLONEL

(To the tune of the Wichita Lineman)

We are the milkers for the colonel
We milk his data through and through
Interpolate, extrapolate is all we ever do
And when we see a pile of data
We become quite blue-ue-ue
For us milkers for the colonel
Will the job ever be through?
Ever be-e through?

We need a small vac-a-tion
Say about a year or two
By that time we should have lo-ost the blues
Because our guess is that by that time
The data will be analyzed
And the work that we so prized
Will all have been milked down to size
Milked down to size.

Little things like that meant a lot to me, for some reason.

* * * * *

Between the shadows, there were still some shafts of sunlight. Good work was taking place, especially in Fred's Clinical Investigation Branch. He was finding new and better ways to treat nerve gas poisoning. Others were evaluating protective equipment, environmental influences and novel methods of agent detection.

At least, I no longer had two jobs! In 1966 I had been Acting Chief of the entire Clinical Research Department and also chief of its Psychopharmacology Branch. In the latter capacity, I was supervising the testing and treatment of intoxication with some new belladonnoids. (Occasionally, I had cynically joked that as department chief I was often so busy that I was obliged to delegate some tasks to myself as branch chief!)

Although I knew that many in the media saw very little merit in military research programs such as ours, I had at least not been personally accused of doing immoral research. Surprisingly I never received even one unsolicited letter or telephone call protesting our work.

Previously, whenever I spoke publicly, I had observed that instead of firing a barrage of confrontational questions, most people listened and reacted in a friendly manner. In fact, they usually limited their questions and comments to

scientific aspects of the subject.

Encouraged by this polite treatment, I requested approval to show an edited videotape entitled "The Many Faces of LSD" at the 1969 meeting of the American Psychiatric Association. Although I'm sure the security officer may have been uneasy about potential backlash, he nevertheless decided to clear it. This surprised me a bit, since the footage showed volunteers under the influence of a drug that had been declared illegal 3-4 years earlier.

I was, however, most grateful to that security officer for deciding to let me show my movie. It was not difficult to imagine the questions that had crossed his mind. Would critics accuse the Army of causing healthy young men to suffer possible psychological trauma and brain damage? Would news editorials trumpet the immoral administration of "acid" to "unwitting guinea pigs?" Perhaps someone would even compare our experiments to those of Dr. Mengele. Would this lead to public demonstrations – demands for the termination of such barbaric practices?

Ironically, the Security Office turned out to have no reason to worry. I optimistically took my film to the meetings, delighted to be able to show that we had documented the effects of LSD under controlled conditions. I welcomed the possibility of engaging a skeptical audience in give-and-take during the question and answer period.

What happened, however, fell a bit short of my fantasies. The meeting organizers scheduled "The Many Faces of LSD" to be shown at 10 A.M. It was to be in a large auditorium and I confidently predicted that an audience of at least 500 psychiatrists would attend – maybe latecomers would even have to stand!

At 10:00 A.M., however, my illusions crumbled. In preference to my film, 2,000 psychiatrists chose to crowd into a hall across the street, where Rennie Davis was mesmerizing them with his self-assured critique of government policies in Vietnam. Rennie was one of the illustrious "Chicago 7" who were lifted to temporary national stardom by their leadership of antiwar protests.

My disappointment increased when even my mentor, Mack Badgley, decided to attend the Rennie Davis presentation instead of my movie! His subsequent admiring description of Rennie didn't enchant me much either.

"He was rather slight in build," said Mack. "But he walked in a very relaxed and confident manner as he approached the podium. Even the way he moved his hands was impressive. For some uncanny reason, there was something spellbinding in the way he spoke."

"Sounds great," I said sourly. "This Rennie must be quite a guy." I wanted a new mentor.

When I quit feeling sorry for myself, I rationalized that most psychiatrists probably tended to lean to the left – at least with regard to the war. They probably couldn't care less about some old Army film about LSD. This was self-evident, since only half a dozen doctors showed up to watch. Also, there were no follow-up questions. The miniscule audience vanished quickly after the showing, apparently hoping to be first in the cafeteria lunch line.

In general, Edgewood's method of controlling information was somewhat mystifying. Evidently it was a fine art. I had a permanent Top Secret clearance but actually I never saw a Top Secret document. As far as I know, no one even whispered a Top Secret in my ear. I did see a couple of Secret documents, but I have long ago forgotten what the Secrets were. Almost every important memo or report, however, was at least marked "Confidential" on the cover as well as at the

top and bottom of each page. Individual paragraphs were marked "C" (Classified) or "U" (Unclassified) in others. When in a cynical mood, I sometimes wondered why they didn't go ahead and classify each word.

I also concluded that everything referring even remotely to something with military relevance was marked "Secret." The "Top Secret" imprimatur, however, was reserved for the few documents that might jeopardize national security in more serious ways. A security "specialist" undertook to judge the sensitivity of each document. Although this person obviously had some general guidelines to follow, I wondered how he (or she) could correctly gauge the security implications of each bit of pharmacological information.

A comment that seemed to sum up the situation

Security classification, however it worked, was a definite impediment to publication in the open literature. George Aghajanian's discovery of a sensitive method of measuring LSD in the bloodstream, for example, was declassified and soon published in a peer-reviewed journal. A discussion of the effects of LSD on individual military performance, on the other hand, was "Confidential." To me it seemed that a novel and ingenious biochemical assay might be a secret worth guarding, while the general effects of LSD on human performance had long been common knowledge.

Enemy scientists had almost certainly studied many incapacitating agent effects by testing their own soldiers or, more pointedly, American POWs. We understood that, starting in the mid-1950s, the Soviets invested heavily in acquiring large quantities of LSD. In 1961, I read an intelligence report indicating that the Russians had shipped trainloads of ergot contaminated rye to Moscow. They had been siphoning it from Iron Curtain satellite nations. The only logical explanation (apart from the small amounts needed to make ergotrate and other drugs used in medical practice) seemed to be that they intended to use it as a precursor to LSD.

Later, I read that they were indeed giving repeated, heavy doses of LSD to suspected spies, hoping to break their cover stories. Supposedly, the KGB even used this technique with Cardinal Mindszenty, to elicit contrived public confessions.

Many classified documents were stamped "Automatically Declassified After 12 years." I suppose by then potential enemies would have pilfered or duplicated the data and the information would be old news. Also, by then, the original investigators would probably have gone on to other pursuits and lost interest in their vaguely remembered research. Consequently, much interesting research never reached medical or pharmacological journals. It's not easy to rewrite and publish studies completed more than a decade ago (not to mention 35

to 50 years, as with this book).

I believe there are very few good reasons for the Army to suppress human pharmacological data. It tends to isolate the researchers and create mistrust among their civilian peers. Within the military fraternity, of course, there has always been considerable sharing of information. The British, the Canadians and the Australians were well aware of research done in American laboratories. This was a reciprocal arrangement, formalized at scheduled intervals by a "Quadripartite Conference" among the English-speaking allies.

Although excessive secrecy no doubt played a part, our program, regarded benignly in the early 1960s as a patriotic necessity, was caught up in the swollen current of public outrage about the war in Vietnam. As William Hammond, Senior Historian at the Army Center of Military History, remarked not long ago in a televised C-SPAN interview, "Context is everything."

* * * * *

18 GOOD AND BAD VIBRATIONS WITHOUT AND WITHIN

If the critics were always right
we should be in deep trouble.

Robert Morley

Were it not for our northern connection to the rest of Maryland, one could have called Edgewood Arsenal a "tight little island." We knew there was a larger world out there, and we watched it on pre-cable network TV stations and read about it in The Washington Post or The Baltimore Sun. But I recall many days passing without my having the slightest idea of what was in the news. John F. Kennedy's assassination and the first landing on the moon kept all of us glued to the screen but in general, couch potatoes were as rare as truffles.

Work, play and family life used up the hours. I spent more time watching "Lost in Space" with my kids than listening to Walter Cronkite telling us "and that's the way it is" or checking out Art Buchwald's latest comedic diatribe. The once-familiar distractions of city life were absent. But at least traffic tie-ups, city noise, billboards and roaming gangs did not exist in our surroundings. In fact, there was not a single traffic light in all of Edgewood Arsenal.

This was nice, but in some ways, it could also be a liability. We were slow to notice the darkening cloud of public disapproval as its growing anti-military shadow began to block out the sun that previously shone on our "classified" research program at Edgewood Arsenal.

While editorials criticized our secrecy, we failed to respond and did little to educate the public. Few government officials were inclined to offer effective rebuttals to the critics. Most of the media, suspicious of all things military, were

stingy in their allocation of space to anyone who spoke in "defense of Defense."

Personally, I thought the relatively strict secrecy policy was overkill. I always believed that truthful advocacy could work wonders. Defense policy makers clearly thought otherwise, which made me somewhat of a heretic. As a natural nonconformist, I always talked freely about our program whenever I had a chance to interact with the public. My first opportunity to do this came in 1969. Colonel Joe Blair, recently promoted from Chief of the Medical Laboratories to Deputy Director of Medical Sciences in the larger Chemical Research and Development Laboratory down the street, asked me to take his place at a meeting in Salt Lake City.

The organizers of the Biennial Western Conference on Anesthesia had invited Joe to present a summary of the medical research going on at Edgewood. Joe called me in and told me that his many other duties had him snowed under. I suspect his reluctance actually came from was his lack of hands-on research since the days when he had made his reputation studying frostbite in Alaska. In any case, he wanted me to be his spokesperson and as usual I jumped at the opportunity.

"Maybe I could give two presentations," I suggested brazenly.

"Oh?" said Dr. Blair.

"Sure, why not?" I continued, noticing he raised no immediate objection. "I can easily do one on incapacitating agents, but I suspect anesthesiologists would also want to hear about nerve agent poisoning and its treatment."

"Sounds reasonable" he replied, "assuming, of course, that they would want you to do that." Joe would rather agree than disagree with any suggestion.

"It would be good publicity for the program." I continued. "We rarely have a chance to explain to civilian practitioners what we are actually doing. A lot of them think we are up to no good."

Joe nodded sadly, acknowledging the truth of my argument. He told me to go ahead and see what response I got. The meeting organizers enthusiastically approved the offer, and I jubilantly set to work on the presentations. In truth, I knew relatively little about nerve agents. By agreeing to lecture on the subject, however, I had created a strong incentive to narrow my knowledge gaps. Fred Sidell was the primary expert on the subject and generously provided me with relevant articles and slides.

The trip to Salt Lake City turned out to be a pleasant interlude. The lecture on "Treatment of Anticholinesterase Poisoning" was scheduled for delivery to the anesthesiologists, but the one on "Incapacitating Agents" was moved to the lecture schedule for the anesthesiologists' wives. I unofficially changed the title to "Fire or Ice" and began by reading the famous poem by Robert Frost:

> "Some say the world will end in fire, some in ice.
> From what I've tasted of desire I hold with those who favor fire.
> But if it had to perish twice, I think I know enough of hate
> To say that for destruction ice is also great and would suffice."

I went on to compare LSD to fire and BZ to ice. The ladies were much entertained by this approach.


Dr. J. S. Ketchum
. . . "ultra cautious"

A debatable description…

While leaving the building for lunch, a reporter approached me, wanting to know more about our program. Perceiving an opportunity to correct some misperceptions about our volunteer testing, I provided him with unclassified information about the type of agents we tested and the way we recruited and treated our volunteers. I also bragged a bit about our rediscovery of the effectiveness of physostigmine.

He took my picture and seemed favorably impressed. The resulting article appeared in The Deseret News, a newspaper widely circulated in the Salt Lake area. My theory that openness was the best policy seemed vindicated by the positive coverage given to the Edgewood program. It definitely appeared to be a beneficial bit of PR for the Chemical Corps.

While I was on a nearby golf course the following day, a young Associated Press reporter began trailing me from hole to hole, asking more questions. Again, I conversed with him quite openly.

"Do you suppose we could have someone visit Edgewood Arsenal and tour the facility," he asked.

"I don't see why not," I replied, as I sliced a tee shot into the lake. "Of course some of the work is classified, so there would be some limitations."

"Of course," he replied.

Once again, I believed this would be a chance to debunk some of the horrific myths appearing in the news media. Ah, the naiveté of those who are unfamiliar with how the media operate!

In due course, the AP sent a letter to the Director of the Medical Laboratories, quoting my invitation, and requesting permission to visit. Unfortunately, Secretary of Defense Laird had just placed an embargo on all media visits to our facility. Sensing a ground swell of anti-Chemical Corps sentiment, the Administration had invoked the "classified" shibboleth, hoping to minimize publicity.

Back came The Associated Press, aggressively reminding Edgewood that I had said such a visit would be okay, and to renege would create an impression of bureaucratic censorship. They demanded that the invitation be honored, subtly hinting at journalistic blackmail. There seemed little alternative but to grant access to a small group of reporters.

I volunteered to escort the visitors around to the various clinical facilities, and spent the entire day with them. A woman reporter led the group, accompanied by a very casually dressed, long-haired photographer. Assuming my most cooperative demeanor, I showed them everything allowable, and answered all their questions frankly. I figured they would put a negative slant on anything that seemed evasive or untruthful. Invoking a little gentle sarcasm to lighten the atmosphere, I made an occasional facetious remark as we made our way through the facilities.

Observing the aftermath of a masked volunteer who had been sprayed with tear gas in the large interior open area of our building, the woman reporter asked what would happen to the small puddle of tear gas that lay on the cement. "Oh I guess it'll be picked up by the wind and carried into downtown Baltimore," I quipped, "incapacitating the entire city." Judging from the expression on her face, I may have overestimated her sense of humor. Sure enough, she later

quoted me precisely, characterizing my comment as "black humor."

During lunch, I sat beside the photographer, trying to convey that Army doctors could also be hip, citing my time in the Haight-Ashbury clinic and my appreciation of rock and roll. I was hoping to soften his automatic response to a military man, stemming from his anti-establishment sentiments. I don't think I succeeded.

After lunch, he asked to take a picture of Dr. Silver, the head of CRDL, COL Blair, his medical deputy, COL Uhrig, the head of the Med Labs and me. He got up on a stepladder and shot a picture of the four of us looking up into the sun. It was not the most flattering portrait, and when it appeared later in the papers, I felt it was a sly attempt to make us all look mildly villainous.

Soon after their visit, a lengthy article, illustrated with several pictures, appeared in numerous major newspapers. I began to receive "for your information" copies from all over the country. Allegedly, 6,000 news publications featured the article, sometimes in whole but mostly in part. I quickly discovered that conservative newspapers tend to edit out critical portions of a controversial story, while liberal papers tend to omit the more favorable passages. As usual, the term "unwitting guinea pigs" appeared again and again.

Dr. Seymour D. Silver, front, director of research labs at Edgewood, and his staff, from left: Col. Henry T. Uhrig, director of medical research labs; Col Joseph R. Blair, deputy director for medical sciences and Lt. Col. James Ketchum, chief of the clinical research department, stand in front of one of the buildings that make up the "nerve gas capital of America."

Associated Press photograph of Edgewood researchers

After the dust cleared, COL Paul Cerar, the Post commander, invited Joe Blair, Hank Uhrig and me to his office.

"Well, Jim," he said, "I imagine you learned something from this experience."

"Yes Sir," I said, "I sure did."

Fortunately, Paul Cerar was an avid tennis player. In fact, we had teamed up in the doubles category, and won the annual Post tournament. The Post newspaper showed a nice photo of us sharing the trophy. I think this moderated his criticism of my intemperate behavior. At least there were no further repercussions.

I recall very few angry critics before 1966, but after 1968 they became prevalent. My first head-to-head encounter with a passionate foe of chemical warfare research, medical or otherwise, came when I wrote to C.R.B. Joyce, requesting a reprint of one of his recent articles. Sending complimentary reprints to fellow investigators was an almost universal courtesy. Nevertheless, our exchange was as follows:

Dear Doctor Joyce:

I was delighted to find your recent report in Life Sciences indicating that taste sensitivity may be used to predict pharmacological effects. This ingenious study provides an approach which may be useful indeed in some of our work here, and I have discussed it with several of my colleagues who have been wrestling rather unsuccessfully with the problem of predicting individual responses to certain chemical substances.

I am wondering if perchance you may be acquainted with any data or ongoing investigations concerning differential sensitivity to materials of the anticholinesterase variety,

for example, eserine (physostigmine). My own limited search of the literature, thus far, does not indicate any definitive work in this area. I realize this may be a bit afield from your principal interests but hope that nonetheless you may have some knowledge on this point.

Your work has fascinated me for some time. Perhaps if you are planning to attend the next CINP meetings there may be an opportunity to meet and discuss areas of mutual interest.

If a reprint of the above article is available, it would be most appreciated.

Sincerely yours,

James S. Ketchum, M.D.
LTC, Medical Corps, USA
Chief, Clinical Research Dept
Medical Research Laboratory
Edgewood Arsenal, Maryland

The London Hospital Medical College
University of London
Department of Pharmacology and Therapeutics

18 February 1969

Dear Colonel Ketchum,

Thank you very much for your letter of 23 January, to which I can now reply after returning to this country.

Although it is usually gratifying for a scientist to receive evidence of interest in his work from colleagues, I must assure you that evidence of such interest from Departments of chemical or biological warfare research fills me with anxiety. I have already received a request for a report from a colleague of yours at Edgewood and wrote him a letter detailing under three headings why I was not prepared even to send him a reprint. I must continue this same firm stand in respect of your perfectly courteous request.

Although I am aware that most of the work that you and Porton, etc., undertake is freely published, there remains the absolutely unacceptable provision that the work of you and your colleagues can always be subject to classification: hence, so can that of anybody who has lent you even the most marginal assistance. Once my own work is published I cannot of course control what is done with it, but I am not obliged to connive at or encourage its utilization in the ways that stand contrary to the basic principles of freely exchanged information upon which the future of our civilization depends.

I should be delighted to meet you in Basel, Switzerland, where we can perhaps continue a discussion, the outcome of which I hope will not be as predictable as is all too frequently the case with those of your British colleagues in this field whom I know.

With best wishes for your enlightenment,

Yours sincerely,
C.R.B. Joyce

I had never before received a refusal to a reprint request. Obviously, I could easily have copied Dr. Joyce's article from library issues of the journal. However, this violation of the customs of scientific courtesy seemed a bit like a violation of "separation between church and state."

But this was just the beginning. In May 1970, *The New England Journal of Medicine* published a vitriolic letter received from a professor of pharmacology at the University of British Columbia in Vancouver:

To the Editor:

Over the years, I have received hundreds of reprint requests for my papers from physicians and others in American military installations. I have never yet received such a request from any military establishment outside the United States. Much of my research is concerned with the biochemical basis of mental deficiency and serious mental illnesses

such as schizophrenia. Although many of the reprints I receive from the military are undoubtedly from physicians giving legitimate care to patients, it is particularly disturbing to receive such requests from persons at places like Fort Detrick and the Edgewood Arsenal. One wonders why there is so much military interest in neurochemistry. I cannot see why part of my research funds, derived from Canadian sources, should be used to convenience the American military, which are waging a totally unjustified and cruel war in Southeast Asia. I am therefore now answering requests from military addresses with the following letter:

I am returning with this letter your recent reprint request, but am not enclosing a reprint of the article you wished.

In recent years I have received an increasing number of requests for my papers from American military addresses, some of them well known as centres where chemical and biological warfare weapons are developed. I can no longer in good conscience extend the courtesy of sending reprints of my work to American military personnel, especially since there is no practical method by which I can judge how the recipient intends to use my work.

As a physician and scientist, I am appalled at the cruel American military aggression in Viet Nam, now escalated over all of Indochina. To waste the enormous wealth of the United States in killing Asians, instead of spending it for better health, housing and nutrition for the poor of the United States and the rest of the world, is grossly immoral. I do not wish my research used for any purposes except for the preservation of health, and the relief of human suffering.

This is perhaps a feeble effort to express my protest at the misuse of science for antihuman purposes. What can a medical scientist do, besides refusing to work on military projects and insisting on the right to publish all his research in the open literature? It seems to me that physicians and medical researchers, both within the United States and abroad, should be taking far more initiative to see that their skills are used only for purposes in accord with the best traditions of medicine. What constructive suggestions have the Journal's readers to offer?

Thomas L. Perry, M.D.
Professor of Pharmacology
University of British Columbia
Vancouver, British Columbia, Canada

I wrote a personal letter to Dr. Perry, expressing regret that he found it so easy to label people he had never spoken to as somehow evil and up to no good. He did not reply, but I was heartened to see six letters of dissent (space permits only the excerpts below), published in a July issue of *The New England Journal of Medicine*, under the heading:

WAR PROTEST CRITICIZED

To: the Editor: I should like to reply to Dr. Thomas Perry's letter published June 18, 1970. Dr. Perry's objections are well intentioned there is no doubt. He is concerned about our inappropriate and immoral national policies. He is concerned about potential misuse of scientific information for purposes other than the good of mankind. How can anyone disagree? Yet his approach will not serve to implement any real change in the basis for these concerns…. If we contemplate changing the course of our nation, must we not direct our efforts toward those capable of seeing that a change takes place!

Edmund J. Lewis, M.D.
Assistant Professor of Medicine
Harvard Medical School
Boston, Mass.

To the Editor: I should like to congratulate Dr. Perry for his ingenuity in contriving a platform for giving vent to political views…. I suggest that he either not publish or publish in a secret journal whose subscribers have identical political beliefs.

H. R. Hellstrom, M.D.

Pittsburgh, PA

To the Editor: Dr. Thomas L. Perry's war-protest letter requested constructive suggestions of the Journal readers. I should like to ask him "constructive to whose way of thinking?" ….His knowledge of such places as Fort Detrick and Edgewood Arsenal seems rather remarkable for a pure scientist. I am certain that the majority of American medical researchers do not have this feel for these installations, let alone similar Canadian military bases.

Joseph D. McGeary, M.D.
Associate Medical Director
Fidelity Mutual Life Insurance Company
Philadelphia, PA.

To the Editor: One wonders how Dr. Perry can insist on the right to publish all his research in the open literature and yet withhold it from the military…. I would point out to the professor that the majority of physicians in the armed forces are not there by desire. They recognize that they have a duty to perform, a very large part of which is to save human life. It is therefore most difficult to protest when by protest, lives might be lost. Finally, I am glad Dr. Perry described his own protest. It is feeble.

F. W. Burke, M.D.
Honolulu, H.I.

To the Editor: The recent letter from Dr. Perry explaining why he now refuses reprints to physicians in the American armed forces deserves a reply. …To withhold reprints from physicians with an American military address will certainly not keep any scientific information out of the hands of the American scientists working on defensive measures against the possible use of such weapons.

Robert F. Jones, M.D.
Associate Professor of Surgery
University of Texas
Southwestern Medical School at Dallas

To the Editor: I do not know if the Journal published [Dr. Perry's] letter to indicate support of his views or to draw reaction from readers. This letter appears to represent a classic case of "spillover egomania" in which total ignorance of a subject far outside one's chosen field is no bar to lengthy discourse. ….The use of such phrases as "totally unjustified and cruel war," "cruel American military aggression," "grossly immoral" and "misuse of science" would lead one to suspect Dr. Perry's objectivity under any circumstances.

Richard H. Bailey, M.D.
Glastonbury, Conn.

There were no letters supporting Dr. Perry in that issue of the *New England Journal* (although some appeared in the next issue). I was surprised to see so much support for the work we were doing.

* * * * *

Meanwhile, I tried to match the excellence of Fred's performance, but it was becoming increasingly difficult. Mostly, my motivation was declining. About eight months before the usual time for reassignment, I decided I no longer wanted to be chief of Clinical Research. I realized that those in coveted leadership positions do not ask to be demoted very often. In fact, I had never heard of such a thing. Many would consider it tantamount to a dereliction of duty.

When Hank Uhrig, heard that Joe Blair had approved my request, he clearly felt that I was being disloyal. But from my standpoint, the opportunity to conduct and publish important research was being lost in a bureaucratic fog of administrative headaches. I remembered how Hank had once told me that he wanted me to replace him as laboratory chief when he retired. To me this was not an enticement. It seemed like a step up into more administrative and political

entanglements that would put a virtual end to personal research.

There was also another reason for my decision. For too long, I had deferred taking the Specialty Board Certification Exam in Psychiatry. Normally, this is something that clinicians try to get out of the way as soon as they become eligible – usually two years after completion of residency training. For almost twelve years, I had only occasionally done any clinical psychiatry. Without practicing a specialty, much of what one learns during residency rapidly fades away. I knew it would take several months of intense study to prepare for the written exam in May.

So I stepped down from being Chief of Clinical Research and spent several hundred hours going through a 1200-page textbook. I made up hundreds of questions and answers and recorded them on several dozen audiocassettes. I played these in the car, in my office, and even fell asleep listening to them. But it paid off. In May 1971 I passed the written exam.

In the meantime, Van had moved into my office. As Chief Scientist, he had lost much of his influence over the clinical program except as a gatekeeper, approving and disapproving proposals. I think he was pleased with the unexpected change, since he seemed to prefer running things to hands-on research.

With a nagging sense of guilt, I wrote and distributed an apologetic letter to all the Department members, explaining my decision. Reading it over later reawakened my discomfort. I felt like Benedict Arnold. However, as Julius Caesar noted, once one crosses the Rubicon there is no turning back.

Now there was no longer a sunny, spacious office for me to occupy. Instead, I was working in a small L-shaped room, originally intended as a supply closet for the janitor. The walls were painted concrete blocks, and it had a 28-inch doorway, too narrow to bring in a desk. It seemed like a medium security prison cell, with only one small window high on the wall. If you stood on a chair, you could look outside and see the cars go by. When I was a kid, we had a similar window in our basement coal bin. During the winter, five tons of anthracite came cascading through the window, down a chute and into the coal bin every few weeks, so my Dad would have enough fuel to shovel into the furnace.

Actually, I did not mind the tomb-like austerity and welcomed the solitude and additional time to write and study. In October, I completed a two-week course in computer programming on the PDP-12, a marked improvement over the PDP-8 we had at Stanford. Computers would eventually become one of my obsessions.

The psychochemical empire was crumbling. I had come back to Edgewood expecting to lead an exciting charge into new research, accompanied by enthusiastic comrades. Instead, it was now clear that I would soon be much like the proverbial month of March – in like a roaring lion, out like a barbecued lamb. Life can be strange. However, as the cabdriver in a Woody Allen movie once said, “Yeah, that’s the way it is with everything.”

* * * * *

19 REARRANGING THE DECK CHAIRS

Our duty is to believe that for which
we have sufficient evidence,
and to suspend our judgment when we have not.

John Lubbock [1803-1865]

The Korean generals come to visit

Actually, life was not quite as gloomy as the above chapter might lead one to believe. A number of interesting, often amusing activities provided pleasant divertissement from my tedious responsibilities and frustrations as Department Chief. I have no complaints, for example, about time spent on personal leave, giving guest lectures elsewhere or serving as tour guide for officials of all kinds – including an intriguing group of Korean Generals.

Also, there were many outside conferences and meetings. I traveled to Virginia, South Carolina, Illinois, Texas, Utah, Alabama, New York and New Hampshire. In California, which I sorely missed, I stayed briefly in San Francisco, Los Angeles and San Diego. The trip to San Diego involved a particularly interesting research symposium on the future of warfare.

My paper on incapacitating agents was mostly a rehash of old material, but included a few new off-the-wall ideas of my own. I also met Joe Coates, a six foot seven inch, very brainy civilian with an Abe Lincoln style beard, who worked at the Institute for Defense Analysis in Washington, DC. We exchanged letters after the conference, but as with most chance meetings, the relationship was brief.

A seminar in Virginia with a group of statisticians was more amusing. I actually enrolled in it by mistake. Its prospectus included a call for "clinical papers." Thinking this meant clinical medical experiments such as ours, Phil Kysor and I signed up to present a paper. We spent hours generating a fancy statistical matrix of performance scores with various cutoffs. Proud of our slides, we were stunned on arrival that to statisticians, "clinical" meant something entirely different. It did not mean clinical pharmacology, medicine or psychology.

In this crowd, our poor attempts at statistical innovation seemed very amateurish. We were drowning amidst advanced models of multivariate analysis, Monte Carlo simulation models, and complex multiple regression equations. The distinguished mathematicians breezily conversed in an unfamiliar patois.

We were definitely outclassed by these specialists. When they realized we were just a couple of headshrinkers, they took pity on us, even helping us put food on our plates at dinner. (A fleeting thought crossed my mind that they might even offer to help us cut those rubber chickens into bite-sized pieces.) Thankfully, they did not berate us for assuming the subject of the conference was right up our alley. They knew we had made a brave (though largely unsuccessful) attempt to convert ordinary rows and columns of numbers into something statistically interesting.

Another incongruous event was the receipt of an engraved invitation, which read as follows:

To Celebrate
The Fifth Anniversary of the
Independence of the Republic of Zambia
The Ambassador and Mrs. Banda
request the pleasure of your company
at a Reception
on Friday, the twenty-fourth of October 1969
from six-thirty until eight-thirty o'clock

Regrets only *The Lincoln Room*
265-9717 *The Washington Hilton Hotel*

Of course, I felt greatly honored by this invitation. It sounded like an important occasion, although in truth I did not have the faintest idea why I was on the guest list. I checked with some of the other senior officers. No one else had been invited nor did anyone have any idea what it was all about.

To be safe, I attired myself "to the nines" in my Dress Blues, shined my shoes and brass insignia and drove to the Washington, DC hotel. I found the ballroom and took my place in the reception line. The Ambassador was regally attired, and both he and Mrs. Banda greeted me cordially, although they seemed puzzled as to who I was. They urged me to enjoy myself. Not knowing what else to do, I moved to the central table, which was laden with champagne-filled glasses, enticing fruit and hors d'oeuvres of every description.

By this time, I noticed that I was the only one in uniform – and the only non-African – in the entire ballroom. I tried to be as suave as possible, casually helping myself to quite a bit of champagne and a few snacks. I struck up a brief conversation with a tall, radiant woman dressed, as were most, in colorful African garb. Then, since no one seemed to be interested, or even aware, of my presence, I quietly took my leave and drove the 65 miles back to Edgewood. Another unsolved mystery for my diary.

Sometime during my second year as Department Chief, another very curious episode occurred. One Monday morning, I entered my office to find a large black steel barrel, resembling an oil drum, parked in the corner of the room. I assumed that there must have been a reason for somebody to put it there and probably not one that I needed to know, so I ignored it for a day or two.

On the second or third day, however, my curiosity overcame my discretion. Having neither asked for nor received any comment or explanation about the black drum, I decided to become Inspector Clouseau. After everyone had gone home, I carefully opened the hasp that held the retaining ring in place around the cover, and peered inside. Neatly labeled, tightly sealed glass canisters, looking like cookie jars, filled the entire drum. I cautiously took one out and examined it. According to the label, it contained approximately three pounds of pure EA 1729 (LSD)!

The next canister had a similar label, indicating about the same amount of EA 1729, expressed to a tenth of a milligram. The remaining canisters, perhaps a dozen or more, looked just like the first two, presumably with similar contents. For a moment, I considered indulging the temptation to remove a very small amount, and save it for some "future experiment." However, I quickly dismissed this idea as being a good way to get in trouble, and not worth the risk. In addition, I knew it was wrong – another rather important consideration. So I replaced the top, re-fastened the hasp and thereafter dismissed the drum and its contents from my mind.

It was Friday, as I recall, when I came to work and found that the drum had vanished. Thirty or forty pounds of chemically pure LSD had spent a week in my office and had now disappeared with no comment from anyone, no receipt form and no other paper work! Enough LSD to intoxicate several hundred million people (by my estimate) had come and gone. I never received any explanation and never asked for one. I calculated, however, that if sold on the street in individual doses, the contents would have been worth close to a billion dollars!

Many years later, I thought about this incident and it still seemed mysterious enough to serve as the basis for a novel. In fact, I spent several months writing 15-20 chapters. Then I gave up, as I realized I lacked a decent plot or the story-telling skill to develop one successfully.

Coincidentally, the movie 2001, with its unexplained black monument on the surface of the moon, had appeared about a year before my encounter with the black drum. The similarity struck me as quite spooky, and remains somewhat spooky as I think about it today.

While I am recounting strange happenings, it would be remiss of me not to recount "the VanSint (sic) prank," that Fred and I concocted for our own amusement.

Science magazine had printed a summary of a pharmacology conference where a prominent scientist, Dr. David Nachmanson, had expounded his formulation of the mode of action of cholinesterase inhibitors. His list of references included a study published earlier by a "Dr. VanSint." Fred and I sensed the opportunity to shake up our beloved Chief Scientist a little bit. We forged a dissenting view addressed from Van to Dr. Nachmanson, filling it with preposterous assertions. We typed it carefully, and signed it "Van M. Sim, M.D." (as distinct from "Dr.VanSint").

Next, we composed a simulated reply from Dr. Nachmanson, addressed to "Dr. VanSint," which included a carbon of the absurdly incorrect letter Nachmanson had (supposedly) received from someone named Van M. Sim, sternly taking Dr. VanSint to task for failing to rein in his young, out-of-line protégé, "Sim." We even arranged to have Nachmanson's (forged) letter typed on official looking stationery and mailed from the city of his residence. It read as follows:

December 30, 1970

Dr. VanSint
Scientific Director
Medical Laboratories
Army Chemical Warfare Center
Edgewood Arsenal, Maryland

Dear Dr. VanSint,

While not wishing to offend either you or your protégé Sim, I must state that your letter has puzzled and disturbed me. I would expect you to support the younger scientists in your laboratory, but in a case where there is a plain error in judgment, it seems to me you ought to take a more objective view. I agree that young Sim has done some interesting work and seems to be conversant with the general field of cholinesterase inhibitors, but I think more supervision is indicated. Actually, I am surprised that a scientist of your rank and reputation would endorse without qualification some of the bald statements he has made publicly.

Perhaps, sir, your own grasp of this field is not what it once was. I have heard that the Army Chemical Warfare Center is constantly subjected to significant concentrations of a variety of chemical products, some of which may have hallucinatory effects. I suggest you investigate the possibility that some covert brain damage may have occurred in the course of your long association with these substances. Your remarks are not those of the man I once knew and respected so highly when I first read your incisive and authoritative accounts in the literature. In short, sir, I think you may have gone daft.

I'm afraid I cannot take any apologia for young Sim very seriously. He has made some grievous errors in his letter to *Science*, and I do not intend to let him off the hook.

Sincerely yours,
David Nachmanson, M.D.

We arranged to mail this letter, along with a copy of the letter we had ghostwritten for Van, from Nachmanson's address. Its contumelious admonishment, accompanied by a copy of a supposed letter from "Dr. VanSint" to Nachmanson, defending "young Sim", duly arrived on Van's desk. When Fred and I innocently stopped by that morning, he called us into his office. Holding both letters up, he roared rhetorically "What in the Hell are these supposed to mean?"

Van looked shaken. We shook our heads and affected shock and perplexity. Then, fearing he might have a stroke, we took pity and disclosed the elaborate prank. Van said nothing for quite a long time, trying to figure it all out. Finally,

he got the joke and relaxed, loudly giving out his familiar and jovial guffaw. Later, Fred and I agreed that Van was actually a pretty good sport, once he understood which sport he was playing.

* * * * *

I had not tried to do any private practice during my first tour at Edgewood, although some of the other doctors sought and received permission to do so for a limited number of hours each week. I finally decided to do the same, obtained a Maryland license and began a very small practice in nearby Bel Air. Among other things, I wanted to revive my clinical skills, since at that time I was planning to apply for Board Certification in psychiatry within the next year or two.

Unable to afford my own office, I contacted the only psychiatrist in Bel Air, and arranged to use his "home office" for a few hours a month. He asked me to pay five dollars an hour for this privilege and I thought this quite reasonable. After finding a couple of patients who were willing to pay twenty-five dollars an hour (a modest fee), I began to do psychotherapy and the results were fairly encouraging.

One Saturday afternoon, as scheduled, I met with one of my two patients in the psychiatrist's living room. We sat down and the session began as usual. While she was talking, however, my eyes drifted to the edge of the rug, where I observed a large, fresh, well-formed dog turd. She, however, didn't appear to notice it and continued describing her latest dreams. I couldn't help wondering, nevertheless, how the good doctor was able to conduct his practice with such an irresponsible dog. Perhaps the unusual décor was an unconscious act of retaliation, by both doctor and dog, for being obliged to vacate the living room. Check with Freud.

My most unusual patient was a young man who lived with his wife in a trailer. His main complaint was his inability to go anywhere without severe anxiety. This problem dovetailed extremely well with my lack of an office. His wife, however, complained that from her point of view, his most serious problem was impotence.

Although I had to drive 25 miles to reach his trailer, the results of treatment were gratifying. Providing him with Dexedrine and psychotherapy for a few months produced remarkable improvement. Not only could he go out for short walks, but he also reported with pride that he had resumed having sex with his wife.

I couldn't resist describing his progress in a letter to my former mentor in psychiatry, Dr. Mack Badgley: "Last week the patient had sexual relations with his wife four nights in a row, exceeding his monthly personal best by at least two. It was also his highest unbroken nightly series, highest quarterly total and highest total not on a weekend for three years. In fact, his wife was now complaining that he was getting well a little too fast for her to keep up with."

* * * * *

I was now obviously becoming a highly skilled psychotherapist (!), but the situation in the lab failed to improve. Although we had an imposing group of experts in a broad range of specialties, productive research continued to languish. If only the prevailing zeitgeist (and my own attitude) had been more positive, we could have accomplished great things.

One project that had great appeal was chemist Bob Ellin's development of a "people sniffer." It consisted of a steel tank large enough to accommodate a

volunteer sitting in his underwear for half an hour. After collecting the emanations from the subject's breathing and perspiration, Bob was able to use a combination of gas chromatography and mass spectroscopy to detect trace quantities of as many as 60 different molecules.

It was the first device of its kind and appeared to have great potential. Physicians had long noted, for example, that distinctive odors are associated with some diseases. Since the "people sniffer" greatly surpassed the human nose in sensitivity, it might pick up serious progressive illnesses at earlier stages, enabling timely treatment.

Bob Ellin, Ph.D, discussing his "people sniffer" with his technician

Fred and I suggested, in a lengthy memo, that when chemical weapons research had run its course, our impressively equipped building could become a center for general medical research. There was no official response to this suggestion. Apparently, the "sniffer's" intended use was limited to the detection of hidden Viet Cong soldiers. We wished the Chemical Corps agenda were not so shortsighted. Valuable humanitarian applications seemed to reside within reach of such advanced capabilities. So much for innovative ideas.

* * * * *

20 FINAL DAYS AT EDGEWOOD

History repeats itself.
That's one of the things wrong with history.
Clarence Darrow

The music had paused and "the jig was up" – but there was still a waltz or two left on my dance card. While my office bore little resemblance to a clinical testing area, I was still a research psychiatrist. I had turned a deaf ear to the tedious rhythms of administration, but the lively beat of innovative research melodies kept my feet tapping.

Psychologist Eddie McCarroll, internist John Markis, chemist John Houff and I put together the orchestral score for a realistic test of infantry skills. Even Van Sim joined the chorus. The theme was EA 3834, not quite as potent as BZ, but much shorter lasting and more rapid in onset. The search for more effective incapacitating agents was not yet over.

Infantry officers rehearsed two teams of four men in the necessary skills of a rifle unit. They reviewed the methods of loading, firing and cleaning rifles, donning gas masks, detecting aggressors, reporting intelligence data, proper use of field phone and compass and the ability to interpret and respond to orders. The infantry officers agreed to rate the test performance of the subjects without knowing the dose assignments.

My mind roams to the Utah desert, where, almost exactly six years ago, Mars generators laid down a cloud of BZ smoke, while we laid down rules and procedures for scoring performance. Now, we prepare to test another drug with volunteers whom some will call "unwitting guinea pigs."

The men spent two days in a classroom, reviewing the elements of tactics, and an additional three days practicing skills and maneuvers in the field. Safely tethered rifles containing live ammunition and actual firing at silhouettes were part of the design. Those who would be the judging officers spent an entire day watching the teams rehearse. Together, they standardized their criteria for scoring the performance of each element in the scenario.

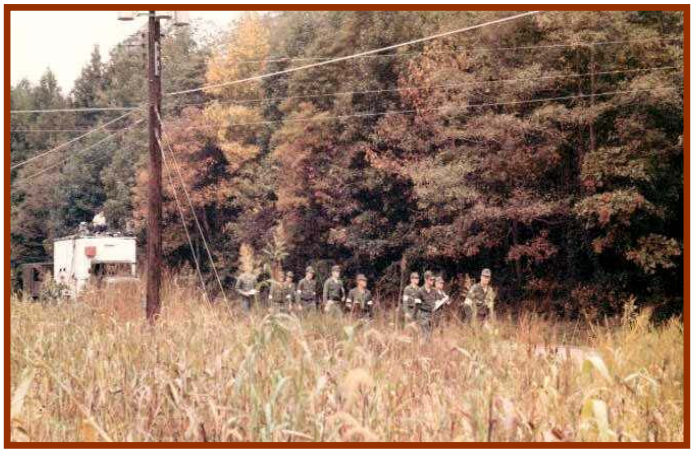
I'm wondering how well the judges can evaluate the efficiency of men who have had time to practice in a safe environment? Would they do as well on a real battlefield?

On the day of the test, dressed in full field gear and carrying their equipment, the men march along a dirt road to a point marked on their protocol map. They enter the woods, where the patrol leader gives them final instructions. He inspects each set of field equipment. A nurse injects each soldier. Some receive an assigned dose of EA 3834 while others receive a placebo.

EA 3834 Field Test – Volunteers on the road

I wonder to what extent placebos affect performance. Over the years, our tests have shown that our volunteers are not "placebo responders." They can judge quite well how their minds and bodies are affected and they are not very suggestible.

The mission instructions are repeated once again: reconnoiter the area indicated on their maps, observe and report "enemy" activity and search for items useful to the intelligence unit. Move cautiously, as if in a combat environment. If a sniper is visible and is firing a weapon from a hiding place in the woods, return fire and resume the mission. When encountering gas, mask immediately. Check to see that the mask is cleared and properly adjusted. When safely across the road and in the clear, remove the mask and return it correctly to its carrying case.



Squad watches for signs of "enemy" activity

I know that when the drug begins to work, some will have difficulty walking in the right direction and others will forget what to do. The judges will be there to write it all down.

At the edge of the woods, you may again receive fire from "aggressors" in a fortified foxhole. If unable to return fire, maneuver and try to secure a safe position. Connect the field telephone to an available wire. Request mines and additional rations, and use the telephone to relay to the squad leader the events that have just occurred. If one of the men no longer responds to commands or seems on the verge of jeopardizing the mission, request his medical evacuation as soon as he is out of the range of enemy fire.

Will they be able to observe and understand what the aggressors are doing? Can they move in a tactically intelligent direction? No doubt, their vision will be blurred by the drug effect, and they will have difficulty reading the markings on the map.

Aid Station provides treatment with physostigmine

Are they nervous? What is it like to be a soldier venturing into dangerous territory? Is it possible to resist the drug effects and still be able to concentrate on the task at hand? Can the volunteer subject overcome a sense of weakness in the legs?

Now map the area by compass and give range estimates to supporting elements. If able to maneuver safely to an observation point, watch and report the details of aggressor activities. Finally, make necessary preparations to defend against an aggressor attack, which may be preceded by a smoke screen.

A medical aid station and an interrogation center are set up in a large tent not far from, but out of view of, the foxholes. An ambulance is ready to evacuate casualties whenever the team leader requests it. Capture and interrogation by aggressors might occur before the ambulance can arrive, If so, make every attempt to withhold information regarding the location and plans of the main forces.

Realism is stressed in field exercise

Now will come the questions. "What is the location of your unit, soldier? Is it planning an attack soon? Where is your commanding officer?" Some cannot recall and some will become confused and give up important information. Some of it will make no sense and some will be false – an advantage to the friendlies. But some will be true, revealing secrets.

When a casualty is safely evacuated to the treatment area, the medical staff will provide diagnosis and treatment with physostigmine, if indicated. If the antidote restores him to normal or near-normal function, he will return to his unit

accompanied by an aid man, who will provide the leader with supplemental oral doses of physostigmine. An additional dose will be entrusted to each casualty in case he feels he is becoming confused again and no has the presence of mind to treat him.

The soldier may be wondering, "What is this stuff they injected me with?" The doctor did it twice, but I only remember one. He said I should swallow this pill if my thinking gets fuzzy. It has been at least an hour. I think I'll take it now, because I'm starting to feel dizzy and my mouth is getting dry again."

Clinical staff monitors the exercise closely

The field exercise terminates at 1500, six hours after agent administration. The men return to the ward by ambulance, receiving additional doses of antidote if needed and remaining under medical care until full recovery. They complete their Symptom Checklists and write summaries of their experience.

* * * * *

The exercise came off satisfactorily and without incident. Performance ratings by the officer-judges correlated closely with the NF scores and the other measurements. At low doses, the men were able to carry out tasks, but needed some help from the team leader. Those who received high doses were unreliable if left on their own.

Lloyd's videotape coverage was comprehensive and performance ratings by the medical staff agreed closely with those by the Infantry judges.

Field exercise is comprehensively documented on videotape

This was the first test in which subjects showed they could return to the field after treatment with physostigmine. It was also the first time the team leader, or the team members themselves, were given physostigmine pills and allowed to give additional treatment while continuing the mission. We had validated the concept of self-treatment during combat, at least in a simulated setting. Without it, performance fell back into the incapacitated range within 2-3 hours.

As I watched, I realized it was probably the last field test of a BZ-like agent I would have a chance to supervise. It might even be the last such test the Chemical Corps would carry out.

Here are the write-ups by two volunteers who received the highest doses. Subject D, who received 8.0 mcg/kg (a total of about 0.6 mg, slightly above the incapacitating dose) wrote as follows:

"I start at the beginning when we were in the woods and received our shots. About 2 minutes, maybe 3, I felt a real dryness in my mouth as if I had been trying to eat the Sierra Desert.

"We started across the road and walked 25 to 30 meters when I really felt the effects (slight dizziness) like after drinking 2 or 3 beers on a hot sunny day. Shortly after, I felt further effects like swaying back and forth. This got to the point where I finally lost almost complete equilibrium.

Finally, we made it to our OR, and that's when things didn't seem important at all. I felt like lying down and just looking at the sky. However, they wouldn't let me do that. So I kept moving around only to be stopped by someone and told to sit down. Nothing seemed to make sense.

I tried to walk away several times so the SGT made me dig a hole. I'd dig about three shovels full and then quit and start walking around again. Also, my speech was as if I was drunk. Then I was evacuated. I remember walking over the sand pile directly behind the foxholes. From that point on I remember very little.

I was interrogated by a fairly big man but I don't remember what he asked or what I answered except for one question. He asked the password and I told him FOXTROT which was wrong. It was number "13." Also, everything seemed slow and easygoing. I didn't give any answers purposely wrong because I felt too relaxed to worry about anything.

Everything else is one big blank until I woke up and LTC Ketchum was sitting beside my cot. We talked about the effects of the drug for a while, and I tried to recall what all had happened but to no avail.

We (LTC and I) agreed that I was ready to return to duty. After returning I felt fine except for a very slight intermittent dizziness and blurry eyes on an object within 3 feet of me.

It is now 1200 hours on Wednesday and the dizziness is gone, but I still have the blurry eyes.

Subject G, who also received 8.0 mcg/kg, wrote:

During this test I found that I had very little control over any of my actions. Although I seemed to have partial control over my physical actions, I could not make my mind and body function as one. It seemed as if my mind would not focus on a task long enough to get anything done.

I think that my only pronounced physical handicap was a loss of vision. These symptoms came on just about 20 minutes after receiving the drug and lasted until I was given the antidote.

I think that I was given the best possible treatment during this test. Safety was quite apparently one of the most important factors. I will also say that I would have no fear of being in another test such as this.

I will say that I could not perform duties in my MOS [ed. Military Occupational Specialty] while under the effects of this drug.

I think that if it wasn't for the close supervision during this test, that I would have fallen asleep and stayed asleep until the drug wore off. With this kind of effects I don't think that I would care what happened to me or where I was or what was going on around me.

I think that if it were not for the supervision of our team leader that this patrol would have ended as a complete failure, with just four or five men who didn't know or care why they were even out there.

These unaltered write-ups are obviously quite articulate. For this test, in particular, we had chosen volunteers with above average intelligence. Some had one or more years of college education and all possessed good writing skills. The test did not answer whether less gifted soldiers would have performed equally well. We knew, however, that in the lab, BZ and other belladonnoids affected basic skills equally, regardless of the subject's intelligence.

There was one particularly interesting result from this experiment. Despite emphatic instructions not to give up any "vital information" to interrogators, the men sometimes unthinkingly blabbed the data. This suggests that one might possibly use belladonnoid agents to gain intelligence from captured individuals. Previous searches by civilian investigators for a so-called "truth serum," however, had not been successful.

Dr. Lincoln Clark, at the University of Oregon, for example, had published an article about this subject years earlier, in which he had tried sodium amytal (the popular notion of a truth serum), and various other drugs. It would appear that agents such as BZ and EA 3834 might challenge the conclusions drawn from Dr. Clark's experiments. (The CIA had already tried LSD for the same purpose and found they could not use it reliably to extract deliberately withheld information.)

Although I had chosen administrative exile (the janitor's supply closet, to be specific), Hank Uhrig did countersign a letter of praise written by Van:

DEPARTMENT OF THE ARMY
HEADQUARTERS, EDGEWOOD ARSENAL
EDGEWOOD ARSENAL, MARYLAND 21010

SMUEA 16 October 1970

Subject: Letter of Appreciation

LTC James S. Ketchum
Clinical Medical Sciences Department
Medical Research Laboratory
Research Laboratories, Edgewood Arsenal
Edgewood Arsenal, MD 21010

1. Congratulations on your completion of an excellent field test program. Your planning and test procedures were excellent. You have aptly demonstrated agent effectiveness as well as therapeutic efficacy of treatment compound and procedures.

2. Because of your careful plan and strict adherence to an excellent protocol, the entire test period provided meaningful information with the safety and care of the individual being of paramount importance throughout.

(signatures)

VAN M. SIM, M.D.
Chief Scientist, Med Rsch Lab
Act Chief, Clinical Medical Sciences Dept.

HENRY T. UHRIG, M.D.
COL, MC
Chief, Medical Research Laboratory

Perhaps Hank took a tranquilizer before he signed that one, but in all fairness, I did not consider him to be a spiteful man. I do think his personality was quite different from mine. He tended to follow Army customs strictly. He was scheduled to retire in a few months; after he did so, he called me a year later at my next assignment and was quite cordial. (His "excuse" for calling was to ask for the reference for George's LSD detection method. Then he asked if I had passed my Board examinations, and I was happy to tell him that I had).

Public disapproval of chemical weapons testing, particularly by physicians, was building. Several members of the department received death threats on the telephone. I never fully understood it. Perhaps the shipment of nerve gas across country for disposal had caused more outrage than we realized.

The Chemical Corps had already sustained a serious black eye after an accident with nerve gas near Dugway Proving Grounds in Utah. In 1968, a small plane had sprayed VX as part of a dissemination test. Unexpectedly, winds blew it in the wrong direction. Although there were no human casualties, many sheep grazing on nearby farms died.

Science magazine reported the incident in detail, including maps and statistics. It was not very good publicity for chemical warfare research. It seems likely, however, that the sheep were not killed directly by VX in the atmosphere. VX stays on the ground for several days and the consumption of large amounts of VX soaked grass was no doubt a major cause, multiplying the direct aerosol effects. It is unreasonable to assume humans would have devoured grass and suffered a similar fate.

Although there were telephone death threats to some physicians in the lab, I never received one. As I wrote in a letter to a friend, "My name was not mentioned – perhaps I was not sufficiently productive to constitute a menace to the dissenters. Who knows? Maybe I was considered to be a disguised asset -- or maybe I was being saved for something worse!" I suppose this was a bit of my familiar "black humor," issued from the privacy of the janitor's closet.

* * * * *

Meanwhile, the wee bit of private practice I had engaged in, starting in late 1969, rekindled my interest in patient care. While cramming for Board exams, I immersed myself in clinical re-education. This fired me up even further. I began to recall my residency in psychiatry at Walter Reed Hospital with great fondness and remembered the satisfaction I had felt when patients under my care showed signs of recovery from a psychotic episode.

I particularly recalled my clinical work in 1958 and early 1959, when my assignment was to care for hospitalized soldiers and their dependents. We had few drugs to work with in those days. We relied mainly on Thorazine in the treatment of psychotic patients. It was the first "major tranquilizer" and preceded by decades the wonder drugs used today. For less severely disturbed patients we used meprobamate (Equanil) which has all but disappeared from today's pharmacies. In fact, the value of lithium, for mood swings, was just beginning to be accepted.

Dexedrine, considered an antidepressant, was good for some patients (but particularly for doctors who had difficulty keeping their eyes open during long lectures and late hours on the ward). How the psychiatric world has changed! Now, before selecting an approach to treatment, psychiatrists must be familiar with both the commercial and generic names of dozens of psychoactive drugs – a task that stretches the capacity of almost every doctor's working memory.

It occurred to me, in my last few months at Edgewood, that our staff might be of some service to the community if we organized a mini-version of the Haight-Ashbury Free Clinic. A surprising number of doctors, nurses and psychologists quickly subscribed to the idea.

We had meetings, designed a program, obtained space in a Bel Air building, coordinated everything with the town psychiatrist and finally presented our proposals to the local council members. Everyone thought it was a great idea. Through early intervention, we might reduce the number of adolescents drifting into dangerous drug use.

We created a roster to provide evening coverage, and helpful publicity appeared in the local newspaper. Everything seemed to be off to a good start. But we had failed to anticipate the most important ingredient: a source of patients.

Although our free clinic bore the fairly hip title "Rap-In," it did not last more than a few months. Only a couple of dozen "clients" ventured from the little rural town's drug-filled shadows. One teenager, for example, called from his attic, where he was tearfully preoccupied with some problem. It may have been related to drug abuse, but he was uncommunicative, and the air was dark and stifling. I went to his house and sat and sweltered beside him in the attic for a while but he wouldn't tell me much. Finally, I rationalized that I couldn't really help him, and that he probably didn't really want my help anyway.

Thus, the brave new idea we had hatched with such enthusiasm ultimately wound up in "the ash heap of history," to paraphrase one of our former Presidents.

As the program was winding down, Fred also found himself with a bit of time on his hands. Dedicated as he was, there was no way he could inspire clinicians who were just counting the days until they could get back to their lucrative practices. Generally not a time-waster, Fred left this bit of whimsy on my desk one day:

THE TOXICITY OF VARIOUS "NON-TOXIC" SUBSTANCES IN MICE

by

Frederick R. Sidell & William P. McShane

When chemicals dissolved in certain vehicles are injected into certain animals, it is sometimes assumed that the vehicle itself is non-toxic and no allowance need be made for the effects it might produce. However, this may not be true; the volume of the vehicle may be more than an animal (particularly a small animal such as a mouse) can handle, or the pH may produce toxic effects. To separate these factors, a large scale study was undertaken to determine the toxicity of certain commonly used solvents.

METHODS

I. Water: After being injected with water the mice appeared sluggish and moped around the cage for a while. They stretched more than usual, apparently because of pressure in the abdomen. After 0.5 to 1.0 hrs, they appeared normal. There were no deaths in a group of three.

II. Buffer: Results were similar to those found with the water. In an initial group of 3 there were no fatalities; a replication using another 3 animals produced no deaths. (Dose was 2.0 ml in all cases.)

III. Saline: After receiving 1.0 ml of saline, all subjects rapidly (within 5 minutes) became comatose and did not respond. After 30-45 min they awoke and became uncomatose and appeared normal. The mouses which received 1.5 ml of saline conducted themselves in the same fashion but perhaps were comatose a bit longer.

Of the initial group of 3 who received 2.0 ml. all became unresponsive within 2-3 minutes, but one did not respond an hour later when his experimental mates did. It was decided that he was to be unresponsive forever and last rites were administered. The experiment was repeated using another group of three and the results were identical. Thus of the six animals who received 2.0 ml of saline, 2 went to the big cheese pile in the sky.

DISCUSSION

The volume of solution injected, up to 2 ml, appeared in itself to be unimportant in producing lethality in mice although most of the subjects had obvious discomfort for 30 minutes or so. Normal saline in doses of 1.0-2.0 ml produced a comatose condition in all animals; at the highest dose, 2 of 6 subjects did not survive the experimental procedure.

CONCLUSIONS

It's not how big it is, it's what's in a solution that does the damage. Sodium chloride in the dose range used is obviously quite toxic and should be removed from the mouse market.

P.S. X^2 with Yates' corrections: No difference between saline and control groups.

It seemed that we had come full circle. I began my literary career at Edgewood with an article suitable for publication in the Journal of Irreproducible Results, and Fred was nearing the end of my career at Edgewood with an article equally suitable for the Journal of Irreproducible Results. Providence seems to formulate destiny in mysterious ways.

Hank Uhrig retired from the Army in January of 1971, but not before writing my annual performance review. It was extremely critical and recommended that I not be promoted to full Colonel. I wrote a lengthy rebuttal, pointing to my accomplishments and suggesting that the review be more balanced. Army regulations allowed my dissenting comments to go to Washington along with Hank's rating.

Evidently, Hank's letter did not arrive in time to influence the promotion board. On the very day of his retirement ceremony, a different letter was en route from Brigadier General Thomas Whelan, Special Assistant to the Surgeon General for Medical Affairs. It offered heartiest congratulations on my selection for promotion to Colonel in the Army of the United States. Fortunately, Hank's timing was not as precise as it had been when he was jogging. My promotion

came through but, as was customary, the formal ceremony did not occur until the end of the year.

After Hank left, my wife and I invited Joe Blair, Van Sim, Fred Sidell and their wives to dinner. The tension in the labs had eased somewhat and everyone enjoyed the evening. Final days were approaching.

Around this time, I received my new orders and Major Scott Peck traveled with me to Fort Sam Houston for a preliminary visit. He was, at the time, an assistant to the Psychiatry Consultant in the Surgeon General's office. I was impressed that he had nevertheless proudly worn his uniform in one of the anti-war parades, without being admonished by the Army. We stayed in Texas for two days and became good friends for several years. Scotty's full name was actually M. Scott Peck IV, and four generations of name preservation had endowed him with a certain touch of magisterial dignity.

M. Scott Peck IV, MD

I used to kid him mercilessly about his pedigree, and he seemed to enjoy it. After we lost touch, I was delighted to see his name on the covers of best-selling books about spiritual growth. Every now and then, I have a recurring urge to write to Scotty, and kid him some more about his pre-celebrity days. Sadly, I waited too long – his death in 2005 was a sad loss to me as well as his many other admirers.

I was selected to head up the Department of Behavioral Science at the Medical Field Service School at Fort Sam Houston, Texas. President Nixon was just beginning to implement his War on Drugs. The psychiatric consultant to the Surgeon General seemed to think I was the right one to develop courses for future drug specialists and counselors.

I remember nothing else of great significance during my last weeks at Edgewood. My family and I packed our bags (and about 19,000 pounds of assorted furniture and books) and headed south to a new home and a new set of adventures. In my own way, like Scott, I was also about to choose a "Road Less Traveled."

* * * * *

21 CIA CONNECTIONS: NOW YOU SEE THEM, NOW YOU DON'T

Civilization does not lie in a greater or lesser degree of refinement,
but in an awareness shared by a whole people.

Albert Camus: ***Notebooks*** **[Ch. I. p. 31]**

What I knew about the CIA in 1970 could fit on the back of a cocktail napkin. What I knew in 1980 could fill a chapter. In fact, it finally does, right here. But "would have, could have…" Two decades passed before I finally read what had been sitting on my garage shelves and in file cabinets for more than 30 years. And it wasn't until I started writing this chapter that I found the way some dots from the early 1960s could have been connected in ways that could have been obvious in 1975, if I'd done the reading and thinking when first I had the chance.

That's what I call not seeing through a glass – one that stayed dark because I forgot to turn on the light. What is the expression? "We get too soon old and

too late smart?" I never used to believe that one but I guess I wasn't old enough.

In 1975, the Inspector General issued a lengthy report on the Use of Volunteers in Chemical Agent Research. (An entire chapter is devoted to this landmark document later in this book.) In the final portion of their report, the IG team takes up the subject of Intelligence Corps Experimentation with Hallucinogenic Drugs. That's the one that turned on the light.

The report notes that the intelligence community was well aware of interest in psychochemical drugs by potential enemies of the United States as far back as the early 1950s. In particular, the CIA wanted to improve its interrogation methods, as well as gain further insight into what other nations might be doing in this regard, with the help of drugs.

The Intelligence Center at Fort Holabird and the Chemical Warfare Laboratories at Edgewood began to work together on a joint psychochemical project in November 1957. On 3 June 1958, the President of the Intelligence Board sent an informal plan (which it had probably formulated several months earlier) to the Medical Research Laboratories. It recommended recruitment of volunteers on a personal basis and letting them know that mental and physical demands would be part of the project. It proposed giving them a very general explanation of the effects of LSD, while withholding any reference to possible intelligence applications of the drug.

According to the test plan, the volunteer group would report to Edgewood, receive a medical exam and pair up with a designated partner. On the first evening of the experiment, they would meet and have a few drinks. The investigators would covertly add LSD "sufficient to provide at least an effective dosage to all concerned" (an interestingly vague description).

During this "happy hour," individual observers would have time to review the dossiers of their assigned subjects, and would pair up with them as the evening progressed. If necessary, the observer would give "additional LSD" (again, no specified amount). Under the guise of conducting a routine preliminary personal interview, the observer would ask certain questions and then explain that the interview would continue tomorrow. When tomorrow came, the observers would tell the subjects that LSD had been added to their drinks the night before, give them an orientation as to the nature and history of the drug they had received, and tell them they had been selected based on their outstanding security consciousness and experience in withholding information.

The clandestine plan provided for subsequent additional visits to Edgewood by some volunteers, for various measurements. These included, among other things, the ability to adhere to a deliberate falsehood under the influence of LSD (while submitting to polygraph testing), and the effect of LSD on simple motor reactions. Environmental conditions could include total isolation and hostile interrogation, the purpose being to reveal how well an unsuspecting subject could withhold information when LSD was augmented by unusual stress.

In 1975, after reviewing all available documents, the Army IG (Inspector General) team had found nothing to indicate that anyone above the level of the President of the Intelligence Board or the Director of the Medical Research Laboratories at Edgewood had ever approved this proposal. Indeed, when interviewed in 1974, the former Commander of the Intelligence Center testified that he was completely unaware of the plan beforehand. The Intelligence Project Officer and the "responsible physician" at the Medical Research Laboratories (presumably Dr. Sim) evidently assumed the project had all the authorization it

needed, since it appeared to be within the provisions of a previous approval to use human volunteers in psychochemical drug studies.

Between August 1958 and May 1960, a total of 30-35 volunteers took part in one or more of the eight projected phases of this test plan. A lack of records made exact information unavailable, but the IG team suggested that some volunteers might have received 20 or more doses of LSD during that two-year period.

The IG cited several violations of the initial 1955 Chief of Staff Memorandum 385, which had established ground rules for volunteer testing with chemical agents. For example, there was inadequate informed consent and, in fact, the researchers sometimes made a deliberate effort to withhold information from the volunteers. They did not even tell some subjects that they would receive a drug, prior to its administration. It is somewhat surprising that none of the volunteers withdrew his consent to continue receiving LSD in accord with these test plans.

Dr. Van M. Sim discussing nerve agent research at a scientific meeting

One witness did say that he had felt obliged to volunteer lest he disappoint his immediate superior, but in general, there appears to have been no discernible pressure or coercion. The volunteers, both officers and enlisted men, were unusually dedicated and felt their participation was an important contribution to National Defense.

In November 1958, Dr. Van Sim wrote to the Commanding General, Army Intelligence Center, reporting that he and the research team had completed the testing with rewarding results. He recommended the experimental use of LSD in real situations. He proposed they test LSD as an aid to interrogation in the field. The Intelligence Center contributed an additional plan to use LSD on foreign nationals overseas. Together, they petitioned the Surgeon General for approval. After reviewing all these proposals, the Surgeon General offered no medical objections.

Accordingly, on 8 August 1960, a liaison team went to Europe to brief key military personnel and obtain their cooperation. Van was a member of the team and returned to report that the European command was ready to select the subjects. They would be foreign nationals, and they would be "non-volunteers." After further correspondence, planning reached a point of readiness in December 1960.

The Assistant Chief of Staff for Intelligence, (ACSI) perhaps sensing impropriety, expressed the opinion that the project should have been coordinated with the CIA and FBI. But after learning that this was scheduled to occur after the tests were completed, the ACSI argued further that the FBI and CIA could even be helpful and might facilitate the use of LSD with higher ranks of foreign nationals. The team, however, declined to follow the ACSI's recommendation.

In January 1961, a Special Purpose Team (SPT) made ready to launch operation Third Chance. At the end of April, they departed to Europe for a 90-day field experimentation program. The goal was to ascertain whether LSD could be a useful aid, either for "interrogation" or for the "exploitability of actual subjects of intelligence interest." The team then chose "recalcitrant subjects of critical interest" to receive the drug. As they had done previously, they arranged a social environment in which consumption of alcoholic beverages would be followed by interrogation in separate rooms.

Ten individuals partook of LSD without their knowledge in 11 "experiments" (one was dosed twice). Nine of them were foreign nationals who were considered to be intelligence sources or actual agents. One was a U.S. soldier who admitted to unlawfully removing classified documents. He insisted he had disposed of all of them in the river, but on suspicion of espionage he was placed in "voluntary protective custody" in an off-post safe house for six weeks.

Two Army medical doctors, one of whom was a psychiatrist, interviewed the soldier under sodium pentothal on 26 May 1961. Later, they repeated the interview using "voluntary hypnosis," followed by several additional psychiatric evaluations. One of the doctors suggested that a "tension method aggravated by tension-producing drugs might be useful."

The team therefore tried interviewing the soldier after giving him LSD surreptitiously on two occasions between 8 and 12 June 1961. These yielded little so further interrogation (as part of operation Third Chance) Military Justice Proceedings were initiated. Instead of a court-martial, however, the judges decided on a discharge under AR 635-209 (for unsuitability) on 23 October. This rather innocuous disposition (which did not permanently dispossess the suspect of all rights as a veteran) seemed preferable in view of the stressful handling of his case. It might also have been chosen to minimize the possibility of unfavorable publicity and exposure of a secret operation.

More than a decade after publication of the IG report, however, the ex-soldier sued the govemment and eventually received a six hundred thousand dollar award through special congressional legislation. I recall meeting with a former member of the California State Senate in the early 1980s, who importuned me over lunch to help prevent approval of this claim of psychological harm. Although I agreed that the former soldier might well be exaggerating his claim of LSD-induced injury and might also have been guilty of espionage, I did not feel my opinion would carry much weight. I had retired from the Army in 1976 and had little interest in participating in a contentious legalistic dispute about LSD.

When the Special Purpose Team had returned to the States in 1961, their enthusiasm continued to bubble forth. They recommended that:

> "a comprehensive field testing program be established in conjunction with appropriate associated U.S. intelligence and security agencies for the scientific derivation of empiric data upon which to standardize the EA 1729 technique; and that future field experimentation utilize real subjects or actual cases for both research purposes and operational advantage."

Cooler heads must have come into play to temper this expansiveness because there is no evidence that the proposal was ever presented to or approved by the ACSI or the Secretary of the Army. It was clear that, on many counts, the project had violated Department of Defense (DOD) and Department of the Army (DA)

policies and procedures from the start. The blame, however, in the view of the IG, had to be shared by the ACSI, the Offices of the Surgeon General and the Chief Chemical Officer.

On went the experiments, nevertheless. Operation Derby Hat next launched another LSD project, seeking to explore the same questions as Third Chance, but this time in the Pacific area (USARPAC.) They chose Hawaii as the test site and scheduled the operation to begin on or about 20 April 1962. The Chemical Corps sent the same medical officer to carry it out.

Intelligence staff officers also agreed to provide "Oriental" subjects, of various nationalities, for use in the LSD experiments. The individuals who actually received LSD, as well as their locations, were redacted from the IG report, which otherwise is almost completely uncensored. (There is reason to doubt that the planned administration of LSD to these unwitting subjects took place as scheduled.)

At the end of October, a U.S. Army officer who had worked on Derby Hat was hospitalized for symptoms thought possibly to be due to covert administration of a drug. The Special Purpose Team (SPT) rushed to Korea to check on this. To decide whether LSD was involved, the physician gave the officer a dose of actual LSD to permit a subjective comparison of the effects with his previous symptoms. The team, according to a witness, concluded that the officer simply had had too much to drink, and was not under the influence of LSD. Ironically, in their eagerness to clarify a medical diagnostic problem, the team had violated a "prime directive" – "thou shalt not give drugs to U.S. citizens without informed consent." They were scolded by the ACSI whose words left no doubt: "You are hereby instructed that under no circumstances will you use or allow to be used material EA 1729 on U.S. Citizens."

What a mess!

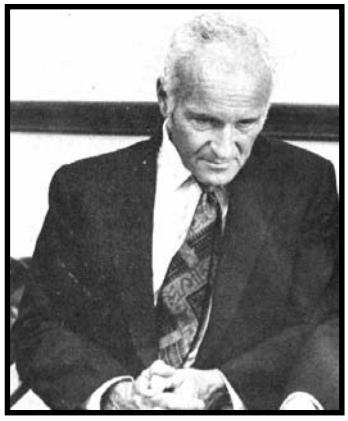
In late November 1962, the SPT was in Tokyo. The Assistant Chief of Staff for Intelligence (ACSI) wrote to the commanding officer of the Research and Development Laboratory (CRDL) at Edgewood Arsenal to say that, based on instructions from the Secretary of Defense, the team (including the two officers from Edgewood) would have to stay in the area for another 60 days. They were told to go on to Saigon. One member of the team, already back in the States, was ordered to join the others in Vietnam. He was also instructed by the ACSI to hand carry a letter to the commander of the US Military Army Command in Vietnam (MACV). "Need to know" was restricted to the Secretary of Defense, the Army Chief of Staff, ACSI and the Chief MACV (but not the Chairman of the Joint Chiefs of Staff or the Secretary of the Army). The letter announced the Secretary of Defense's decision to use LSD on Viet Cong POWs as well as to insist that the Vietnamese provide suitable subjects. (The IG team could not find the actual letter.)

Two of the three-man SPT provided sworn testimony that they never gave, helped or observed the administration of LSD to anyone in South Vietnam. Reasons given were varied and included difficulty in finding appropriate subjects, inability to enlist Vietnamese cooperation and lack of a suitable site for the secret procedures.

Finally, at the conclusion of a 10 April 1963 briefing on Operation Derby Hat, the deputy ACSI directed that no further field testing with EA 1729 (LSD) be

undertaken. "The discontinuance was based on a lack of data, inconclusiveness of the testing and the legal, political and moral problems inherent in the use of EA 1729." An interesting cross-link between this meeting (closing the door on LSD field testing, at least by the SPT), and the 1975 IG report is described in John Marks' The Search for the Manchurian Candidate. Marks, however, did not publish this excellent book until several years later, when he had the advantage of additional sources of information.

As I think back, there was one occasion, in 1962, when I was asked by Edgewood psychologist Ernie Clovis to provide medical coverage (as a disinterested observer) while a candidate for the CIA was brought to my "padded ward" and interrogated by (I presume) another CIA agent. I did so, but never received any explanation of the purpose. The unidentified civilians sat at a desk while the interrogator posed mundane questions, which the candidate, although smiling at times, seemed able to answer. Then they disappeared and I heard no more about it.



Sidney Gottlieb, M.D. – Head of MK-ULTRA's secret LSD program

In the beginning and throughout the duration of my work at Edgewood Arsenal, it was my firm belief that in future conflicts the skilful use of incapacitating agents might minimize casualties. I was never aware, however, of the CIA's use of LSD on unwitting citizens, and indeed this did not become widely publicized until 1999, after the death of Dr. Sidney Gottlieb. As chief supervisor of the secret LSD programs, Gottlieb had insisted that giving LSD covertly to unwitting Americans would provide important information as to how an unsuspecting enemy agent might react. He obviously assumed this "experiment" was justified in the furtherance of National Defense. Today, of course, few would regard this practice as other than an indefensible violation of individual civil rights.

During my years at Edgewood, I was also completely unaware that the CIA had been quietly carrying out a separate secret program of research with LSD and other compounds. Only recently, in preparation to testify as an expert witness in a suit involving alleged covert administration of LSD to a former Deputy U.S. Marshal in 1957, did I take time to read the tall pile of documents given to me by my friend Dr. Sidney Cohen a few years before his death. It is the same material that was available to those who took part in congressional investigations conducted by Senators Rockefeller, Church, Kennedy and others in the mid- and late 1970s.

Retired Army Colonel George White, Gottlieb's head of "Midnight Climax" and other "cutout" secret operations with LSD in San Francisco and New York

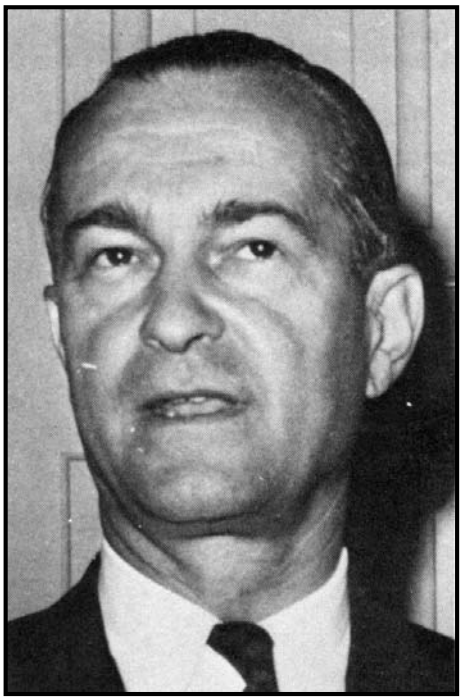
The documents were an incomplete subset of memoranda and reports from the MK-ULTRA program. They do include a description of some subsidiary projects, such as Bluebird, Artichoke and Derby Hat. In January, 1963 Gottlieb, at Helms' direction, had already destroyed most of the other documents from the earlier CIA activities. Still others were withheld or heavily redacted. Those that remain refer to some of the "experiments" initiated in the 1950's under the direction of Dr. Gottlieb. To me, they seemed scientifically unsophisticated and often done at the whim of the local agent in charge.

As one example, Colonel George White (as Morgan Hall), ostensibly working for the bureau of Narcotics and Dangerous Drugs, also directed projects such as Midnight Climax – paying prostitutes in San Francisco to give LSD to their customers.

LSD was sometimes (supposedly) given to the prostitutes themselves. George White has been depicted as sometimes drinking martinis and smoking grass while sitting on a secret toilet, observing the consequences of these "experiments" through a two-way mirror. Once, while heavily intoxicated, he is

alleged to have lain on the floor and spelled out his initials by shooting holes in the ceiling with a .22 caliber pistol.

Many other unwitting citizens from all walks of life, including government employees, were targets of covert LSD administration, often carried out without a systematic protocol. In summary, this freewheeling program was clearly ill-advised, and left a severe blemish on the CIA's reputation. Much blame must be laid at the feet of Richard Helms, who approved the projects, and tried to keep detailed knowledge of their existence from his boss, CIA chief Allen Dulles.



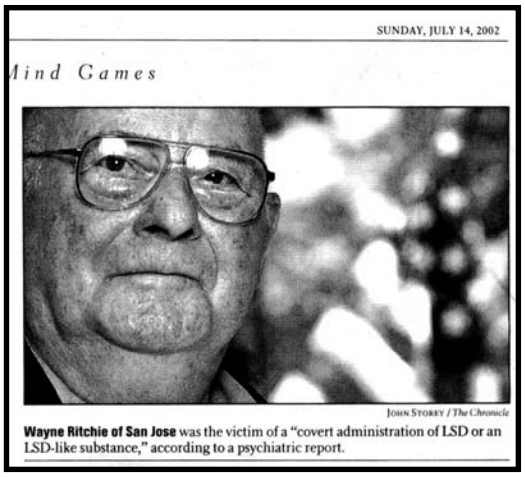
Richard Helms – CIA Chief and sole supervisor of Sidney Gottlieb's LSD projects under MK-ULTRA

In March 1999, when some details of Gottlieb's secret experiments were revealed in his obituary, Deputy US Marshal Wayne Ritchie was browsing through his newspaper in San Jose. His eyes widened when he read that in the late 1950s, George White had been administering LSD covertly to ordinary citizens in San Francisco. His memory flashed to the 21st of December, 1957.

On that day, Ritchie attended the annual Christmas party that regularly took place in the Federal Building, close to the Marshal's office where he worked. After only a few drinks, far less than he often consumed on weekends without any problem, he returned to the office to relieve his boss and cover the desk until quitting time.

Within half an hour he began to feel strangely uncomfortable. As he sat alone in the office his thoughts took on a paranoid tone – something entirely out of character for a man who had always been free of any noticeable psychological problems. Ritchie was in fact regarded as a perfectly normal, highly efficient and imperturbable officer. He had served four years in the Marines with distinction, worked for a year at Alcatraz as a guard (where he was given an official commendation in writing by the superintendent – a unique occurrence) and was respected and liked by inmates and fellow officers alike. During more than three years as a deputy marshal, his relaxed style and detailed knowledge of firearms led, for example, to his being placed in charge of the gun cage and given responsibility for instructing fellow deputy marshals on the firing range.

But on that day, a sense of being disliked and secretly laughed at by his fellow officers came out of nowhere. He felt more and more that his working the full day when everyone else had been sent home early was a reason for their disdain. He was increasingly convinced that they secretly wanted to get him off the force. Soon, he began to think that the people across the hall, whom he hardly



SUNDAY, JULY 14, 2002

Mind Games

JOHN STORKEY / *The Chronicle*

Wayne Ritchie of San Jose was the victim of a "covert administration of LSD or an LSD-like substance," according to a psychiatric report.

Wayne Ritchie – a Deputy Marshal in San Francisco who believes he was given LSD covertly in 1957

knew, also wanted him out. Rather than feeling angry, he became very disappointed by these insights. Too distraught to remain, he locked the office early – a very serious breach of protocol – and walked directly home. It was the first time he had not used his car to return to his apartment six blocks away. He felt a strong need to be with his live-in girl friend, whom he felt would certainly provide reassurance and comfort. He also felt as though he were walking in a tunnel, unaware of the holiday shoppers crowding the sidewalks.

As he entered his apartment, his live-in girlfriend commented (as she often did) that San Francisco could not match New York, where she'd rather be. Shocked by what seemed to be rejection even by his sweetheart, he left immediately without conversation and headed to the bar owned by his good friend Tony. After serving him one drink, Tony seemed deliberately to turn his back and move to another customer. So Tony, too, was against him!

Ike Feldman – a member of Sydney Gottlieb's and George White's CIA team who admitted placing LSD in the drinks of unwitting citizens in San Francisco in 1957 as part of the MK-ULTRA program

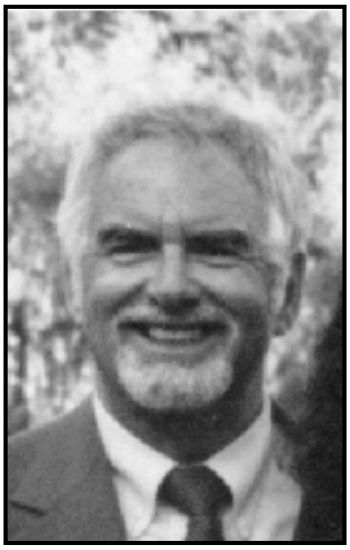
Unsure what to do, Wayne wandered along the street, stopping at three unfamiliar bars where he ordered Calso, a non-alcoholic drink, wanting to stay sober. Gradually he developed a bizarre plan that would help both his department and his girl friend. He would hold up a bar, asking for just enough money to buy her an airplane ticket to New York. Then he would undoubtedly be charged with a felony and fired from the force. Surely, everybody would then be satisfied.

Walking back to the office, Wayne armed himself with two pistols, something he had never done before. He drove his car from the parking lot to a tough downtown neighborhood and entered an all-black bar. The noise inside assured him that the bartender would have sufficient cash for his purposes. Although an expert in martial arts as well as at handling weapons, he was promptly knocked out with his own pistol (presumably by the bartender) and awoke in a supply room with police officers standing over him and asking what he was doing there with a gun. "One gun!" he replied, "I have two guns!" (referring to the holster he was lying on).

When he arrived in lockup (after a visit to a nearby clinic where his scalp wound was sewn up), Wayne gradually came to his senses. It suddenly dawned on him that he had committed an unforgiveable act for which he deserved to lose his job and serve prison time. He cried like a baby and even asked a nearby fellow officer for a pistol and one bullet in order to end his life and "save the State some money" – of course this was refused. He then asked for pen and paper and before midnight wrote a letter of resignation. Three months later he appeared in court and was chagrined when he was given probation. He wanted to plead guilty, but his attorney insisted otherwise. The judge fined him $500 and told him not to drink for five years.

From March 1957 until March 1999, Wayne Ritchie lived a life of unremitting guilt, unable to understand his criminal actions and recurrently thinking of suicide. He tried to do penance by taking a low level job as a painter and devoted much of his time to repairing and painting the interior of the church he had joined.

On March 13, 1999, within minutes of reading about the covert LSD program operated by George White and his CIA subordinates, a "light went on" and he suddenly realized he must have been one of those unwitting private citizens used as guinea pigs. George White and his associates had been working close to the Marshal's office and there was bad blood between his boss and White. He reasoned that since his boss declined to attend the party, he had become the "second choice."



Dr. J. Thomas Ungerleider, UCLA professor, good friend and LSD expert

After speaking immediately to an FBI agent, he sought records from the government but was advised that there was no record of any "Wayne Ritchie" serving as a deputy marshal in 1957. This Kafkaesque denial of his existence was only reversed when he was able to produce W-2 forms from 1957. Then, he received 20 pages of employment records including his service in the Marines and at Alcatraz.

Within a few days Wayne found a New York attorney, Sid Bender, who had represented a similar plaintiff in a previous case. Bender filed a claim against the United States asserting a civil rights violation. Based on a referral by Dr. Thomas Ungerleider, acknowledged LSD expert, I was asked to perform an independent psychiatric evaluation. After interviewing Wayne at length, I found his story compelling. For the next four years, I produced several reports and rebuttals of statements by opposing psychiatrists hired by the CIA. Eventually the case was heard as a bench trial by Marilyn Patel, Chief Judge in the 9th District Court, in the Federal Building in San Francisco.

Following four days of testimony (two-and-a-half of which I spent testifying for the prosecution), Judge Patel was unconvinced and dismissed the case without requiring the defense to present their psychiatric witness. Since I believed the defense theory was easily refutable, both psychiatrically and pharmacologically, it seemed very unfair that it was exempted it from the hearing. The Court of Appeals eventually agreed to hear Wayne's claim of civil rights abridgement in May, 2006. The appeal was rejected, although one judge allegedly commented: "If this man's story is true, he has paid a terrible price in the name of National Security." To me the whole incident is a sad commentary on the dark side of the CIA. Further appeals were planned by Wayne's attorney, Sidney Bender, the final outcomes of which were still pending as of December 2006.

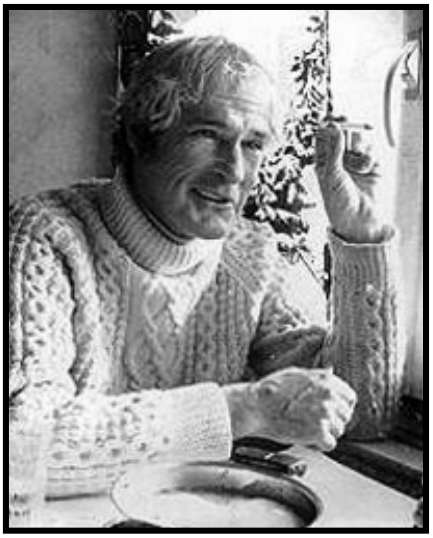
* * * * *

One day in the mid-1960s, while I was at Edgewood, three CIA agents came to our lab. One was a doctor who asked if he could discuss some matters of importance. Always happy to give information to authorized individuals, I invited him into my office. He introduced himself as "Dr. Johnny Johnston," a transparently simpleminded pseudonym, but since CIA agents supposedly rarely give their real name, it didn't seem unusual. Dr. Johnston told me he had some questions about how various chemical agents, if given surreptitiously, might affect an unfriendly foreign leader. I briefly described the agents we had studied. He wondered how they might be administered. I told him about the relative ineffectiveness of the percutaneous route, the ease of detection of some agents but not others, and whatever else I thought might be relevant.

I never heard what use was made of this information, but we subsequently had a couple of additional visits from the same group. "Johnny Johnston" also queried me further, although I cannot now remember the details. I do remember that when the men showed up in the hallway of our facility one day, I treated their visit rather offhandedly. I called out to Fred Sidell, "Hey Fred, the CIA is here again!" The agents winced and gestured to me vigorously to "hush up."

In 1970, I took part in a brainstorming session at our parent organization, the Chemical Research and Development Laboratories (CRDL). Its chief, Dr. Seymour "Cy" Silver, Ben Witten, head of the Chemistry Division and the three CIA agents who had visited me previously were all present. The topic was the feasibility of intervening in a hostage situation at the Tel Aviv airport. Hijackers were holding the occupants of an airliner captive and making unacceptable demands. We considered the pros and cons of using incapacitating agents and various other options. As it turned out, we could not imagine a scenario in which any available agent could be pumped into the airliner without the hijackers possibly reacting violently and killing passengers. Ultimately, the standoff was resolved by other means.

While at a research meeting at another Post, a vaguely familiar civilian psychologist casually asked me whether I would like to join the CIA. We were walking outside at the time and he was very nonchalant in manner. I answered with equal nonchalance that I did not think I would like being in the CIA. I said I felt that clandestine work was unnatural to me, since I liked to talk about what I was doing, and could not imagine living a secret life (as must be obvious from the personalized contents of this book). He accepted my decision with equanimity, and I was never asked again.



Timothy Leary – Psychologist, LSD pioneer and "new age" philosopher

There is no doubt that many groups and organizations shared an interest in LSD. These included civilian scientists (initially), the CIA and intelligence community, the U.S. military, cultish groups (such as those initiated by Tim Leary and his disciples), the "Counterculture" of the late 1960s and many ordinary recreational drug users throughout the country. The CIA and the US Army Chemical Corps, two branches of government with different goals, evidently collaborated to a significant degree beginning in the 1950s and continuing (secretly) into the early 1960s. While I was at Edgewood, I was unaware that anyone in the Medical Research Laboratories was involved in such collaboration. Information that came to light in the mid-1970s, however, leaves little doubt that at least two individuals at Edgewood did, in a sense, lead a compartmentalized double life, and participated in some highly secret CIA projects, both in the U.S. and overseas.

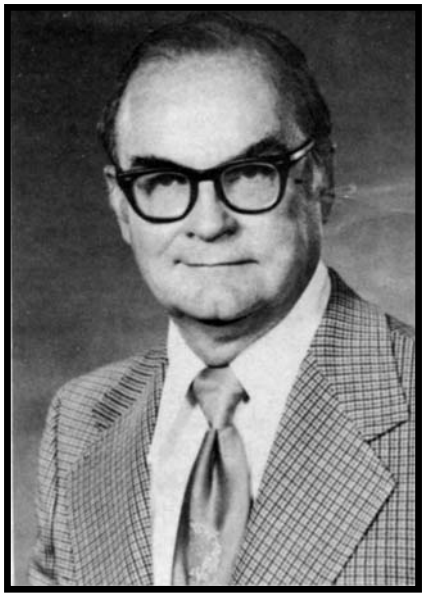
Many books and articles have been published about the shady and nefarious activities of the CIA in relation to LSD, supposedly contemporaneously with our own officially approved medical research. I have read several of them and it is distressing how often our clinical research program has been confused with the CIA's covert use of LSD. Some authors do not even refer to the drugs we studied by their correct names, and attribute properties to them that are quite fanciful. A primary purpose of this book, therefore, is to provide truthful, comprehensive, accurate information about the Edgewood Arsenal medical research program, and what we actually learned from our studies.

* * * * *

22 ON INTO THE 70s AND 80s

Great boldness is seldom without some absurdity.

Francis Bacon: ***Of Boldness***



Retired Colonel Stuart Baker, MD, former Psychiatry Consultant to the Surgeon General, and VA Chief of US Substance Abuse Programs

Starting in June 1971, my professional life changed and the years at Edgewood Arsenal were soon left far behind. Until October 1973 I was at Fort Sam Houston in San Antonio, Texas, designing and teaching courses in substance abuse and psychopharmacology. As Chief of the Behavioral Science Department, I watched its roster swell from 35 when I arrived to almost 100 a year later.

This phenomenal expansion was made possible by a generous infusion of funding, intended to bolster President Nixon's announced Drug Abuse Counteroffensive. My activities were quite varied. I taught a 50-hour course in psychopharmacology. I traveled to Chicago to take the second part of my Psychiatry Board Certification exams – and passed them. The Association of Bexar County Physicians invited me to give a lecture. The audience of conservative Texas doctors was not overly pleased, however, when I suggested that the War on Drugs was rather ineffective and that perhaps we needed to consider a different approach.

No matter. The following year, Stu Baker, an old friend who was now the Consultant in Psychiatry to the Surgeon General told me he had just been given $150,000 to apply to drug and alcohol education. Could I figure out a way to spend it?

As usual, my imagination soon waxed grandiose. I proposed a perspective larger than the problems of substance abuse in America. Why not visit other countries, such as England, France, Germany, Israel, Sweden, Japan and Thailand? Why not check out various

treatment modalities used in the United States? Why not videotape interviews with generals and corporals, Navy, Air Force and Army commanders, Free Clinic supervisors, heads of off-beat programs such as Esalen and Synanon, laboratory scientists and law enforcement officers, the head of the DEA, the Surgeon General, the newly appointed Drug Czar, the head of the Office of Drug Education and some other key administrators in Washington? Wouldn't that would be a good list to start with?

My visionary proposal required approval by the decision makers in the Pentagon. Before making a presentation to a brass-laden group in Washington, I decided a good name for the two-week course would be "Project Jonathan," inspired by Richard Bach's Jonathan Livingston Seagull (which was on the best-seller list at the time and suggested a captivating, existential approach to life.) "Being there!" was its motto. I read an excerpt from the book to a bemused audience of colonels and generals. I excitedly described how the course would use edited videotapes from round-the-world interviews as "trigger films" to stimulate group discussion. Active participation would be the key to learning!

Sun setting over the Land of the Rising Sun

Remarkably, they bought the package. I proceeded to schedule trips to Europe, the Far East, and a number of stateside locations. Although I looked forward to doing all the interviewing, my boss, Major General Orr, decided the extensive itinerary I had planned would require too much time away from my desk. He did allow me to go to Japan and Thailand and to a number of locations in the District of Columbia, Texas and California, but an internist from the Surgeon General's staff went to all the European locations.

My trip to Tokyo was the most intriguing. The Chief of the Tokyo Bureau of Narcotics agreed, for the first time ever, to submit to an interview by a US military doctor. I had to provide questions in advance and we spoke to each other in a Japanese living room, perched on traditional cushions. Since he spoke no English and my knowledge of Japanese was non-existent, the resulting dialogue needed translation to be of any use to Army students. Fortunately, our go-between in setting up the unusual encounter was a fluently bilingual Japanese colonel, who generously spent many days creating a synchronized voice over translation – no small task!

My short stay in Japan was a great adventure. I stayed in the Okura Hotel, where the finest accommodations cost $35 a night – paid for out of Army funds, of course. Realizing I had an extra day or two for sightseeing, I suddenly had a hankering for a game of basketball. The desk clerk was puzzled by this request, but wrote out a note in Japanese for me to give the cab driver, who took me to a Japanese YMCA. There, for a dollar, I became a member for a single day.

What followed was inexplicable. After I said I wanted to play some basketball, the desk manager summoned a young man to take me to the gym. Once there, he tossed a basketball to me and I took a jump shot or two. Then I thought he should be doing more than just chasing and returning the ball. I urged him to take some shots himself, but his basketball skills proved to be limited.

"Is there any way to get some other players and have a game?" I asked.

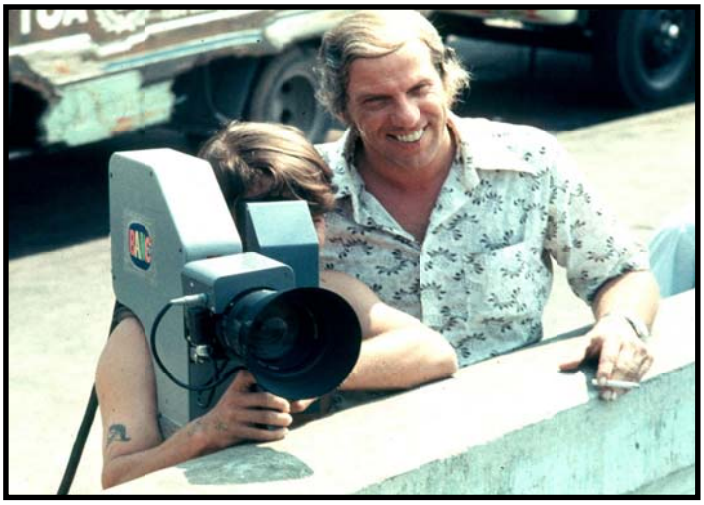
He whistled. Immediately, nine young Japanese men came through a door, dressed in team outfits. It took only a minute of hand communication to create two teams and the game began. A few moments later, two girls suddenly entered

Bangkok boy takes the plunge

the gym from another door. They sat on the sidelines holding up a bamboo rod, with cloth numbers attached, which they flipped over as the score changed. When some pre-ordained period had elapsed, the game abruptly ended. Since the players were all quite short, I had done quite well – aside from accidentally loosening a young opponent's front tooth with a swinging arm. Instead of expressing annoyance, however, he apologized to me and indicated that he would be perfectly fine.

At that moment, ten girls in uniform came running onto the court. An unseen scheduler had evidently dictated that it was now their time to play. I took another taxi back to the hotel, scratching my head.

After more videotaping in Thailand, I was soon at my desk again at Fort Sam Houston. The final product was seven 4-hour blocks of "trigger" tapes. They needed approval by the Surgeon General and I was a bit worried about the final edited material, which I had contracted out to a pair of high-energy innovators. They had recently received favorable publicity in Time Magazine but their creative concepts proved to be a bit idiosyncratic. Nevertheless, the two-week course finally came together and was extensively reviewed in Washington. Stu Baker eventually called me and said, with a touch of sarcasm: "This turkey will fly." It did, and continued to do so for a number of years, providing substance abuse administrators and counselors from all over the Army with a slightly odd educational experience.



Camera man and director take in the Bangkok scene.

Following my time at Fort Sam Houston, I completed the last of my 20 years of military service as Chief of Psychiatry at Fort Benning, Georgia. Anticipating retirement and a return to civilian life, I worked on clinical skills, treating many patients on the psychiatry ward of the Martin Army Hospital and at its Mental Health Clinic. Somehow, I managed to retire unscathed, and even received the Legion of Merit – the highest permitted for service limited to the United States. (I used to tell people that the reason I never served overseas was that the Army got nervous when I was out of the country for any extended period.)

I found an attractive job in California as Chief of the Substance Abuse Program at the Brentwood/UCLA Veterans Administration Hospital in Los Angeles. This position included an appointment as Assistant Professor of Psychiatry in Residence at UCLA, requiring a combination of administrative, instructional and clinical duties. I was once again a civilian psychiatrist.

In 1979, however, the ghost of Edgewood Arsenal reappeared. The Church of Scientology was becoming increasingly annoyed at problems created by the Federal Government – having to pay their income taxes, for example. They took out a page-long advertisement in several major newspapers, promising legal representation and medical re-evaluation for all "guinea pigs" (there they go again)

used in military testing with BZ in the 1960s. Surprisingly, only a few former volunteers responded to this enticing invitation. Evidently, most of the hundreds who had been through the BZ test program had no bone to pick with the Chemical Corps.

Part of the Scientology offensive was to seek interviews with physicians who had taken part in the Edgewood program. One afternoon, while I was sitting in my office at the UCLA/Brentwood VA Hospital, a young reporter walked in and asked if he might talk with me briefly. "Come on in and sit down," I said.

His name was Vaughan Young and he looked like a world-weary traveler – a bit unshaven, wearing a wrinkled shirt and hiking boots, and carrying a backpack. He told me he had recently spent a harrowing few months in Europe, ferreting out the inner workings of Interpol. He survived that scary venture and now was investigating the Army's research with BZ, for the Church of Scientology. My name had been mentioned.

Well, BZ was still my favorite subject. Instead of dismissing him with "Sorry, no comment," I engaged him in a lively four-hour conversation. I answered all his questions, and even described the movies we had made. Vaughan was clearly surprised and warmly thanked me. No one connected with Edgewood had been willing to talk to him.

A few days later, he called me up.

"Listen to this, Dr. Ketchum," he said. Over the phone, I heard the soundtrack from "Armor for the Inner Man," the six-minute film that I had put together for Doug Lindsey in 1962: "…This armor for the inner man must be fabricated from organic molecules, not metals…etc." How in the world did he get that film?

"Those are the very same words you quoted to me when I came to visit," said Vaughan. "Now I feel I can trust the rest of what you told me."

Well, that was flattering, I suppose. A few days later, he called me again.

"I guess this time I'm calling you just like I used to call my mother when I was about to do something she might disapprove of," he said, a bit sheepishly.

"And what would that be?" I asked.

"If you look at Science magazine when it comes out tomorrow, you may not be too happy with its comments about BZ. I wanted you to know about it ahead of time, because I appreciated your honesty when we talked."

I had indeed been honest and it was certainly true that I liked to read Science magazine. (By now, in fact, you must think Science is the only magazine I ever read!)

"Thanks for calling, Vaughan," I said. "I hope it's not too incriminating."

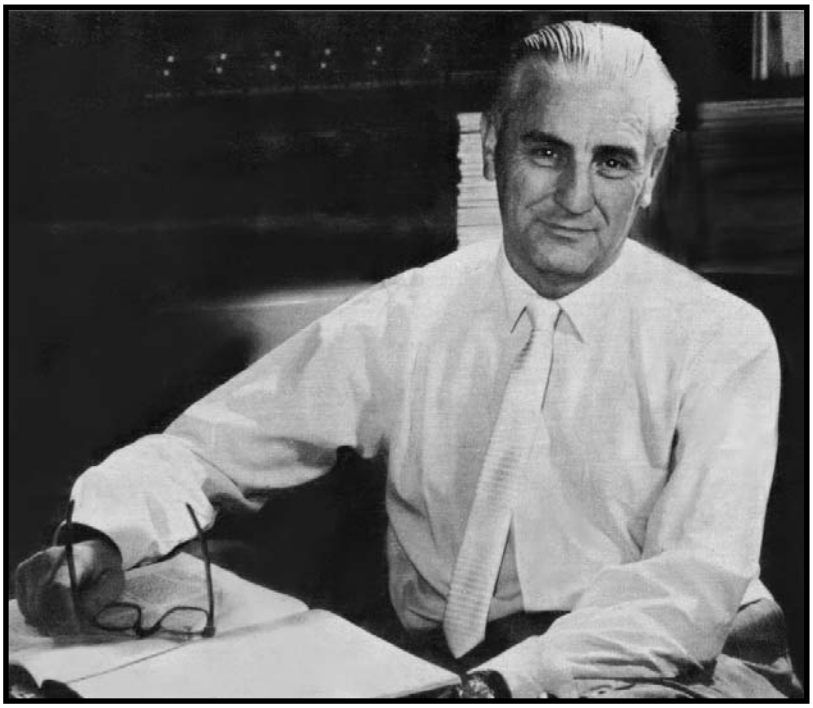
The Science article was brief, nestled in the News section. It said the Army had tested some kind of "super-hallucinogen" called BZ, a drug far more potent than LSD, in hundreds of "enlisted guinea pigs." Other than the fact that BZ is actually less potent than LSD, is not a "super-hallucinogen" (or a hallucinogen at all in the popular LSD sense – nor is LSD itself properly described as an hallucinogen), and the subjects were willing, informed volunteers and not "human guinea pigs," I could find no real fault with their summary.

Piqued though I was by these distortions, Vaughan made it up to me, in a

sense, by providing me with a copy of the extensive 1975 IG report on the testing of drugs in volunteers (described in a previous chapter). At the time, I was unaware of its existence. It looked interesting, but after browsing through it briefly, I put it away for more than 20 years.

I did know that, prodded along by a series of congressional hearings and inquiries, the Army had assigned LTC David McFarling to carry out a long-term follow-up study of LSD outcomes, later published in 1980. Then, about a year after my contacts with Vaughan Young, two different panels of experts looked for possible long-term toxic effects of incapacitating and nerve agents under the aegis of the National Academy of Sciences (the findings of the first panel were discussed earlier in this book).

Not long after our volunteer studies with glycolates ended, BZ acquired new life and a new name: "QNB" (short for 3-quinuclidinyl benzilate). Dr. Hank Yamamura, who had spent his required military service at the Edgewood labs, recognized the potential of BZ as a potent and persistent anticholinergic drug, useful in labeling receptors in the nervous system. He worked with Dr. Solomon Snyder, at Johns Hopkins, and helped to establish QNB as the standard drug with which to study the muscarinic type of acetylcholine receptor.



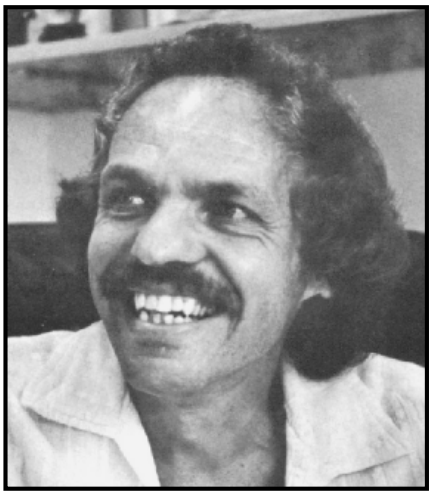
Dr. Sidney Cohen, MD: LSD pioneer,
Professor of Psychiatry at UCLA, and good friend

BZ came up again a few years later, when I chatted with a young researcher at a conference. He was explaining a poster dealing with QNB effects in animals. When I mentioned that we had studied the drug in more than 300 military volunteers, he became quite excited. Why hadn't I published the effects in humans in the open literature? I could only answer that I intended to – "some day real soon". Evidently, the existence of studies of QNB in human subjects was unknown to many specialists in the field. "Real soon," however, proved to be "in a couple of decades."

Some visitors to Edgewood Arsenal later became close associates. I first met Sidney Cohen, for example, when he came to our laboratory in the 1960s. He was running the program in psychopharmacology at NIMH at the time, but the psychedelic world knew him best for his use of LSD in psychotherapy sessions in the 1950s. Among those he introduced to LSD were Aldous Huxley, Henry Luce (founder of Time Magazine) and Luce's congressional representative wife, Clare Boothe Luce. Sidney also wrote The Beyond Within: The L.S.D. Story, a psychedelic classic.

In 1965, I met Sid again at Harold Abramson's Conference on "The Uses of LSD in Psychotherapy and Alcoholism." We didn't become well acquainted,

however, until 1976 when I began work at the UCLA/Brentwood VA Hospital. Later, we taught a weekend seminar on abusable drugs together, and wrote a chapter on the "Medical Management of Drug Abuse Emergencies" with Tom Ungerleider,



Arnold Mandell, MD, Chief of Psychiatry
At UC San Diego, LSD expert,
and intrepid, versatile author

In 1978, I joined with Tom and Dr. David Smith (founder of the Haight-Ashbury Free Clinic) in support of Dr. Arnold Mandell, Chief of Psychiatry at UC San Diego. Arnie had been taken to task when he tried to wean football players from amphetamines (without keeping adequate notes) and consequently had his prescribing license suspended. Eventually he regained it on appeal. I also teamed up with Tom and five other doctors to petition the FDA (unsuccessfully) to set clear standards for generic drugs.

When we managed to secure Joint Commission for the Accreditation of Hospitals (JCAH) approval of our Substance Abuse Program for two years (in contrast to only one year for the rest of the Brentwood VA Hospital) my boss, Dr. Milton Greenblatt, was both amused by the irony and impressed, making all the weeks of work worthwhile.

Milt had already become one of my heroes. From 1986 to 1989, I worked for him once again, as a ward psychiatrist at the UCLA/Olive View Hospital in Sylmar, California. For decades earlier, as Director of Research at the Boston Psychopathic Hospital, Milt was involved with some of the earliest U.S. research with LSD. In 1949, his colleague, Dr. Robert Hyde, took the first official dose of LSD in this country.

Louis Jolyon "Jolly" West, MD
As UCLA Chairman of Psychiatry, he was a major
contributor to LSD research and many other
cutting-edge behavioral topics.

Dr. Louis Jolyon ("Jolly") West was another psychiatrist whom almost every colleague admired tremendously, although some have since marginalized him. A few have falsely portrayed him as just another player on the dark side of LSD history.

Jolly was a wunderkind who became Chairman of Psychiatry Department at the University of Oklahoma at the age of 29. I first met him in 1962, at a cocktail party sponsored by the American Psychiatric Association during their annual convention. By then, I had heard about his infamous elephant blunder at the Lincoln Park Zoo in Chicago.

Jolly's Folly, as I now like to think of it, was his decision to give an injection of 273 mg of LSD to the only elephant in Chicago's Lincoln Park Zoo. He was curious as to whether LSD could elicit the rutting phenomenon known

as "musth," but picked an excessively large dose (273 mg) to give intravenously and ended up with a trumpeting cry and a dead elephant. He asked me what dose I would have used and I suggested about ten milligrams, based on the principle that 100 mcg could have a substantial effect in humans and it is well established that large animals usually respond to lower doses per kilogram than do smaller ones. Jolly was always at the cutting edge of psychiatric research and I had several opportunities to work with him when he became Chief of Psychiatry at UCLA. Truly, he was one of the greats.

Intermittently, media curiosity about my work at Edgewood kept alive my memories of the 1960s. In 1980, Sylvia Chase, a well-known interviewer for the weekly television show 20/20, called from New York. She wondered if I would mind being filmed while talking about my work with BZ. No problem – we scheduled it for a Saturday morning in my Encino office.

Sylvia arrived with her producer and camera crew. While they were setting up, we had some time to chat before the interview. She confided that she had a severe headache and was not feeling too well. I offered some Darvon for her headache, but she politely declined. But it looked as though we had established some rapport. It helped me remain relaxed throughout the hour or so of interviewing,

The cameras started rolling.

> Sylvia: Dr. Ketchum, just what happens when volunteers get high doses of BZ?
>
> Me: Well, they gradually go into a stupor and when they start to wake up, they crawl around on the floor, frequently take off their clothes, hallucinate and talk nonsense.

I believe she was expecting something like "they get sleepy for a while but are soon back to normal." That, of course, would have been a nice way of saying practically nothing.

As we continued, her producer started showing signs of frustration. From the corner of my eye, I could see that he was unhappy with the way the interview was going. Apparently, my jovial frankness and pride in the patriotic work we had done was not what he wanted Sylvia to elicit. I well knew, however, that confrontation leading to defensiveness was the name of the game in programs such as 20/20.

The producer started crawling on the floor, staying just out of range of the cameras. He began furtively handing notes to Sylvia on small pieces of paper. She read one, looked up and brightly asked "Did you know you were known as 'Mr. BZ?'" "No, I really didn't," I replied, mildly startled. (Later, my wife commented indignantly: "I should think she would at least have had the decency to refer to you as 'Dr. BZ'").

The interview continued:

> Sylvia: Dr. Ketchum, do you really think the experiments you did on soldiers were morally justified?
>
> Me: Of course. We knew the Soviet Union was spending ten times as much as we were on chemical warfare research, so we would have been crazy not to keep up with them.

I'm not sure whether the interview had any effect on Sylvia's headache, but I did inquire about it again when the filming was completed. I once more offered to prescribe something and she again politely declined. When they left, I believed the 20/20 team was not entirely happy with the interview. Sylvia had seemingly wanted to provoke me into becoming defensive or irritable. Instead, I had given only pleasant answers to their questions. In any case, the segment never aired.

I figured that from then on, lingering echoes from the sounds of Edgewood Arsenal would soon fade into silence. But I was wrong.

* * * * *

23 TO THE END OF THE CENTURY AND BEYOND

Who knows whether in retirement I shall be tempted to the last infirmity of mundane minds, which is to write a book.
Geoffrey Fisher

A beautiful summer evening in 1981 and I am relaxing in the richly paneled living room of Dr. Leo Hollister, professor of psychiatry and pharmacology at Stanford University. The room must be sixty feet long, with a very high vaulted ceiling. Large, gilded framed oil paintings of exotic animals and tribal Africans line the walls. It commands a view of a lavish garden through its tall windows, which allow a lambent twilight to surround an opulent grand piano. The young runner-up in the latest Moscow piano competitions is playing a favorite Chopin prelude, as we sip champagne and talk about the progress of our research project. His rendition is soft and persistent, like rain slanting on a windowpane.

As Leo Hollister's co-investigator and on-site supervisor, I have just finished Saturday's testing. We are doing a controlled evaluation of the effects of marijuana and alcohol on driving behavior. The Department of Justice in Sacramento, California has underwritten the study, dreamed up by one of their young criminologists, Victor Reeve. After finding in a preliminary screening study that 11% of California motorists stopped for erratic driving had THC in their blood, Victor had recruited Leo and me to help in a more systematic study. Most of the drivers had also been under the influence of alcohol. What was the contribution of each to their impaired performance?

There had been no controlled studies of this combination of drugs in a standardized driving environment. Fortunately, the high-speed chase course, used to train California Highway Patrol (CHP) officers in hot pursuit skills, was an ideal setting and was available for the experiment.

Hollister's worldwide reputation as a clinical psychopharmacologist was well established. In the 1950s, he had done extensive research with LSD, and

later some more with marijuana and other psychoactive drugs. Along with Louis Jolyon West, Harold Wolff, Daniel Freedman, Sidney Cohen, Harold Isbell and dozens of other respected drug experts, some of his funds had come indirectly from the CIA. I suspect that at the time, he and most of the other recipients of such grants were unaware of the secret agenda that made the money available.

As the junior investigator, I took on the task of writing a lengthy protocol. I also supervised most of the on-site testing. It was a complex operation, reminiscent of the 1964 Project Dork tests in the Utah desert. I had to drive 360 miles to Sacramento on many weekends in the summers of 1980 and 1981, arriving Friday night and returning to Los Angeles late Sunday.

Of the 200 applicants I interviewed before the experiment started, we chose about 50 to take part in some phase of the actual testing. Then, after preliminary range finding and rehearsal, we began a controlled double-blind study. On each of four consecutive weekends, two groups of four men took part in a six-hour test – one group on Saturday and the other on Sunday.

Starting at 9 A.M. each volunteer, on four weekends in random sequence, drank alcohol on one occasion, smoked marijuana on another, ingested both substances on a third and received a placebo version of both on the fourth weekend. Alcohol was given as 80-proof vodka (7 oz. mixed with orange juice plus a placebo cigarette), and marijuana was administered in the form of a National Institute of Drugs and Alcohol (NIDA) cigarette containing 18mg of THC (plus a placebo alcohol drink). On each occasion, no one knew whether he would get drunk, stoned, both or neither.

Each hour the subjects rotated through four 15-minute blocks:

1. Tests of cognitive performance on the NF, VITA and an electronic tracking task.

2. Measurement of heart rate and blood pressure, and completion of a Symptom Checklist (SCL) and Behavior Checklist (BCL).

3. Driving performance on the pursuit course in cars equipped to measure steering and reaction time. A CHP officer sat with the subject in each car, noting and scoring general behavior. During each driving test, the subject also underwent a standard roadside sobriety test.

4. Drawing of blood samples for determination of levels of alcohol and THC. During this phase, there were a few minutes to relax or attend to bodily functions.

We were surprised to learn that a healthy young man can drink 7 ounces of vodka in orange juice in 20 minutes, without attaining a blood level of 0.10 (the standard upper limit of sobriety at the time). Furthermore, after 5 hours the alcohol blood level was almost back to zero. When he smoked a NIDA cigarette, THC usually reached a peak level at 30 minutes, and then fell to almost undetectable levels over the next three hours. Generally, drugged subjects reported feeling moderately high or euphoric at first, and sleepy later. Usually, they failed one or more roadside sobriety tests after either drug but could still drive fairly well and could still take cognitive tests, obtaining scores better than we predicted.

Most interesting was that the combination of both drugs did not substantially increase the impairment produced by either one alone. In fact, there was some indication that one drug tended to counteract the other to some extent. Alcohol had more effect on steering skills, while THC had more effect on timing skills.

Blood levels of both drugs correlated fairly closely with all scores, returning to baseline within six hours.

A psychologist-led team took over after we completed the clinical studies in 1980 and 1981. They did a final analysis of the data and published the final report. I was sorry to see that it was a dry, statistically technical document, virtually devoid of clinical descriptions. It was never widely distributed or publicized.

About fifteen years later, I wrote to Leo and suggested we rewrite and publish the results in a form acceptable to a journal. He was eager to do so, but health and other commitments interfered. Unexpectedly, Leo died in December 2000. His death made it unlikely that the results of our study would ever be available to the public, which is why I have chosen to summarize it here, with more details in the appendix.

While our marijuana-alcohol driving experiments were in progress, I received a letter from the National Academy of Sciences. The Army had asked its National Research Council to do a long-term outcome analysis of Edgewood's drug studies and invited me to serve on the review panel. During 1980 and 1981, I made four "red-eye" round trips to Washington, D.C. for the meetings. I also spent a lot of additional time assembling and summarizing research reports for the group to review. The sketchy clinical notes that had been provided by an Edgewood technician were woefully inadequate. (A previous chapter has discussed the details of the panel's findings.)

The early 1980s proved to be as hectic and interesting as the 1960s had been. By leaving the VA in late 1979 to do private practice, I also left behind my status as "in-residence" assistant professor of psychiatry at UCLA. I acquired instead the less prestigious appointment of clinical assistant professor of psychiatry (which I retain, although on "inactive status").

Milton Greenblatt, MD, in a lighter moment

Ironically, I kept running into and developing relationships with researchers who had studied LSD in the early years, trying to understand its remarkable properties. As mentioned earlier, Milt Greenblatt, my boss at UCLA/Brentwood, had been one of the first LSD pioneers. At the Boston Psychopathic Hospital, like other academicians, he too had, perhaps unknowingly, received research funds from the CIA.

After working for Milt for three years at UCLA, running the affiliated VA Substance Abuse Program, I decided to strike out on my own and become a private practitioner. Seven years later, when I grew tired of full-time private practice, he hired me again, this time as ward psychiatrist at the Olive View Hospital in Sylmar, California. I had a great time there, teaching UCLA medical students and USC physician assistant students, but as the workload kept increasing and finally exceeded my limits, I left in 1989 to resume my private practice.

In the early 1980s, I had become more closely affiliated with Sid Cohen. He, like I, was on the National Academy of Sciences blue-ribbon panel that evaluated possible long-term effects of BZ and related incapacitating agents. A funny, memorable incident occurred when I failed to make a hotel reservation prior to the meeting and he offered to share his hotel room. When bedtime arrived, it was incongruous, somehow, to see the illustrious professor in his boxer underwear. On our way to breakfast, he was amused when I confided that I had

even had a sex dream about him. Freud's theories must contain a grain of truth.

Throughout the 1970s and early 1980s, Sid wrote a monthly newsletter on drugs for the Vista Hill Foundation in San Diego. Once, I suggested he devote an issue to caffeine. Knowing I was a compulsive collector of drug research articles, he invited me to write it. It was a surprising departure from his custom of writing all the reviews himself. Procrastination took over, however. I finally gave Sid my collection of several dozen articles on caffeine and he wrote the review himself.

I spoke with Sid for the last time in May 1986, just before he entered the banquet hall where his many friends and colleagues had assembled to honor his lifetime contributions. Before we went in, I asked if he would have any time to help me with a computerized psychopharmacology database I was developing.

"I'm willing," he said. "But it had better be this year," he added, knowing my dilatory tendencies. It was a sadly prophetic remark. When he spoke on the banquet hall podium that night, he said euphorically "I feel like a rock star." Sid died of heart disease the following year and a special memorial service honored him at UCLA.

* * * * *

In 1986, a second reminder of Edgewood Arsenal, also named "Leo," came my way. Leo Abood, a biochemist who had worked on structure vs. activity relationships among belladonnoids, had been a visiting lecturer at Edgewood in the 1960s. He was particularly interested in synthetic belladonnoids and helped identify several potent compounds for us to test. But, as the result of some kind of lapse, Leo apparently gave an incorrect impression about the relative potency of BZ at a Stanford seminar, shortly prior to my arrival as a post-doctoral fellow in 1966.

He left the impression that BZ was hundreds of times more potent than LSD. At one of Karl Pribram's weekly seminars, I almost came to blows about this misconception with Dr. Fred Melges, a staff psychiatrist. Quoting Abood, he insisted I just didn't know what I was talking about when I said that LSD was actually more potent than BZ. Telling him I was the one who did the studies with BZ seemed to have no effect. I guess the Army can take a researcher out of the credible category pretty fast.

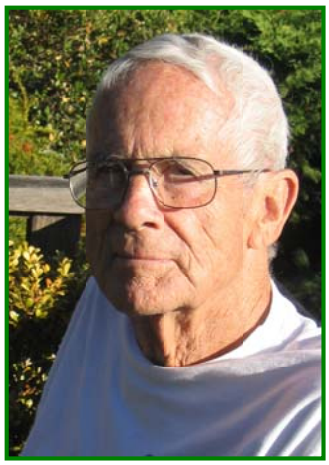
Abood never knew about this little incident. Nevertheless, twenty years later, in 1986, I was pleasantly surprised when he invited me to join a dozen other researchers at a unique symposium in Maryland. Its purpose was to brainstorm chemical countermeasures to possible terrorist attacks, especially the hijacking of airplanes.

One participant at the 1986 seminar was Dr. Theodore Stanley, Chief of Anesthesiology at the University of Utah. He suggested the possibility of filling a hijacked airliner with Xenon (an inert gaseous element). Everybody would immediately become unconscious, but fresh air could quickly revive them, once the hijackers were under control. He estimated, however, that the amount of Xenon required would be expensive – at $10 a liter, the occupied area of an airliner, would cost several million dollars, even if it could be effectively disseminated.

To show how fast memories fade, I recently contacted Ted Stanley after finding out by surfing the Net that he was an expert on the opioid drugs. I wanted to get his ideas about the "gas" used in "the Moscow incident." We had pleasant conversations on the phone, but neither of us remembered the other.

Only when I accidentally dug out the transactions of that 1986 seminar did I recall that we had spent two days together in the same small room! After the meetings, Leo had suggested that he and I collaborate on a book, but I demurred. I was determined to write my own book, but characteristically procrastinated another fifteen years.

In 1989, still another after-image of Edgewood appeared. Enoch "Noch" Callaway, a distinguished professor of psychiatry at the University of California in San Francisco (UCSF), unexpectedly called me at home. He had done some of the earliest research with atropine at Edgewood Arsenal in the early 1950s. Although unaware of this at the time, I had called him on impulse one morning in 1967 from Karl Pribram's lab, to ask a question about his latest article in the American Journal of Psychiatry.



Enoch Callaway, MD

Although that call was almost 25 years in the past, Noch and I remembered it. He was calling, however, as a research partner at Neurobiology Technologies Inc., located north of San Francisco, and wanted to hire me as a consultant. He outlined his belief that a combination of atropine and physostigmine could treat nicotine addiction. The idea did have a superficial theoretical appeal, but I didn't think it would work. Nevertheless, it was hard to turn down the chance to be a paid consultant.

Noch had lined up an impressive team of drug experts, including Nobel laureate Rosalind Yalow. He seemed to think that among my unpublished data was previously classified information that might be helpful. He kept saying, "We're waiting for Jim to publish his magnum opus so we can learn more about atropine-like drugs and the properties of physostigmine." I was afraid to say, "Noch, you might have to wait another 15 years."

The contract continued into 1991. I attended meetings, wrote proposals for pilot studies and enjoyed gourmet dinners at great restaurants. None of the contemplated clinical trials, however, ever materialized. At our last group meeting, I was to present some of the results of my work with BZ and other belladonnoids. I ran out of time, and ended up showing one of the poster-sized composite graphs we had created during Project Dork in 1964. At dinner, my wife chatted with Roz Yalow. "Your husband's presentation was fascinating," Roz told her diplomatically, "It was…well, it was all right there!" She should have said, "Is that all there is?"

Always the optimist, I did not allow myself to dwell on shortfalls. In 1990, I received another phone call, this time from Washington, DC. The caller asked whether I would take part in a TV interview. As usual, I was ready to cooperate. He told me that Michael Bilton, producer of a British monthly documentary program called First Thursday, was planning to make an hour-long special about the Edgewood Arsenal research and he wanted my views represented. He might come to Woodland Hills from England to discuss it with me.

Not long thereafter, Michael did arrive in California and we talked for quite a while. Encouraged, he returned with a film crew in a few weeks. The

interview went pretty much as I had expected. I did my best to be candid. My wife Judy dressed me in a lavender cashmere sweater over a fashionable open-collar shirt. I sat in the big easy chair next to my computer, beneath a large wall map of California. It all seemed very cool.

Michael Bilton, Producer of *Bad Trip to Edgewood*

After the shoot, we spent the evening socializing with Michael and his director. We had spirited discussions of just about everything. It was clear that, although we liked each other personally, we were far apart in some of our political beliefs. I could only hope that the final production would not make me look too evil!

The film, Bad Trip to Edgewood, was actually quite charitable toward me personally, but left no doubt as to the editorial views of the makers. Funereal music and views of smokestacks at the Arsenal dominated the first scene, after which the film progressed through pictures of an LSD-drugged cat jumping fearfully away from a mouse in the same cage, and one of a monkey with his head and jaws immobilized by clamps in order to make him inhale an aerosol dose of some unidentified substance. These were just segments of Edgewood stock footage from the late 1950s – ancient history, but suitably shocking for Michael's purposes.

I had a couple of minutes to present my side of the story, but the film seemed to be speeded up a bit, making my voice come out several notes higher than normal. I had the paranoid feeling that the speed-up might be a subtle attempt to make me sound less manly, but perhaps it was just a way to compress available time.

Although the production was less favorable than I had hoped for, at least Michael had not criticized me directly for the supposed misdeeds committed by the Chemical Corps. He told me that he had also interviewed and filmed Alexander Shulgin, the internationally admired biochemist who tested and first described the experiential aspects of a number of psychedelic substances, including "Ecstasy." Dr. Shulgin disapproved of Edgewood's use of volunteers to test the incapacitating properties of drugs. Michael had planned to use him as an articulate counterpoise to my position. However, in the final edit, time constraints necessitated the omission of Dr. Shulgin's comments.

Michael later dropped by to visit while he was in California and we had some stimulating dialogues. After returning to England, however, he typed a 14-page single-spaced letter expressing the basis of his views. I replied with 14 pages of my own, in which I labeled him a "victimologist," as demonstrated by his previous books on the My Lai tragedy and the brief war in Grenada. I cited the numerous men of integrity, both in and out of the military, who had agreed at the time that our work was proper and necessary, so either they were all wrong, or perhaps Michael had lost some of his historical perspective. In the end, we amicably agreed to disagree.

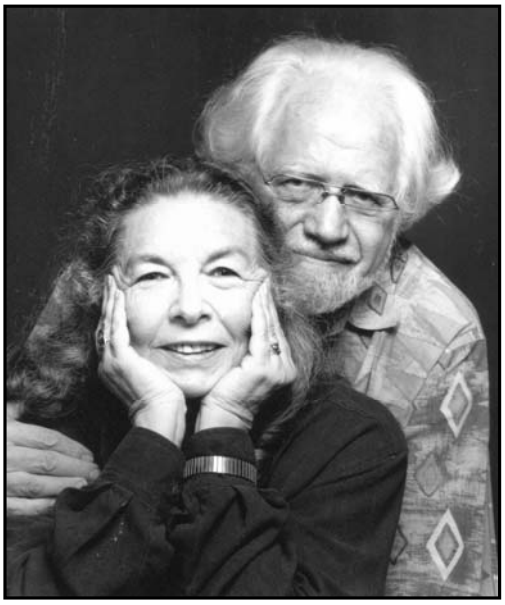
After Bad Trip to Edgewood aired in the United States, the Canadians wanted to follow it with a small production of their own. Like the British, they also sent a film crew to interview me briefly. Their production echoed the sentiments of Michael Bilton's film.

In 1997, Alan Hornblum, an investigative reporter working for the Philadelphia Police Department, called me about a book he was writing. It dealt mostly with research done by Dr. Albert Kligman, Chief of Dermatology at the University of Pennsylvania. Primarily, Alan was concerned about certain irregularities in Kligman's testing of inmates at Holmesburg Prison.

Since Edgewood Arsenal was one of the organizations that had contracted with Kligman, and I had been a project officer of one of the studies, he wanted to ask me about the military work done under my supervision. (In an earlier chapter, I have described in detail my interactions with Professor Kligman.)

I was happy to help, and we talked at length on the phone. Later, I wrote to him several times, answering more of his questions. He completed his book five years later, titling it Acres of Skin. His treatment of our work at Holmesburg was quite fair, even complimentary in part. He later arranged for me to join him in a live radio discussion on National Public Radio, along with a representative of the inmate population. The hour-long discussion went quite well, with no serious criticism of our studies. It focused more on Dr. Kligman and some of the questionable procedures he had used in testing cosmetic preparations on prisoner volunteers. Once again, openness seemed to have helped shield me from hostile criticism.

I soon had another interesting, rather ironic, encounter. At a 1993 event in Santa Cruz honoring the 50th anniversary of the accidental discovery of the subjective effects of LSD by Albert Hofmann, I met Dr. Alexander "Sasha" (my intended counterpoise in Bad Trip to Edgewood) in the cafeteria line. As we chatted, it became apparent that we agreed far more than we differed. We hit it off so well, in fact, that he and his wife Ann later invited Judy and me to lunch at their home in Lafayette, California.



Ann and "Sasha" Shulgin

Sasha had recently published his critically acclaimed PIHKAL, a Chemical Love Story ("Phenethylamines I Have Known and Loved."). A lengthy book, the first part deals with his personal history and love affair with Ann. The second part is a technical compendium of the various psychedelic compounds he had developed. It includes structures, methods of synthesis and subjective effects as recorded by a group of special friends, who visited periodically to evaluate personally the latest of his psychoactive molecules.

Sasha had some peyote plants (the natural source of mescaline) growing in front of his house. The DEA had not asked him to remove them, which surprised me in view of Sasha's firm advocacy of the "repeal" of the "prohibition" of marijuana and psychedelic drugs – a view, incidentally, with which I fully sympathized.

But the immunity of the peyote was not to last. It ended in a disruptive and heartbreaking incident that was totally unexpected. In Ann's words:

"When the DEA people came on the day of what I called 'The Invasion,' the peyote cacti were right there for all to see (yes, Sasha's license allowed him to possess them), but not one agent recognized them as peyote. It wasn't until the head agent asked Sasha directly, 'You wouldn't by any chance have peyote somewhere around here,' or words to that effect, and Sasha said, 'Yes, they're right behind you, against the wall.' The whole group turned around and looked at the plants they had ignored for hours, and each of them took a step backwards, as if Sasha had pointed out a bunch of pythons. It was absolutely clear that they hadn't recognized the peyote, and I think that during past visits by DEA agents, over the years, none of them had recognized the peyote cacti either. So it wasn't a matter of "overlooking" the peyote for this or that reason; they simply didn't know it when they saw it."

When I asked if I could see Sasha's laboratory, he led me around to the back of the house, where what looked like an old wooden storage shed stood apart from the main dwelling. It may even have had a creaky door, but I'm not sure. Inside, it was dimly lit and almost windowless, with cobwebs in the rafters. On numerous wooden shelves and several bench tops were an array of beakers, fractionation columns, distillation gizmos and assorted canisters and bottles. This was the lair of a mad scientist if ever there was one, I thought.

But Sasha was by no means mad – he was just a free spirit, not particularly concerned with appearances as long as he could synthesize and study his family of intriguing psychochemicals. He and his wife proved to be most generous friends. Sasha has lent or given me several useful books and articles in the past few years on subjects relating to LSD and other psychedelic drugs. He recently provided me with a great deal of difficult-to-find information that has helped in the preparation of this book.

A BBC radio news analyst called me in November 2002, shortly after the incident in which Chechen terrorists took more than 1,000 civilians hostage in the Moscow Theater. He asked if I would comment briefly on whether the gas might have been BZ, which some had suggested might have been the chemical used. This seemed like a chance to de-mystify BZ a bit. I explained that BZ was merely a more potent version of the familiar drug atropine, and would not have been a feasible choice for such a rescue attempt. I suggested that etorphine (a highly potent morphine-like drug) or Fentanyl were more likely to create the reported effects. This proved to be the consensus of various experts, as reported in (guess what?) Science magazine.

Another reminder of my Edgewood days was a call in May 2006 from Bret Baer, a news commentator on Fox TV. He was following up a report by the wife of a former Edgewood volunteer that an electronic chip had apparently been implanted in her husband's brain – perhaps to turn him into an assassin. I had had friendly telephone conversations with the former volunteer's wife several times, but had told her I could not confirm that any such chip had been implanted and in fact I strongly doubted it. Bret said he had seen an x-ray she provided which a radiologist said showed a tiny foreign body near the ethmoid bone. I assured him that no one in our program at Edgewood could have carried out such an arcane procedure nor, in my opinion, would have even considered doing so.

Looking back, I have regrets about many things in my life, but my participation in the research program at Edgewood Arsenal is not one of them.

* * * * *

24 BELATED ALARMS: WHAT HAVE WE DONE?

Conscience has no more to do with gallantry
than it has with politics.
Richard Brinsley Sheridan: *The Duenna* II. iv

In the wee hours of the morning of 18 November 1953, Frank Olson, a CIA biologist at Fort Detrick, went to his death through a window on the 10th floor of the Statler hotel, where another CIA member was monitoring him. Olson had developed symptoms of depression following the ingestion of a glass of LSD-spiked cointreau. As if suddenly awakening to find smoke coming from the basement, Congress and the military establishment alerted their emergency teams in charge of sleuthing and damage control.

Olson's LSD trip had occurred two weeks earlier, during a CIA weekend retreat in the countryside. During their secret meeting, Dr. Sidney Gottlieb, head of the MK-ULTRA project, distributed glasses of LSD dissolved in cointreau to Olson and the several other CIA members. None was aware that his drink had been spiked. Within half an hour, all of them began to notice effects. At this point, Gottlieb told them about the LSD. Soon, no one was able to concentrate on the conversation. Uncontrollable laughter and confusion reigned. The meeting ended with the men in a jovial, euphoric state.

Olson, however, reacted differently. He became depressed and paranoid. Over the weekend, he kept telling his wife he was incompetent. Gottlieb called Dr. Harold Abramson, who tried to help, providing medication and reassurance. When the depression did not lift, Abramson became concerned and arranged for hospitalization at Chestnut Lodge, a private psychiatric hospital.

While awaiting admission, Olson and Lashbrook, a CIA colleague, slept in a hotel room at the Statler. The colleague allegedly kept one eye open. But at 2 A.M., Olson plunged through the window to his death. Evidence suggests that he may have been pushed. An operator recalled Lashbrook talking to someone (perhaps Abramson or Gottlieb), saying simply "He's gone." An expert calculated that – even with the help of a running start from the other end of the room – Olson could not have generated enough force to dive through both the closed blinds and the window glass. Later, after an investigation and legal proceedings, the government provided monetary compensation to Olson's widow and President Ford issued an apology.

The reverberations from this catastrophe reinforced a growing demand to investigate just what had been going on with CIA drug testing. A committee chaired by Senator Frank Church was the first to look into the matter. Senator

Nelson Rockefeller headed a second committee of inquiry on a related subject. Senator Edward Kennedy, however, chaired the most widely publicized commission. His committee focused on MK-ULTRA, a highly secret CIA project aimed towards the control of human behavior with drugs.

As the result of these hearings, the Defense Department felt compelled to provide a complete accounting of its drug testing. The Inspector General of the Army was instructed to undertake a searching review of the Chemical Corps' volunteer program. The review was to focus on procedures used in the testing of LSD, BZ and other incapacitating agents.

The IG immediately gave orders to the Surgeon General, the Assistant Chief of Staff for Intelligence and the Commander of the U.S. Army Materiel Command to support the investigation fully. He directed them to provide the IG with access to all installations, testing facilities and records. They were to obtain copies of everything pertaining to "hallucinogenic drugs."

Researchers responded to this assignment promptly and vigorously, finishing their report in less than a year. Fred Sidell told me that a truck from Washington DC came empty and left loaded "to the gunnels" with multiple copies of everything in the Clinical Research Department document library, plus an unknown amount of material from other files.

The IG report authors stressed that they had been given a monumental task. They stated:

> This mission was unlike the usual directive for inquiry or investigation normally assigned to the Inspector General for action. Instead of determining the facts and circumstances of a specific wrong(s) or allegation(s), the mission was to conduct a form of historical research; research which would determine exactly what the Army had done in chemical agent testing during the period 1950-1975.
>
> [It was] a period which probably had as many changes, programs, and problems as any comparable period in history: post-World War II; the Korean War; the Cold War; reorganization of Department of Defense; reorganizations of Department of the Army; the war in Vietnam; and major advances in medicine, the sciences, nuclear weapons, missiles and aircraft. The sheer volume and frequency of change alone provided some indication of the magnitude of the task to be performed. From the outset, the research effort proved to be difficult and cumbersome.

The team may have slightly overstated the obstacles. Most of the information they sought (at least for studies done after 1960) were in conscientiously numbered, filed and listed volunteer folders. Computer printouts, correspondence, and testimony from relevant witnesses were still available. These resources should have been enough to answer almost all the IG's questions.

What went on before 1961 was more difficult to reconstruct, since record keeping during that period was incomplete. The IG team, however, located 95% of all charts produced from 1955-1975, most of them covering testing that took place during the "turbulent 1960s."

Roughly 90% of the LSD testing took place prior to 1961, and many records had been retired or destroyed in accordance with "normal destruction schedules." After 1960, however, there was no such "destruction schedule." While I was at Edgewood, we took pains to keep all records secure in a central "data library."

Clandestine work done in collaboration with the CIA was specifically exempted from the directive. Van Sim's estimate that "3,000 exposures" to LSD took place during the 1950s, however, is suspect. His 1961 summary does not substantiate this

number. He may have inflated the figure to add gravity to his report.

Although our records improved greatly after 1960, it would be unfair to minimize the daunting task that faced the IG authors. Their team undoubtedly expended thousands of man-hours carrying out its mission. Merely thumbing through the estimated 100,000 pages of material must itself have been a Sisyphean task.

The final IG report begins by alluding to the uncovering of LSD investigations at civilian institutions, and those performed jointly with the US Army Intelligence Center. These, however, were CIA supported studies. They were not part of the approved Edgewood Arsenal volunteer program.

If the secret work of the CIA had been excluded from consideration, the researchers wouldn't have found much. Gottlieb had destroyed most of those records in 1973 as directed by CIA director Helms. It is no surprise that the IG had difficulty investigating them. As the report writers explain in their prologue: "Where neither documentary or testimonial evidence was available, then license was taken by drawing logical conclusions or assumptions based on evidence available, past performance, or other indicators." (Unfortunately, the need for such assumptions would tend to weaken the reliability of their conclusions.)

After a well-written chapter devoted to a history of chemical warfare, the authors proceed to a general consideration of psychochemicals. They begin with some definitions designed to clarify the ambiguities around such terms as "psychotropics," "psychochemicals" and various categories of "incapacitating agents." They emphasized Colonel Douglas Lindsey's definition of "Incapacitating – Non-Lethal Agents" from his 1959 report entitled "Selective Malfunctioning of the Human Machine, New Horizons in Chemical Warfare."

> "Incapacitating – Non-Lethal Agents are defined as those compounds which when delivered or employed in an effective dose can interfere with an individual's performance of duty for a militarily significant period of time, but which will allow him to recover completely without medical aid."

It would be difficult to improve on this definition.

The authors then specify the various categories of incapacitating agents, including BZ and related belladonnoids. They provide an historical summary of the use of various psychedelic drugs, including the story of LSD's discovery and subsequent study of its effects, beginning in the 1940s. They also note that the government had searched for a "humane weapons system" for several years before recognizing the potential of psychedelic drugs. LSD studies first began because of the intelligence community's wish "to determine an enemy's capabilities for using psychochemical agents as a weapon against our national security."

This surge of interest culminated in the appointment by the Department of Defense of an "Ad Hoc Study Group on Psychochemical Agents" in June of 1955. Harold G. Wolff (who has received special attention in this book) headed this group, subsequently referred to as "the Wolff Committee." The group's report in November 1955 was an important determinant of Army planning with respect to the clinical study of LSD.

Chapter III of the IG report is devoted to a history of "the threat." It concisely summarizes the changing American mentality following our success in World War II. After focusing almost completely on nuclear weapons, a succession of scientific and technical advances awakened military planners to the need also to consider the potentially serious threat posed by chemical and biological weapons. As intelligence reports about Soviet investment in psychoactive substances accumulated, their concern increased. In early 1951, for example, intelligence sources reported that Russia was experimenting with a

psychotropic drug called "ketjabung." Supposedly, ketjabung could render an individual's behavior vulnerable to external manipulation without his awareness.

Not long thereafter, a Harvard physician returned from a visit to Europe and reported that several countries were looking into the possible military use of LSD. This galvanized our strategists, who were already aware of the USSR's heavy investment in nerve agents. They knew about the huge stockpiles of such items as tabun (GA), and sarin (GB), developed by the Soviet Union with the help of experts brought from Germany after the war.

In the early 1950s, it appeared that the United States had fallen far behind the Soviets with respect to its chemical warfare capability. Franklin Roosevelt had expressed vehement disdain for such weapons and sternly asserted that we would never use them unless our enemies used them first. But this policy began to soften, particularly when planners recognized the possibility of developing psychochemical weapons. Perhaps these would not produce the repugnant, inhumane effects Roosevelt had decried. Many also argued that we needed to be informed about – and prepared for – some future enemy attack with these new substances.

Chemical warfare research and development had already been authorized and conducted during the 1950s, including experiments with human volunteers. These programs were heavily cloaked in secrecy, primarily because of fears that the public, or even Congress, might object and try to discontinue such research.

The IG report cites many of the earliest high profile articles that appeared in widely read newspapers and magazines. Many of them actually remonstrated against the U.S. defense posture, stressing our failure to respond adequately to an obvious chemical and biological warfare threat. Apparently encouraged by this unexpected endorsement of a more robust Chemical, Biological and Radiological (CBR) program in the US, both houses of the Congress began to conduct hearings. In 1958, the House of Representatives submitted a comprehensive report entitled Research in CBR, which contained the following conclusions:

> As a result of its hearing and further study on the problems of research in CBR, this committee offers the following recommendations [paraphrased here for the sake of brevity]:
>
> 1. The United States must maintain intelligence efforts to keep abreast of foreign CBR developments in time to develop adequate defenses and countermeasures.
> 2. Surveillance of foreign activities might be the only way to suspect imminent use of CBR against the United States.
> 3. Public understanding of the dangers and uses of CBR is needed, if proper support is to be given to our defenses and countermeasures.
> 4. Before considering international disarmament, we must not overlook the great potential of CBR and the ease of evading detection of CBR activities.
> 5. A higher level of long-term support is needed to make possible better CBR detection and protective measures.
> 6. CBR-proof shelters, masks, protective clothing and public instruction are an important part of defense plans.
> 7. Methods to detect and guard against CBR sabotage will require positive and imaginative attention.
> 8. CBR weapons are designed to do a different job, rather than compete with nuclear weapons.
> 9. We do not judge the morality of CBR, but must recognize that it may be used against us.
> 10. Some forms of CBR offer the prospect of winning battles without taking human life or destroying property, and would be preferable to the use of force. Such "gentle" weapons could defeat us, destroying our way of life as seriously as force.

11. We recognize that other countries are pursuing vigorous programs of CBR development, and a strong capability in this field is our best guarantee against its use. This will require a strong research effort.
12. CBR research receives only one-thousandth of our total defense budget. The committee recommends tripling this.
13. For CBR is to be effective as a deterrent, we need to manufacture and deploy appropriate munitions.
14. CBR would be relatively inexpensive compared to other modern forms of warfare and could use delivery techniques already developed for nuclear weapons.
15. CBR research has already yielded peacetime benefits, including antidotes for poisons, new serums to prevent disease, greater understanding of how diseases spread, new insecticides, and greater fundamental knowledge of life processes. Possible military and peaceful applications of chemical and biological knowledge overlap.
16. We are in a research and development race with the Soviet Union, whether for peaceful or military purposes. Full public understanding and support of CBR efforts is needed.

Seventeen years later, sentiments changed and Congress ordered the destruction of all CBR weapons, including the "gentle" weapons of incapacitation referred to above. For a wider historical perspective, however, we must go back further.

The Chemical Corps originally established the Chemical Warfare Service (CWS) in 1918, motivated by the horrors of gas warfare that they witnessed during WW I. In 1922, it created a Medical Research Division. Its mission was to defend against chemical agents.

The research scientists recognized that they could not fulfill this mission by animal experiments alone. Employees at Edgewood Arsenal volunteered, but research deficiencies, including a lack of controls and the preconceptions of subjects familiar with the agents, limited the value of these studies.

Accordingly, in 1942, the Adjutant General, in the name of the Secretary of War, issued formal authority to recruit and use enlisted volunteers. Until the 1950s, this authorization allowed testing at Edgewood Arsenal and other field laboratories around the country. Although the U.S. had acquired the German techniques of making nerve agents following WW II, there were still insufficient experimental data to justify testing these agents in man.

The CWS spent several years doing animal studies to establish the safety of proceeding with such tests in volunteers. Rules governing the use of humans in medical experiments originated during the Nuremberg Military Tribunals. (These principles, in their unabridged form, are in the appendix.) The main points were as follows:

1. The voluntary consent of the human subject is absolutely essential and should be based on sufficient knowledge of the test, without coercion of any kind.
2. The experiment should be expected to yield fruitful results for the good of society, unprocurable by other methods.
3. The experiment should have justifiable goals and be based on data from animals and clinical briefing of the subject.
4. Unnecessary suffering or injury should be avoided.
5. If death or disabling injury is expected, no one other than the physician doing the test should be a subject.
6. Humanitarian benefit must outweigh any risk
7. All possible safeguards should be provided.
8. Only scientifically qualified persons should conduct the experiments and they should exercise maximum skill and care of the subject.
9. The human subject should be allowed to stop the experiment if he feels unable to continue.

10. The scientist in charge should stop the experiment if he believes continuation is like to cause injury or death.

In 1950, the Council gave the Secretary of the Army the responsibility and authority for any program conducted or sponsored by the Army. The Secretary was to ensure adherence to both the Organization of the Army Act and the Nuremberg code. There was no evidence that he delegated this authority to a lower level.

The Secretary of Defense also responded to the Council's recommendations by issuing a "Top Secret" memo along similar lines to the service secretaries (Army, Navy, Air Force and Marines). He specified that each secretary must approve any protocol originating in his branch of service, name the person in charge and inform the Secretary of Defense of each approval.

Meanwhile, members of the Medical and Related Problems Committee of the Chemical Corps Advisory Council were busy creating some of their own rules. They separated hazardous from non-hazardous experiments so that only the latter would require higher-level approval. They sought blanket approval for experiments already in progress, hoping to avoid unnecessary red tape. The Council made informed consent essential, however, and demanded sufficient evidence be made available to show that the soldier was truly able to freely volunteer.

The Secretary of the Army agreed with most of these additional rules and downgraded the "Top Secret" classification, making the guidelines available to subordinate elements. In June 1953, the he sent Army Chief of Staff Memorandum 385 to the Army Chief Chemical Officer and the Surgeon General, entitled Use of Volunteers in Research. It required observance of the Nuremberg rules and the Secretary of the Army's approval, as well as written comment by the Surgeon General. There was, however, to be no distinction between hazardous and non-hazardous experiments.

The Commander of the Chemical Corps Research and Engineering Command, the Chief Chemical Officer, and the Surgeon General forwarded a plan developed by the Chemical Corps, listing seven investigative studies in progress. After its approval, they downgraded the original Secretary of Defense's memorandum to "Confidential."

The review process went all the way up to the Secretary of Defense, and included experiments conducted by contractors. This meant that studies with volunteer subjects at many prestigious universities throughout the country would need approval in writing by the Secretary of the Army. It is uncertain whether this actually took place.

The Department of Defense memo may still have been too highly classified, leading to inadvertent violation of its rules. One example of a violation was the Top Hat program in which volunteers tested decontamination methods for various toxic substances. The authors observe that those operating under this protocol may have thought this study was not subject to the above policies.

Investigators soon treated the rules as more permissive than they really were. One request for approval of seven studies already in progress, titled "Retention of Nerve Gas Vapor in the Human Respiratory Tract" did not specify a particular gas. This presented the Surgeon General with a problem. He could not reasonably review all the data on all the possible nerve agents. Also, there was no description of emergency treatment procedures. Nevertheless, he approved the proposal. The IG writers comment that this reduced the detailed review process to "a perfunctory action for the purpose of obtaining blanket approval for ongoing research projects."

In 1954, despite the establishment of a framework for human testing, there was still no provision for procuring enlisted volunteers. Local enlisted personnel and lab

technicians were insufficient in number to support a large testing program. An orientation team solicited nearby installations for volunteers and on 2 May 1955, the first contingent of 16 soldiers from Second Army Headquarters arrived at the Arsenal.

In September 1955, the Commander of the Edgewood Arsenal Medical Laboratories formally requested permission to use volunteers in research involving nonlethal psychochemicals. This was largely a result of the Wolff Committee's final report, which included a detailed plan for field experiments involving small units.

In January 1956, the Office of the Assistant Chief Chemical Officer for Planning and Doctrine came up with its own comments on the "Wolff Report." They recommended that a "training lecture" be prepared for those scheduled to receive LSD, but not to those who were to receive only a placebo. The IG report writers made the cogent observation that not informing a placebo volunteer about a drug he "might" receive would be a de facto violation of the requirement to provide full information to every participant. It might also make a truly "double blind" experiment impossible. They used the term "selective compliance" for the normative practice of limiting the pre-test information in placebo subjects.

In 1958, Van Sim requested 200 volunteers, to help study the effects of psychochemicals on military tasks. Although the Chief of the Chemical Corps Chief approved this request, the Secretary of the Army apparently had no direct role in the approval. This omission established two precedents: (1) a "class" of chemical agents ("psychochemicals") could be studied without specificity; and (2) an approval could be valid without written endorsement by the Secretary of the Army.

These precedents undercut the original policy. In 1958, the Surgeon General and the Chief Chemical Officer approved a similar proposal for the use of certain nerve agents, once more bypassing the Secretary of the Army. This further eroded Army Chief of Staff Memorandum 385. The report goes on to delineate other examples of procedural slackening.

In 1962, a new policy stated clear rules for the conduct of research, similar to those in the 1953 memorandum. By this time, the intensity of incapacitating agent research had risen to a peak. President Kennedy's desire to expand the spectrum of defense research included "Project 112," a program that placed a high priority on developing a chemical incapacitating agent. The primary candidate was BZ, and planning for BZ munitions, stockpiles and storage facilities was already in progress.

In March 1962, Army Regulation 70-25 firmly reinforced the requirement to submit for review every detailed proposal for a human study, including the name of the responsible physician. The chief of the Edgewood labs would forward any proposal through the Surgeon General, the Chief of Research and Development, and finally to the Secretary of the Army.

As I reviewed this detailed history, I wondered if AR 70-25 (or even the pre-existing regulation) was ever followed to the letter while I was conducting drug studies. I can't recall being obliged to submit this type of detailed proposal or waiting for formal approval as they traveled through the long chain of command that AR 70-25 specified. In fact, between 1962 and 1966, when I was designing studies with one drug or another almost monthly, I usually received approval from our Department Chief by merely submitting a detailed memo describing my intentions.

Indeed, I was not plagued with the endless delays that should have occurred if six or seven authorities were reviewing a meticulous protocol. Perhaps, without my knowledge, my superiors were routinely submitting paper work on my behalf in accordance with the stringent requirements of AR 70-25, but it seems doubtful.

For example, we carried out the elaborate field test at Dugway Proving

Grounds (Project Dork, described earlier), at the behest of a four-star General and with the support of the Secretary of the Army. My superiors personally opposed it. The protocol was a 15-page double spaced document I typed in one day. By supplying this directly to the major who had brought the general's request to Edgewood, I short-circuited the usual chain of command – not a good general practice. Nevertheless, the IG writers commented that Project Dork had complied with all the requirements!

I am not arguing that this method was necessarily the way studies should be done, but it certainly was a good way to get them done. I think I was granted extra latitude because of my previous work. Today, it seems that funding only goes to researchers who have mastered the art of creative writing. Some hire specialists just to help them assemble bulletproof protocols.

Bureaucracies flourish in the academic world just as they do in the political world. Perhaps it is true that "only in the military" can one sometimes act with a minimum of administrative hindrance. The hindrance increases with each additional layer of review. Reviewers feel obliged to object, or request changes, to some part of the proposal. To "sign off" on a proposal without comment might suggest a lack of interest.

At any level, rejection means revisions and another climb up the approval ladder. This can be frustrating when the reviewers are less qualified than the originators to evaluate a complex proposal. Expertise grows progressively more rarefied as the proposal floats higher into the upper stratospheres of authority.

One solution might be to initially scrutinize proposals from investigators who lack a solid track record, and then to give a less stringent review as the performance improves. But today's bureaucrats seem inclined to go slow in all matters, preferring to head off one questionable study than to "fast-track" a hundred well-designed studies by established researchers.

After 1962, still more rules were adopted to insure ironclad control from the top. The Surgeon General and Chief of the Chemical Corps were added to the decision-making hierarchy. Committees and Review Boards replaced individual reviewers. The Army Investigational Drug Review Board provides an instructive example.

The Review Board created two different routes to approval, depending on the source of the proposal. This led to nonsensical inconsistencies. Some projects were reviewed with a fine-toothed comb while others received only casual attention. Progress sometimes moved in unanticipated directions thanks to the lack of clear-cut guidelines.

The following paragraphs sum up the welter of control mechanisms that ultimately governed drug studies at Edgewood (as well as throughout the entire Army).

> On 10 September 1975 LTG Richard R. Taylor, the Surgeon General of the Army, testified before Congress that, "in October 1974, the Surgeon General established the Human Use Review Office under the direction of the Assistant Surgeon General for Research and Development.
>
> "The Human Use Review Office was charged with administering and coordinating activities of the Army Investigational Drug Review Board, the U.S. Army Medical Research and Development Command Contract Review Board and the Surgeon General's Human Use Committee and Clinical Investigation Committee, to insure uniform application of ethical standards for human research studies conducted within or sponsored by the Army Medical Department and other Army Agencies.
>
> "The Human Use Review Committee is the central Army processing point for all extramural and intramural human subject research which requires approval under provisions of Army Regulations." While discussing Defense Against Chemical

> Weapons, Lieutenant General Taylor reported: "Furthermore, the review mechanisms applied to Edgewood have been tightened over the last two years so that protocols are reviewed by the Army Investigational Drug Review Board and Human Subjects Research Review Board and relevant Department of Defense and Food and Drug Administration regulations are followed."

What a bureaucratic tangle!

The report then turns to the volunteer consent form:

> "I, ---------- , certify that I received, read and understand a document entitled Medical Research Volunteer Program, dated 15 March 1955, copy of which is annexed hereto, and that the general nature of the experiments I have volunteered to participate in have been explained from the standpoint of possible hazards to my health. It is my understanding that the experiment is so designed and based on the results of animal experimentation, of the natural history of the disease, or other problems under study that the anticipated results will justify the performance of the experiment. I understand further that the experiment will be so conducted as to avoid all unnecessary physical and mental suffering and injury, and that I will be at liberty to request that the experiment be terminated if in my opinion I have reached the physical or mental state where continuation of the experiment becomes impossible.
>
> I recognize that in the pursuit of certain experiments transitory discomfiture may occur and when such reactions seem especially likely to occur I will be so advised. I recognize, also, that under these circumstances, I must rely upon the skill and wisdom of the physician supervising the experiment to institute whatever medical or surgical measures are indicated to protect me against the possibility of serious or permanent injury and/or disability, or death.
>
> I certify that no coercion, element of fraud or deceit, undue moral suasion or other adverse pressure has been brought to bear in my volunteering for this study. I have done so of my own free will, completely aware of all hazards, rewards and recognition involved.
>
> Date: _____ Witness: _____
> Signed: _____ Witness: _____

The IG report criticizes this consent form for not guaranteeing adequate discussion of the nature and hazards of the experiment. This was particularly true for the early volunteer records. Establishment of trust, however, was always a priority. No one can predict all the symptoms or mishaps that might conceivably occur. Ultimately, the volunteer's confidence in the physician's integrity and concern for his well-being is paramount. The concept of "informed consent" remains as slippery today as it was in the sixties. Honest communication remains more important than fine print in a contract.

Some former volunteers did eventually claim that investigators failed to provide adequate instructions. The IG report cites these examples:

> An Army Times Article of 14 February 1959, titled "2 Men Cited as Human Guinea Pigs," from Camp Irwin, CA, which states: "Neither of the men was told what he was doing. Regularly they swallowed pills, took shots and underwent periods in the gas chamber, but neither of the men knew what he was taking or what the experiments might prove."
>
> Personal Letter from Army Private to the Commander of the Medical Research Laboratory, dated 5 December 1970, requesting details of the type of psychochemical drug, dose and possible effects on his future offspring.
>
> Personal inquiry from Army Specialist on 11 August 1967 requesting knowledge of a drug he had received seven months earlier and its possible effect on his mental health.

The reader can decide whether these items suffice to demonstrate widespread failure to provide adequate briefing, or alarming negligence by the investigators. The letters make no accusations; they merely request more information. While at Edgewood, the only letter I received from a former volunteer was from a young helicopter pilot who had received LSD as well as BZ on separate occasions. A year after the experiments, he wrote to announce that he was the father of a healthy baby boy, and said that he had fond recollections of the Edgewood program.

Fred Sidell recalls one "volunteer" who filed an official complaint that he had been psychologically damaged by the effects of Edgewood Arsenal LSD, years after the program closed. When his chart was located in the archives, it turned out that he had gone home within a few days of arriving at Edgewood and never received any drugs at all.

The IG writers did say that most evidence showed that soldiers freely volunteered for experiments, and that investigators were duly concerned about their "informed consent." To quote from the report:

> "Several factors were apparently weighed by the medical investigators in an evaluation of the depth of knowledge made available to the volunteer.
>
> "These factors were: security requirements surrounding the experimental agent or testing procedure; invalidation of the objectivity of the test results through suggestion of what was expected of the volunteer under the influence of the drug agent (placebo effect); depth of available knowledge and personal convictions of the investigator regarding effects of the experimental compound; and a judgment of what information would be of value to the volunteer subject in making his decision. This is not to say that these factors, when reviewed in respect to present knowledge, were valid considerations, but rather it is to point out that there was apparent concern at the time the experiments were conducted."

Fair enough.

> "While acknowledging that advising a subject that he is about to receive an experimental agent called EA 1476 or EA 1729 or any other laboratory related nomenclature would appear to be nothing more than paying "lip service" to the requirement...it would seem appropriate that the volunteer should have been provided, sometime during the volunteer period, the medical name of the drug in the event of future adverse reactions."

This was not really a practical recommendation. As mentioned earlier, almost all the agents we tested had no medical name. Had we told the volunteer he had just ingested (1-methyl-4-piperidyl) alpha-cyclobutylmandelate, how much better informed would he be? Furthermore, since many chemical structures were classified, writing down specific information about them might jeopardize security (e.g., an enemy could see the chemical name and become aware of the Army's interest in the compound). Finally, no benefit was likely to come from a former volunteer telling his doctor the name of a mysterious chemical formula he had once received.

The writers acknowledged that there was no way to verify that all the medical evidence available was presented or, indeed, how much should be provided, given the complexity of the knowledge involved. They also questioned "how it could it be determined that what was reported as fact by one investigator was accepted as such by another?"

The report allows that the problem of voluntary consent was not peculiar to the Army. It quotes Dr. Henry K. Beecher of Harvard Medical School, in the New England Medical Journal, "…In any precise sense, statements regarding consent are meaningless unless one knows how fully the patient was informed of all risks, and if these are not known, that fact should also be made clear. A far more dependable safeguard than consent is the presence of a truly responsible investigator." Amen.

Another comment mitigates somewhat the criticisms in the report:

> "Evidence that more than 7,000 volunteers were tested at Edgewood Arsenal without a single fatality or serious injury must be accepted as supporting evidence of the ability of the U.S. Army and the medical staff to fulfill their responsibilities."

While discussing the possibility that the Army used improper inducements to recruit volunteers, the report cites the following benefits to the volunteer:

> "30 days of temporary duty (TDY) at $1.50 per diem or $45 per month (more than half of a private's monthly pay in many cases); promise of a three-day pass each weekend; better living and recreational accommodations than normally available at many troop installations, such as air-conditioned rooms and hospital type beds; relief from all fatigue type details; an opportunity to receive a medical examination not normally available during other military duty assignments; a guarantee of a letter of commendation that would be placed in the volunteer's official personnel file; and a sense of patriotic contribution to the national security. These rewards may appear minimal when viewed in terms of today's Army and economy; however, in the 1950's and early 1960's they represented substantial rewards. No evidence was found to indicate that any of the privileges were unauthorized or illegal. However, the emphasis placed on them during recruiting efforts appeared to be an attempt to influence the prospective subject's decision by offering promises of special privileges or rewards."

This is a fair summary of the attractions offered to would-be volunteers. (Civilian investigators also frequently provide generous financial inducements to attract volunteers for their drug studies.) But our volunteers did not receive any additional privileges or compensation for participating in two or more different experiments. Subjects who had already experienced the delirium produced by BZ were often willing (or even offered) to repeat the experience two weeks later. Asked to put a price on a second consent, one man said $25. This willingness can hardly be attributed to the previously mentioned inducements, since they were already earned.

The report cites examples of studies that failed to comply with Army Chief of Staff Memorandum 385. In one incident, LSD was given covertly to the former commander of the Chemical Corps Research and Development Command. When asked what he knew about the use of LSD in the volunteer program, he said he had volunteered to take part in the chemical research program himself and had taken the regular physical and psychiatric examinations to make sure he was okay. He said, "I agreed that I would take the drug, but when it was to be administered would be up to the medical investigator."

He then related his experience at Fort Bragg, where he monitored a test conducted with members of the XVIII Airborne Corps Artillery: "I was there to observe what was going on and also to brief the CG, XVIII Airborne Corps. I went to the site with the project officer and a major; it was early and it was cold. I was asked if I wanted some hot coffee, which I did. I was given the coffee and apparently it had LSD in it – they told me, later, it had a dose of 200 micrograms of LSD." When he had to brief the Corps Commander, who was a "very rough customer," he had a very difficult time. Asked if he would have voluntarily taken LSD at that time, he responded in the negative."

Brigadier General Lloyd Fellenz (the victim of the LSD-spiked coffee) had previously told me this same story. He and I often played tennis in 1961, when he was Post Commander at Edgewood. One day, after we finished battling on the court, he told me about drinking coffee containing LSD at Fort Bragg before observing a military field exercise. He said that he started to feel unusual while walking along a dirt road. He suspected that perhaps he had been included in the "volunteer" group, based on his consent several months earlier.

Glancing over his shoulder, he saw Van Sim "ambling down the road about 100 yards back, kicking at the rocks and dirt." This confirmed his suspicions. He was

mightily annoyed, realizing he still had to get through the day. He somehow managed, despite the rather large (200 mcg) LSD dose he had received. Later he lay on his bed at home, and saw fantastic colors and images appearing on the ceiling.

The IG report emphasizes that the intent of Chief of Staff Memorandum 385 was not fully observed in this case. In particular, "the scientist in charge must be prepared to terminate the experiment at any stage … if deemed necessary to avoid injury, disability or death."

In this instance, there was no apparent danger, but the IG also cited a later Disposition Form (DF) filled out by Van Sim for the Director of Medical Research. He wrote, "There have been statements that we can terminate a test after it has started, implying that we have antidotal compounds for EA 1729. We do not have such a compound. At best, all we can do is attenuate the acute reaction, not prevent nor terminate it."

The IG report adds, "One of the basic conditions designed to safeguard the well-being of the soldier volunteer was not followed."

Were we, indeed, supposed to be able to "terminate the experiment at any stage" by having an effective antidote at hand? If so, many of the studies we did at Edgewood technically violated this rule. Not only was there nothing that could reverse the effects of LSD (there is still no true antidote today) but in 1960 and 1961 we also had no antidote for BZ. We did not recognize physostigmine's effectiveness until 1962.

Nor were there effective antidotes to the cognitive effects of major tranquilizers such as Prolixin, or sedatives such as Seconal. I'm not sure why the IG did not apply their criticism about the lack of an LSD antidote to our much more extensive work with belladonnoids. Until THA and physostigmine came along, I always knew, after giving BZ that I would have to let it run its course. Fortunately, there were no major crises.

The report describes another test Van Sim conducted at Fort Bragg in late 1958, involving twenty members of the 7th Special Forces. Eight members were placed at guard posts and given a dose of LSD. They were instructed to keep anyone without a special pass from entering the area. After LSD, predictably, they neglected to guard the entrance.

Twelve other members of the same group received LSD. They were then intensively interrogated by trained military intelligence personnel to see if they could retain a cover story while under its influence. Even interrogators with limited experience were able to induce a subject to sign documents that might place him in jeopardy. A higher dose of LSD often induced a state of fear and anxiety. Subjects were then sometimes willing to trade secret information in exchange for a promise of a return to normalcy.

Van Sim also proposed performing an additional, completely realistic experiment at night. After covertly giving LSD to the subject, the investigators would maintain continuous covert surveillance. He never carried out this test, since the researchers felt they had already learned enough about the effects of LSD from the two previous experiments. The IG report comments as follows:

> Had this proposal been accomplished, it would have resulted in at least two violations of Chief of Staff Memorandum 385; the first being the clandestine administration of the drug – violating the informed voluntary consent provision and thus negating the ability to withdraw at any time; and secondly the value and necessity of the experiment. The first violation was discussed earlier. The other violation mentioned concerns the following principle of Chief Of Staff Memorandum 385: "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study and not random and unnecessary in nature.

> Although no record was found which would indicate that the proposal was carried out, the fact that it was made by a responsible individual casts a cloud over the degree of integrity practiced in complying with the principles of Chief of Staff Memorandum 385. Research records for the Special Forces personnel who participated in the field-testing of LSD were not available for review.
>
> Information as to protocol procedures during the tests was obtained from the project officer who stated: "Each of them was informed of the fact that this was a test of a drug; I don't know if they were told the name or the fact it was hallucinogenic. I do know that each signed a consent statement and each was given the same examinations before undergoing the tests . . . . We concluded the test and reactions were inconclusive, . . . there was so much variance in the reaction that we could not use it with any degree of dependability, and at that point the project was dropped Because of the nature of some of the reactions of the individuals to the drug, particularly under interrogation by professional military intelligence personnel. I recommended, and my boss agreed, to destroy all of the individual records of the evaluations because things occurred during the interrogation situation, while they were under the drug, that could have been taken out of context later and used against them in an adverse manner, and so, to protect the individuals who were involuntarily reacting to this situation, I destroyed the individual records involved." (This testimony was provided by Colonel Lawrence W. Jackley on 24 July 1975.)

Clearly, there were some untoward reactions to LSD, particularly during the interrogation designed to extract signatures to false statements. These reactions were considered serious enough to justify the destruction of the narrative records. In my opinion, aggressive interrogation of an LSD-intoxicated subject, to elicit compliance with a request that violates the subject's intent, is psychiatrically contraindicated. I can only wonder why Colonel Jackley did not reveal (or perhaps the IG decided not to report) the details of "some of the reactions of the individuals" that led to destruction of the records. The IG leaves this to the reader's imagination.

The report also notes that instructors urged many classes of students at the US Army Chemical Corps School at Fort McClellan, Alabama to take a dose of LSD. They would thus better understand the effects of the compound, and could provide clinical data that would help to assess its value. The IG team considered this a subversion of the original directive. The term "demonstration" in Van's report also seemed to run counter to the following:

1. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study and not random and unnecessary in nature.
2. The number of volunteers used shall be kept at a minimum consistent with this principle.

Strictly applied, some Edgewood studies probably violated Memorandum 385. But the definition of "fruitful results for the good of society" poses a semantic problem. Some of the drug research carried out at universities with civilian volunteers in the 1960s might also be difficult to justify, if no particular social benefits were anticipated. Many critics eagerly discuss the broader question of whether chemical warfare research can ever be good for society.

In my opinion, discussions about the morality of chemical research must invoke some degree of ethical relativism. This also applies to almost every "gray area" of research and development, in and out of the military. The broadly stated rules in Memorandum 385 lead to interpretational problems that would test the judicial capacity of a modern day Solomon. Once again, the best safeguard against impropriety is the integrity of the individual investigator, as well as a "decent respect for the opinions of knowledgeable colleagues and superiors" (to rephrase the beliefs of the framers of the Declaration of Independence).

"Demonstration" exercises with LSD, involving attendees at the Chemical Corps School ran into a roadblock in November 1960. When Colonel Douglas

Lindsey received a letter approving an LSD demonstration and directing him to provide medical support, Doug stood up to the establishment. Lindsey stated he would only agree to LSD tests relevant to scientific research, not to demonstrations. He issued this policy statement to guide the use of LSD-25 in human subjects:

> No moral or ethical basis exists for the exposure of human subjects to pharmacologically active agents for purposes of "demonstrations." The choice of the term "demonstration" in the basic reference is one of the most telling arguments contained therein. Whereas no legal basis has ever been established for experimentation on humans, nevertheless the officer and civilian physicians of the Chemical Corps feel morally, ethically and professionally justified (both as physicians, and as professional civil and military servants of the nation) in using human subjects for research in, or under the control of, the Chemical Research and Development Laboratories. Any use of LSD-25 in which we participate will be an experiment, not a demonstration.

With this memo, Lindsey dropped the hammer on some sensitive toes. Three months later, when I reported for duty at Edgewood, I heard that his refusal had given a three-star General a bad case of heartburn. In doing this, Doug showed himself to be courageous, enlightened and principled. His memorandum corroborated my own impressions of Colonel Doug Lindsey's character.

The higher-ups continued to seek cooperation from Lindsey for these demonstrations, but were unsuccessful. He had the advantage of being the designated "responsible physician" for all drug tests and continued to assert his prerogatives. Eventually, the Commanding General of the Chemical Corps R & D Command lent him support.

The lengthy IG report concludes with a detailed account of the field test we conducted in November 1964 at Dugway Proving Grounds, Utah (Project Dork). The fact that the request to carry out this test came via a Department of the Army representative, bearing an urgent requirement to test the feasibility of disseminating BZ to volunteers at distances of 500 and 1,000 yards, seemed to satisfy the IG team that the test was necessary and properly authorized.

After recounting the manner in which Project Dork was carried out, including the "stringent medical and other safety controls in effect" and the use of physostigmine to control severe reactions, the IG team concluded: "Evidence available in the referenced reports indicated full compliance with Chief of Staff Memorandum 385."

It was gratifying to encounter this salutary appraisal in the IG report. Eventually, it seems, we got it right.

* * * * *

25 CHEMICAL WARFARE THEN AND NOW: A REALITY CHECK

Nothing overshadows truth so completely as authority.

Alberti: Del Principe III

Today the reality is that chemical warfare research with military volunteers is essentially non-existent (except for some neuroprotection and treatment studies) and seems unlikely to be approved in the foreseeable future. Even in the civilian community, research involving the administration of chemicals of any kind, including therapeutic drugs, to human subjects has become difficult and must satisfy an increasingly long list of criteria.

The Reality of Chemical Warfare Testing in the 1960s

The story we have told in this book reflects some of the differences between standards considered acceptable in the 1960s and those that prevail today. For example, in 1961 we were required only to provide a relatively simple protocol, sometimes no more than a detailed memorandum describing: the intended procedures, the goal and expected usefulness of the experiment, and assurances that existing precautions, including "informed consent," would be included. Although more extensive review of planned studies by higher echelons up to the Secretary of the Army had been prescribed by AR 70-25 in 1955 (as discussed earlier) it did not always take place. Many studies were apparently assumed to have been authorized by a more stringent, AR 70-25 compliant, general proposal submitted and approved earlier.

For example, testing of psychochemicals such as LSD, proposed and approved in accordance with AR 70-25 in 1957, was evidently regarded as covered by this approval. Thus, approval of BZ testing was later interpreted as a blanket go-ahead for similar testing with chemically related drugs. Except in the case of Project Dork, specifically authorized by 4-star General Dick in 1964 (who evidently had been given such authority at the Department of Defense level), local authorization by the Director of the Medical Laboratories was deemed sufficient in most cases. Not until 1975, when the IG conducted a

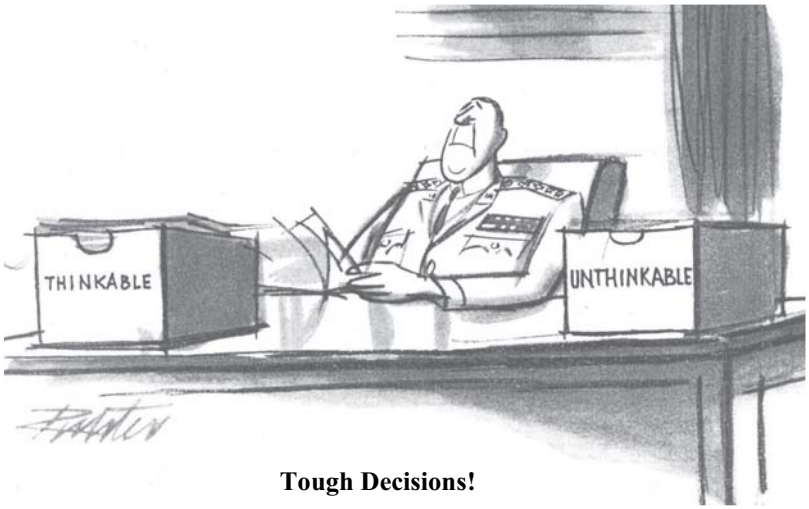
general review of the testing activities, was it clear to Edgewood commanders that considerable abridgement of the provisions of AR 70-25 had taken place. Many of the studies done by me and members of my department were therefore not as fully authorized as we believed.

But we in the military were not alone in undertaking experiments without specific "high level" review and approval. In civilian academic institutions, the proposals were often relatively concise, and usually went forward with little more than a signature by the department chairman, perhaps accompanied by a pro forma countersignature by the dean or his designated chief of research.

Similarly, at Edgewood, and elsewhere, critical reviews often took place only after completion, or perhaps at specified intervals during lengthy or complex studies. A detailed presentation of results by the investigator, in verbal or written form at the completion of a particular study was when supervisors would raise questions or render critiques of the work already done.

Of course it is unlikely that the Surgeon General, or any of the other high ranking non-medical staff officers who were officially responsible (according to AR 70-25) for signing off on a complex technical protocol, particularly welcomed the task. Often they had to depend on technically competent subordinates to advise them, and they too might not relish advising on delicate issues involving human subjects. After all, the testing often included chemical agents with which they were not particularly familiar.

True, there were annual general reviews of our testing activities by a panel of respected experts in the field of pharmacology, generally recruited from civilian universities and serving at the request of the Chemical Corps. But no formal follow-up reviews of outcomes and ethical proprieties of our testing program took place until 1975, more than 20 years after the initiation of chemical agent studies in Army volunteers. Perhaps this was because no un-nerving incidents had occurred in the Edgewood program, or perhaps it was in deference to the classified nature of the program and a wish to maintain a low profile. In hindsight, of course, none of these reasons were truly adequate. Nor, by today's standards, were they adequate to justify a similar lack of detailed follow-ups, ethical reviews and critiques in many university programs that involved human subjects.



Tough Decisions!

The Reality of Chemical Warfare Research Today

Back to the future. The situation with regard to human testing today is vastly different. Considerations of human civil rights (some of them seeming to be included in the name of what some call "political correctness") now cause conscientious investigators to ask themselves many questions before submitting a proposal.

"Have we overlooked anything?" This is a general worry that hectors every research group as they prepare to submit their protocols to university review

committees. The questions whirling in the heads of the most punctilious investigators might include conundrums such as the following:

Have we included all the necessary safeguards? Is the information we plan to provide to the volunteer sufficiently detailed? How can we be sure that he or she really understands the purpose of the study? Should we include a test to confirm that the subject knows exactly what measurements we will be using, how often they will take place, how long they will take and what might go wrong?

Is the manner in which the technician will draw blood samples quite clear? Does the consent form adequately emphasize the freedom to refuse the test if the volunteer has a change of heart after signing the form? Should we allow three days for the volunteer to cancel his consent, just as with other contracts? Will we be able terminate the test at any point if he requests it? What do we do to stop the action of a drug if, after taking effect, it is causing discomfort and the subject wants to discontinue?

Do we always have an effective antidote available that can terminate the symptoms? Or, will we be at a point of no return, unable to accommodate a volunteer who wants to stop immediately? Is there a crash cart available to deal with anaphylactic shock, a sudden dangerous fall in blood pressure or some other unforeseen emergency? Is the degree of discomfort likely to be excessive in some cases, going beyond what one or more review authorities would consider humane?

Will the results we hope for have sufficient medical value to make the study worthwhile? Does it offer adequate likelihood of research benefit to warrant the possibility of unnecessary discomfort and anxiety in placebo subjects without acquiring any real information about the drug itself? Without placebos, will our study lack the controls required to be sure the results are meaningful? Do we have enough insurance to cover possible lawsuits? If our experiment is successful, will we be able to demonstrate that our drug is significantly better for a particular purpose than existing ones? Are sufficient safeguards in place to prevent accidental injuries? Are we paying the subjects too much for their participation, leaving ourselves open to accusations that we are using undue influence, or even a subtle form of coercion, in order to persuade them to participate?

There are always more questions. Is the battery of lab tests we plan to administer before and after the experiment sufficiently comprehensive to rule out pre-test abnormalities that might make the candidate more vulnerable to drug effects? We know, for example, that a significant fraction of the population lacks an enzyme normally required to metabolize certain antidepressants. Should we get DNA analysis of each volunteer's genome to make sure it does not contain such an abnormality?

How about diversity? Have we built in a non-discriminatory policy for the selection of subjects? Will we include women in the experimental cohort and, for that matter, can we afford to exclude older subjects who are otherwise in good physical health and want to participate? After all, they might be the ones most likely to benefit from our drug.

Perhaps this is the way it should be – in essence, a zero defect policy for all research proposals. On the other hand, perhaps the process has become so laborious and frustrating that researchers postpone or abandon useful experiments. Ethics is not a simple subject. Today it is a new profession. Practitioners, called "ethicists", have increasing power to judge whether certain kinds of experiments are permissible. Their opinions, although not always binding, strongly influence both investigators and review committees.

In today's climate of zero tolerance of harm, a human research protocol must pass through many levels of review before it may proceed. In most proposed drug experiments, researchers must today gain the approval of the FDA and various committees within the sponsoring organization. In the 1960s, acceptable standards for initiating an investigation – including the standards for informed consent – were far more permissive. The FDA in its present form did not exist in 1961.

For the same reason, standards for prescribing physicians have become progressively more stringent. Doctors now are expected to provide detailed information to the patient – not only the anticipated benefits of a drug but also all adverse effects with a likelihood of occurrence greater than 1%. Only after receiving this information (and in some cases answering written questions showing that she understands) should the patient be allowed to sign a permission form.

As a practicing physician, I can say with confidence that such exceptional thoroughness is a rule "more honored in the breach than in the observance." Yet, there has so far been no widespread condemnation of physicians for failing to provide information to patients in accordance with these rigorous requirements.

In the field of immunization, for example, an exceptionally low probability of a serious or lethal reaction seems to have become the latest national requirement. Smallpox vaccination was routine for almost all children several decades ago and considered extremely safe. Now many regard it as a dangerous procedure because of the possibility of disastrous results – severe complications or even death – in as few as one case in a million.

As emphasized half a century ago by Dr. Henry Beecher, the integrity of the doctor is far more important than the requirements of any printed list of everything that might go awry. A key factor in determining volunteer attitudes at Edgewood Arsenal was trust, and we did our best to merit it. Our laboratory tailored the wording of the consent form to satisfy as completely as possible the principles enumerated in the 1947 Nuremberg Rules concerning human experimentation. Later, we also did our best to conform to the criteria enunciated in the Helsinki Declaration of 1964 (a copy of the actual consent form is included in an earlier chapter summarizing the Inspector General's 1975 review of the Edgewood volunteer program).

Probably the most controversial aspect of our consent procedures was the omission of the name of the particular agent we intended to administer. Regrettably, this was usually unavoidable, due to security regulations. Furthermore, most of the compounds of interest had no recognizable names, only numbers. To provide their names and chemical structures would not be very useful, except to a few biochemists and pharmacologists (in the case of BZ or LSD, most of the volunteers found out their names, anyway).

My own practice was to refer to agents such as BZ or other related glycolates as similar to belladonna or atropine – "belladonnoids" if you will. Since the terms atropine and belladonna were also unfamiliar to many volunteers, I said that the effects would vary from person to person, but generally, they would include dryness of the mouth, sleepiness, difficulty in solving problems, and altered perceptions. I assured them that both the nursing staff and I would monitor them closely. I explained that extensive pre-clinical studies in several animal species had revealed no permanent ill effects. I told them we believed the drug to be safe, and would discuss the effects in detail after the test was over. Very few volunteers chose to withdraw after this orientation.

True, we could not state with absolute certainty that no one would ever suffer after effects, possibly delayed by decades. Drugs, however, rarely (if ever) produce undesirable effects months or years after their use. Even if this should occur by some obscure mechanism, ultimately we needed to weigh the risk against the possible benefits of the study. "What benefits?" one might ask. "What is the advantage of knowing how much of a synthetic compound is required to produce this or that effect, when the only real interest comes from the military community?"

Herein lays one of the greatest ethical puzzlements. Does the acquisition of knowledge that may facilitate the development of a weapon of war, or even a useful method of treatment of a chemical warfare injury, warrant even a negligible risk to the life and well-being of a volunteer subject? Traditionally, at least in the military, the answer has been "yes." Boot Camp, live-fire exercises, Ranger, Special Forces and Seal training regimens – all carry inherent risks. And although rare, deaths do sometimes occur during such procedures. Military personnel voluntarily accept the dangers, whether they sign up for regular service in the Infantry or in elite high-risk units. They do not sign informed consent forms before undertaking each individual task. Ultimately, the "benefits" to humanity may consist of nothing more than improved knowledge of the limits of human endurance and courage.

Reliable knowledge of the typical effects of a chemical agent over a range of dosage, and under various conditions, provides the basis for rational preventive or remedial measures. Undeniably, this information may also be useful in designing weapons. On the other hand, the development of relatively safe incapacitating agents may pave the way to methods to battle enemy forces with a minimum of lethal outcomes. Many risks, many choices, and many ways to interpret benefits are all parts of a complex equation.

As physicians, our primary mission was to learn to recognize, treat and if possible, develop effective antidotes to substances having potential usefulness as weapons of war. And as was discussed in earlier chapters, we did indeed develop an antidote to many of these substances, including BZ, even though prevailing textbooks of pharmacology asserted that no such medication was available. Today, the antidote we "re-discovered" is a standard item in emergency rooms, where it helps to diagnose and reverse the effects of a variety of anticholinergic drugs. We were able to establish its effectiveness only by deliberately producing delirium in normal young men. It would not be easy in today's world to get approval for such studies.

How Realistic are Fears about Chemical Warfare Today?

The specter of chemical death persists. Like atom bombs, chemical weapons have been classified as "weapons of mass destruction." But were they, and are they? Nerve agents such as VX and sarin can certainly kill swiftly. But so can hundreds of familiar drugs and poisons. The real question is whether anyone within the limits of current technology can, in fact, use them effectively as lethal weapons on the battlefield.

When the U.S. was preparing to invade Iraq, there was great concern that our soldiers would be exposed to nerve agents. They were required not only to mask, but also to wear full body protective suits despite scorching temperatures. To me, this is overkill. The suits are extremely uncomfortable, and studies have shown that they hinder military performance by 40-50%.

Before hostilities in Iraq began, I composed the following letter. I was going to send it to the New York Times. Due to its length, and believing that it would have little effect, I put it aside. But since it is still surprisingly relevant, I include it here:

To: The Editor:

Although in general I fully support the President concerning his assessment of the Iraqi threat, I feel the Administration has been negligent in failing to explain the limitations of chemical weapons.

As a physician who spent the better part of ten years conducting medical research with chemical agents during the 60's, I have followed closely the portrayal of nerve agents (such as VX) by government and media representatives. It seems to me that fear of death through exposure to these substances has become irrational, ignoring scientific reality.

Yes, it is true that a drop of VX on the skin (if not removed) can cause death. This is, however, a misleading and panic-inspiring way to represent its lethality. The amount of VX in a warhead will normally be lethal (assuming a full minute of unprotected inhalation and optimal wind conditions) out to a radius of 100-150 yards. A hot atmosphere or a stiff breeze would limit its spread still further.

Unlike conventional explosives, which have instantaneous effects, chemical clouds take time to reach their target. This allows additional time to move out of the way or into a protective enclosure. In the case of civilians, anyone inside a soundly constructed house or car would almost certainly have full protection, even at distances as short as 50 meters, provided the doors and windows are closed. Putting duct tape and plastic over windows (or, as reported recently in one case, over the entire house) makes no sense. The blast effect of a warhead exploding closer than 50 meters would probably be more lethal than its contents of nerve gas. Furthermore, quick decontamination can prevent effects through the skin. Even ordinary clothing provides considerable protection.

How could terrorists deliver VX? One expert was asked this question on television. His answer: "crop dusters." But how would a crop duster flown by a terrorist be able to reach an urban area and fly at altitudes low enough to be effective? Even in rural areas, unless able to fly directly over homes or pedestrians, crop dusters could scarcely present a real threat. Experts on crop dusters have pointed out that they can only spread particles at least 20-40 microns in diameter, while nerve agent particles are much smaller.

In Japan, a number of years ago, a terrorist attack with sarin killed a dozen individuals confined to a subway car out of roughly a thousand people in the nearby vicinity. Sarin has little effect on the skin, due to rapid evaporation. It is true that the Iraqis killed many Kurds with nerve gas, but the victims were unprepared, had no training, no detection devices, no masks or other protection, no antidote and no practical way to avoid the gas. None of these vulnerabilities would be the case in a conflict with American troops.

Why have there been no terrorist attacks with nerve agents in the many months since 9-11? The answer seems obvious: chemical weapons are not particularly effective! At best, they cause deaths in a circumscribed area where there is no protection and no escape. Two hundred kilograms of conventional high explosive, (the capacity of a SCUD missile) can cause more deaths than the same amount of "nerve gas." Any statement that such agents will cause tens of thousand of casualties is gross hyperbole. What is worse, it unnecessarily fans the flames of panic.

I recall a televised CNN reporter describing a SCUD missile landing in Tel Aviv during Desert Storm. She was on an upper floor of a hotel half a mile away, watching through a closed window. Nevertheless, "just to be safe," she felt it necessary to put on a gas mask. If knowledgeable, on-location observers have such a distorted concept of the risks posed by nerve agents, how can one expect the public to be adequately informed?

I am puzzled by the failure of the Department of Defense and/or the Secretary of Homeland Security to issue more realistic guidance concerning the actual likelihood (or lack thereof) of Americans becoming victims of a "nerve gas" attack. Perhaps the Times can have some beneficial influence in this regard.

Sincerely yours,

James S. Ketchum, M.D.
Colonel, US Army Medical Corps (retired)

Quite by coincidence, Fred Sidell forwarded the following E-mail letter to me just as I was composing the above. Whereas I have never seen a battlefield, a seasoned soldier composed this note. I was gratified to see that the following article by SFC Thomas, posted on the Internet, makes many of the same points as my letter:

> From: SFC Red Thomas (Ret)
> Armor Master Gunner
> Mesa, AZ
>
> (Unlimited reproduction and distribution is authorized. Just give me credit for my work, and keep in context.)
>
> Chemical Weapons: Chemical weapons are categorized as nerve, blood, blister, and incapacitating agents. Contrary to the hype of reporters and politicians, they are not weapons of mass destruction; they are "area denial," and terror weapons that don't destroy anything. When you leave the area you almost always leave the risk. That's the difference; you can leave the area and the risk, but soldiers may have to stay put and sit through it and that's why they need all that spiffy gear.
>
> "These are not gasses; they are vapors and/or air borne particles. The agent must be delivered in sufficient quantity to kill/injure, and that defines when/how it's used. Every day we have a morning and evening inversion where "stuff," suspended in the air gets pushed down. This inversion is why allergies (pollen) and air pollution are worst at these times of the day.
>
> "So, a chemical attack will have its best effect an hour or so on either side of sunrise/sunset. Also, being vapors and airborne particles they are heavier than air so they will seek low places like ditches, basements and underground garages. This stuff won't work when it's freezing, it doesn't last when it's hot, and wind spreads it thin too fast. They've got to get this stuff on you, or get you to inhale it, for it to work. They also have to get the concentration of chemicals high enough to kill or wound you. Too little and it's nothing, too much and it's wasted.
>
> "What I hope you've gathered by this point is that a chemical weapons attack that kills a lot of people is incredibly hard to do with military grade agents and equipment, so you can imagine how hard it will be for terrorists. The more you know about this stuff the more you realize how hard it is to use.
>
> "We'll start by talking about nerve agents. You have these in your house; plain old bug killer (like Raid) is a nerve agent. All nerve agents work the same way; they are cholinesterase inhibitors that mess up the signals your nervous system uses to make your body function. It can harm you if you get it on your skin but it works best if they can get you to inhale it. If you don't die in the first minute and you can leave the area you're probably gonna live. The military's antidote for all nerve agents is atropine and pralidoxime chloride. Neither one of these does anything to cure the nerve agent; they send your body into overdrive to keep you alive for five minutes, after that the agent is used up. Your best protection is fresh air and staying calm.
>
> "Listed below are the symptoms for nerve agent poisoning:
>
> "Sudden headache, dimness of vision (someone you're looking at will have pinpointed pupils), runny nose, excessive saliva or drooling, difficulty breathing, tightness in the chest, nausea, stomach cramps and twitching of exposed skin where a liquid just got on you.
>
> "If you are in public and you start experiencing these symptoms, first ask yourself, did anything out of the ordinary just happen, a loud pop? Did someone spray something on the crowd? Are other people getting sick too? Is there an odor of new mown hay, green corn, something fruity, or camphor where it shouldn't be? If the answer is yes, then calmly (if you panic you breathe faster and inhale more air/poison) leave the area and head up wind, or outside.
>
> "Fresh air is the best "right now antidote." If you have a blob of liquid that looks like molasses or Karo syrup on you; blot it or scrape it off and away from yourself with anything disposable. This stuff works based on your body weight; what a crop duster uses to kill bugs won't hurt you unless you stand there and breathe it in real deep, then lick the residue off the ground for a while. Remember they have to

do all the work, they have to get the concentration up and keep it up for several minutes while all you have to do is quit getting it on you/quit breathing by putting space between you and the attack…."

The next section of Sergeant Red Thomas' article deals with other kinds of poisons, and nuclear weapons. He then resumes:

"….Bottom line on chemical weapons (it's the same if they use industrial chemical spills); they are intended to make you panic, to terrorize you, to herd you like sheep to the wolves. If there is an attack, leave the area and go upwind, or to the sides of the wind stream. They have to get the stuff to you, and on you. You're more likely to be hurt by a drunk driver on any given day than be hurt by one of these attacks. Our odds get better if you leave the area. Soap, water, time, and fresh air really deal this stuff a knock-out punch. Don't let fear of an isolated attack rule your life. The odds are really on your side…

"…Overall preparation for any terrorist attack is the same as you'd take for a big storm. If you want a gas mask, fine, go get one. I know this stuff and I'm not getting one and I told my Mom not to bother with one, either (how's that for confidence). We have a week's worth of cash, several days' worth of canned goods and plenty of soap and water. We don't leave stuff out to attract bugs or rodents so we don't have them.

"These people can't conceive a nation this big, with this much resources. These weapons are made to cause panic, terror, and to demoralize. If we don't run around like sheep they won't use this stuff after they find out it's no fun. The government is going nuts over this stuff because they have to protect every inch of America. You've only gotta protect yourself, and by doing that, you help the country.

"Finally, there are millions of caveats to everything I wrote here and you can think up specific scenarios where my advice isn't the best. This letter is supposed to help the greatest number of people under the greatest number of situations. If you don't like my work, don't nit pick, just sit down and explain chemical, nuclear, and biological warfare in a document around three pages long yourself. This is how we the people of the United States can rob these people of their most desired goal, your terror."

SFC Red Thomas (Ret)
Armor Master Gunner
Mesa, AZ

Although this insightful letter deals with lethal agents such as VX, it applies equally to incapacitating agents. It is true that in 1964, the Chemical Corps standardized BZ as a weapon. To my knowledge, it has not been used in any major combat situation. We have now destroyed our stockpiled munitions, leaving the waters to close over more than a decade of research, and millions of dollars.

In Acid Dreams, an articulate, widely read book on LSD by Martin A. Lee and Bruce Shlain, the authors discuss military research with chemical agents (although they primarily focus on the CIA's activities). Their description of Major General William Creasy's success in gaining congressional support and funding for the Edgewood Arsenal research program is, however, a bit exaggerated. Creasy may have been persuasive, but he was not the first to dream of finding "humane" chemical weapons. Congress and the Joint Chiefs of Staff had already made a deliberate strategic decision, further catalyzed by Creasy's argument. They were presumably neither naïve nor intellectually incompetent. Perhaps they were overly sanguine, but history is replete with legislation that in retrospect seem to have been unduly optimistic.

It would surely be unwise to endorse the use of incapacitating agents until our national and military conscience has become sturdily rooted in a humane philosophy. I believe we have come a long way in this regard. Today, in Iraq, we make extreme efforts to avoid "collateral damage." Relatively safe and treatable incapacitating agents could help in such efforts.

We have signed on to constraints that prevent the use of incapacitating

agents as weapons of war. However, as the nature of the enemy changes, methods of combat may need to change. Perhaps some of the rules adopted at a time when adversaries were clearly identifiable are no longer appropriate.

The Moscow Matter

In November 2002, the Russians used one or more drugs to end an intractable standoff with Chechen terrorists. They had taken control of a Moscow theater with automatic weapons and bombs strapped to their bodies. They were prepared to kill themselves and 800 innocent civilians. With the help of a potent gas, however, Special Forces were able to rescue more than 80% of the audience. In all probability, none would have survived without this chemical intervention.

Russia remains secretive about this operation. Reporters learned that they drilled holes in the floor and used vents high on the wall to pump gas into the theater. Regrettably, however, they were unable to learn the precise nature of the gas, beyond the admission by a Russian scientist that it was a derivative of Fentanyl. Several highly potent drugs fit that definition, including carfentanil, sufentanil, alfentanil, remifentanil and etorphine. Any of these can produce anesthesia, lasting from minutes to hours. A Russian medical authority later added that they used 5x the effective dose in order to guarantee a rapid effect on the terrorists. It is not clear exactly what this means.

The interior volume of the theater, estimated from illustrations, was probably less than three hundred thousand cubic feet, i.e., about 10,000 cubic meters. Based on doses used for anesthesia, a concentration of as little as 2-3 mg per cubic meter of a super-potent Fentanyl derivative might be sufficient for a building that size, if instantaneous incapacitation is not required. This assumes continuous inhalation for about 30 minutes. Thus, if evenly distributed, the total amount of drug required might be in the range of a few dozen grams – almost certainly less than a pound. If the Russian authority pumped in 5x the effective dose (as it claimed), its uneven distribution in the air would likely have caused many deaths. But only one in six died.

Hoping to resolve this conundrum, I searched the Internet and (as mentioned earlier) spoke by telephone with Dr. Theodore Stanley, Professor and Chairman of Anesthesiology at the University of Utah. Dr. Stanley is an authority on morphine and Fentanyl-like compounds. Although very helpful, some of his answers seemed to conflict with other authorities.

Some articles, for example, include an identical table of effective and lethal doses of high potency Fentanyl derivatives. The estimated safety margins are as high as 30,000. I could find no source for these data. I sent out several inquiries but thus far have received no definitive answers. I also discussed the questions with Harry Salem, who continues to study the toxicology of opioids at Edgewood. He is hopeful that the concomitant use of drugs tailored to suppress the effect of potent opioids on respiration may produce much safer agents.

The clinical use of sufentanil, for example, requires great caution. Unless the anesthesiologist assists breathing, lethal depression of respiration can occur, even with moderate overdosage. Other drugs in this category have the same problem, including both Fentanyl itself and its original parent drug, morphine. Judging from anesthesiology reports, all have single digit safety margins in man. This contradicts one Russian's claim that the drug used could not cause death.

It also seems inexplicable that a few of the Special Forces soldiers who rushed into the theater reportedly collapsed in a matter of seconds, while some members of the audience were able to stagger out under their own power. How

could someone endure 40 minutes of continuous exposure to a drug that could supposedly cause terrorists and audience alike to fall into a stupor in less than a minute? An opioid addict might withstand high doses of a Fentanyl-like drug, but it seems unlikely that many opioid addicts were in the audience.

Many of the civilians allegedly used their own moistened clothing as improvised masks. Could this have provided significant protection? Again, lack of access to individual accounts prevents one from fully evaluating these questions. The Russians seemed very concerned about adverse international publicity. This may have something to do with the high level of secrecy (although many officials on both sides of the ocean have been known to practice secrecy as a matter of habit). This is unfortunate. Full disclosure could be a valuable contribution to pharmacological knowledge and help resolve some aspects of the incapacitating agent debate.

Some observers speculate that the Russians used a drug unknown to the rest of the world to accomplish the theater rescue. Perhaps a combination of drugs was used. I found a research report that describes certain compounds that can partially block the respiratory depression, produced by sufentanil in rats, without interfering with the anesthetic effects. Dr. Stanley found this interesting but was dubious about its applicability to humans. It would be nice to have more data.

The Unreality of Public Knowledge about BZ

One baffling discrepancy I encountered, as I reviewed everything I could find on BZ, pertains to its safety margin. There is plenty of dissent, even outrage, about the use of BZ, but at the same time, it is sometimes described as a very safe drug. In one table, the lethal dose by injection is 40x the incapacitating dose. This is the figure I published as an estimate, based on several indirect lines of evidence.

The incapacitating dose by inhalation (the ICt_{50}) in the same table is officially 112 mg min/m^3 (one of several estimates, all within a narrow range, established by Edgewood studies). The lethal dose (LCt_{50}) by inhalation, however, is often said to be 200,000 mg min/m^3. If this is correct, the safety margin is 200,000 divided by 112, roughly 2,000!

But the safety margin of BZ should be the same by both routes of administration! It makes no difference how it is given. The total amount taken into the body is the only relevant number. How can BZ have a 40-fold safety margin (sometimes called therapeutic index) when injected, but a 2,000-fold safety margin when given as an aerosol? No one seems to have noticed this glaring discrepancy. No official source is ever given, and no one I contacted knew where this grossly inaccurate aerosol safety estimate came from. The usual statement is "The lethal dose by inhalation is reported to be 200,000 mg min/m^3" and the resulting safety margin then becomes 2,000, which would make it appear to be a highly non-lethal drug. (I recently learned that the 200,000 figure is based on rat tail withdrawal from a hot plate, an unsuitable value to be applied to humans.)

Errors of this magnitude could lead a prospective user to assume that even very high concentrations of aerosolized BZ would probably not cause death – a dangerous assumption about a drug that in actual use would produce a roughly bell-shaped curve of concentration with a range covering several orders of magnitude – depending on the distance of a sampler from the source, wind speed, and other factors. Although BZ is probably safer in man than any of the morphine or Fentanyl drugs, it is not that safe!

Other Unrealities about Army Volunteer Testing in the 1960s:

Many authors make statements about Edgewood drug testing that are disturbingly incorrect. Some examples:

> 1. Two thousand volunteers received LSD at Edgewood as part of the official testing program after 1960. The actual number was about 100.
>
> 2. Three thousand individual volunteer exposures to LSD took place under the supervision of Dr. Van Sim before 1961 (his own estimate, according to his summary report). Adding up the numbers given for the separate tests, this estimate appears to have been inflated by at least a factor of two. It is hard to be precise because the records are incomplete, and some volunteers received multiple doses.
>
> 3. From 1960-75, 2,000 volunteers received LSD from Edgewood physicians, in order to study its usefulness in interrogation. We actually tested LSD's effects in just under 100 subjects after 1960. We measured performance skills only, and never used it as an aid to interrogation. LSD had been studied in a small number of volunteers as an interrogation tool, but this was before 1961. It is true that LSD was also used operationally in highly secret MKULTRA projects. Sworn testimony (but no documents) gives the total number of unwitting subjects at less than 100. After 1960, a dozen or so individuals were given LSD covertly in secret overseas operations by a small "Special Purpose Team (SPT)." Neither I nor any member of our clinical staff knew about or would have endorsed this use. As mentioned earlier, I only learned about it in 2001 when I first read the IG report prepared in 1975.
>
> 4. Volunteers were "unwitting guinea pigs." As noted in my discussion of the media in earlier chapters, I take strong issue with this widely used epithet. Not only is it an indictment of our program, but an insult to the volunteers, who took part with their eyes wide open, and were justly proud of their contributions to national defense.
>
> 5. BZ is not more potent than LSD. Our dose-response studies showed that it requires only one-quarter of a milligram of LSD to produce incapacitation, while BZ requires approximately half a milligram.

Although the testing of drugs in Edgewood volunteers ended in 1975, the search for a safe and effective incapacitating agent continues. It is classified and I am not privy to the details. Both the Russians and the Americans now use the term "calmative agents." This may be the next alias for incapacitating drugs although it is a poor choice and creates the illusion that a new generation of low-lethality chemicals – called "biochemical weapons" – exists. If adopted, the term should apply to BZ and other belladonnoids as well as to THC derivatives, antihistamines and butyrophenones such as Haldol. These, however, are omitted from the roster of the supposedly new and more dangerous "biochemical calmatives." Changing the terminology has long been an effective way to reshape established opinions and stereotypes.

The ethical dilemmas remain. Chemical warfare watchers find it difficult to condemn the use of a "gas" to avert the death of hundreds of innocent civilians. What alternative would the critics recommend? The new terrorist tactic of kidnapping and killing innocents – or using them as human shields – invites us to rethink the standard arguments against incapacitating chemical agents. Traditionally, soldiers wear uniforms and fight on battlefields. Now terrorists pose as ordinary citizens, and rely on the conscience of coalition troops to protect them from indiscriminate attack with conventional weapons..

Ironically, the 1993 Chemical Warfare Convention, endorsed by the U.S., prohibited even the use of tear gas (although it remains permissible to use it in

handling prison riots and civil disturbances within a nation's own borders). The CWC also forbids the use of such drugs as sodium amytal, benign sedatives (when used within an acceptable dose range) that might be helpful in the interrogation of terrorists. It seems to me that these rules are irrational.

One draftee research physician visited Edgewood in 1965 to decide if he would like an assignment to our laboratory. He decided against it, commenting that he was against gas warfare. One of us asked if he would prefer "solid warfare." The visiting doctor's answer was that he would feel "embarrassed" if an incapacitating agent took away his ability to fight. Maybe this partly explains the aversion to such weapons – the fear that drugs will usurp individual determination to resist, to display courage – perhaps even to behave heroically.

To me, the political and ideological forces that drive official policies have become tragic obstacles to a rational discussion of chemical weapons, even the "gentler" forms. Congressional and public opinion continues to be opposed to any form of chemical weaponry. Thus, it may be a long time before we witness another attempt to use non-lethal chemical weapons, even against the most lethal of enemies. This is not necessarily good news.

The Reality About the End of this Book

Well, this is the end of my personal story about my "Life in the Chemical Corps" – at least the "life" part of it. It started as an Army assignment at a little known lab called Edgewood Arsenal, and went on from there. It led to numerous further activities in the drug field, including teaching and more research. It brought me into contact, and often into lasting friendships, with others in the drug research community. The world of psychoactive drugs became my permanent focus, ultimately impelling me to write this history of our incapacitating research in the 1960s and the many spin-offs arising from my experiences during that decade.

But it is not the last page of the story. I have relegated the details of the "science" part of my drug research to the appendix. There you will find a more detailed technical account of the studies described in earlier chapters. Some of the specifics of our drug studies have never been publicly disseminated and if you are scientifically inclined, you will want to read the details. Up to now, this book has been a subjective presentation of my own experiences and opinions. The appendix, however, is a more impersonal compilation of what we learned – information that should be made available to the research community. Viewed dispassionately, it is certainly of greater importance than my personal story. But as you have probably judged by now, I usually have more fun talking about myself!

* * * * *

APPENDIX

APPENDIX CONTENTS

Introduction

Physicians, pharmacologists, and other readers with a scientific background will be interested in this appendix. Here they will find additional details of the research which was described in less technical terminology in the main part of the book. The methodology, chronology of investigations with each class of agents, objectives of each study, a list of references and more complete versions of abridged or previously mentioned findings are included.

More important, this appendix discusses the specific results of the research itself, much of it in tabular and graphic formats. While the preceding chapters were autobiographical in tone, and intended primarily for the general reader, here we focus on the less personal, more professional aspects of our work. It is organized in "textbook" style, enumerating the pharmacological specifics of our research odyssey and the clinical procedures that helped us along our particular "road less traveled."

In the main narrative portion of this book we have described in detail some observations of the "scenery," the people we met, and the human-interest aspects of our journey through unexplored territory.

In the following pages, we describe some of the more objective aspects of the Edgewood studies: the "geography and topography," and the "readings on the dials" of our measuring instruments as well as the implications of what we learned while traveling in the "land of incapacitating agents."

Development of Methodology and Design

As described in the main narrative, we selected volunteers from those who attended a briefing by our recruiting team at their home installation and stayed to complete the MMPI and a comprehensive personal history form. The latter included items relating to current health, prior illnesses, education, past legal or disciplinary infractions either in or out of the Army, drug or alcohol problems and reasons for volunteering,

We designed our studies to establish potency, onset and duration of physiological and cognitive effects, dose/response relationships, and methods of treatment. For compounds of greatest interest, we measured the relative effectiveness by various routes of administration.

Initially, most studies were single blind. As the range between minimal and maximal dose effect was established, we shifted the design to double blind whenever possible. We rarely used placebo drugs, except in treatment studies, where placebo treatment was needed to validate treatment effectiveness.

We found quite early that our volunteers were not "placebo responders." This was apparent when we used very low doses of active drug and found no significant deviation from baseline responses. To give placebos routinely would have doubled the workload and exposed volunteers to many more hours of testing with little benefit, since the lowest doses had already been found to have little or no effect and the differences between responses to increasing doses were obvious.

Except for the early studies of BZ, where we assigned doses in arithmetic sequence (e.g., 1.0, 2.0, 3.0, 4.0 mcg/kg, etc.), we found it most efficient to use a logarithmic series, using progressive increases of 40%. Usually, no more than six subjects at each of four or five such logarithmically spaced dose levels were sufficient to span the range of response intensity from negligible to maximal, with acceptable reliability in terms of confidence limits.

Statistical techniques included calculation of means, medians, regression equations, and correlations, as well as chi-square and other non-parametric methods of analysis. Probit analysis[1], whereby the integral fractions of subjects at each dose who attained a given response criterion were plotted against the log of dose, was especially useful. The MED_{50} and ID_{50} were of greatest interest. Other descriptive parameters were gradually added to permit comparisons among the drugs we tested, the great majority of which were belladonnoids, but included LSD, alcohol, and major tranquilizers. These parameters are listed and defined on the following page.

When examined together, these values provide mathematical "profiles" of the drugs we studied and allow numerically precise comparisons with other agents. The use of operational definitions not only makes it simpler to characterize a drug, but allows accurate predictions of its effects at various doses. Obviously, such predictions have practical as well as academic significance.

To minimize stress on the volunteers, however, we did not intentionally administer much more than the ID_{50}. Until we were able to develop a more sophisticated technique to control inhalation dosage, however, some subjects received higher than intended amounts. As an example, one volunteer breathed BZ very deeply and rapidly and retained an amount equal to three times the ICt_{50}. He was incapacitated within 20 minutes.

Appendix

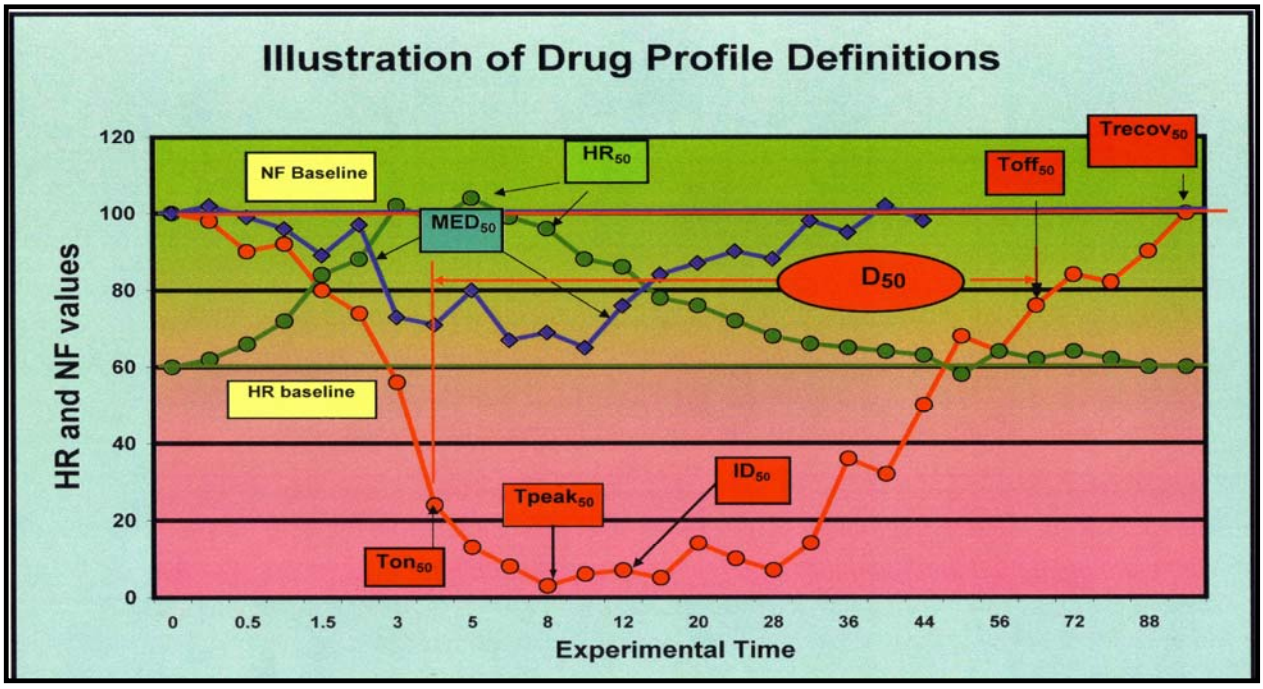


Figure 1 – Illustration of some of defined response parameters (using typical BZ values at as example)

1. Minimal effective dose (MED_{50}) - Lowest im dose required to produce 3 of 5 successive Number Facility (NF) scores below 75% of baseline.
2. Incapacitating dose by either im (ID_{50}) or aerosol (ICt_{50}) route - Lowest dose required to produce two successive NF scores below 10% of baseline.
3. Steepness index - Ratio between the ID_{50} and MED_{50}. A high steepness index indicates that the magnitude of effects will increase more rapidly as the dose is increased.
4. Onset time (Ton_{50}) - Time at which the first of two successive NF scores below 25% of baseline occurs in subjects who subsequently become incapacitated.
5. Offset time ($Toff_{50}$) - the time at which the first of two successive NF scores above 25% of baseline occurs during recovery from an incapacitating dose.
6. Peak Time ($Tpeak_{50}$) – the time at which the lowest NF scores occur in subjects who receive the ID_{50}.
7. Partial recovery time – ($Toff_{50}$) – the time at which the first NF score above 75% of baseline occurs in the median ID_{50} or ICt_{50} subject.
8. Full Recovery Time ($Trecov_{50}$) – the time at which the NF score returns to 100% in the median ID_{50} or Ict_{50} subject.
9. Duration (D_{50}) – the interval between Ton_{50} and $Toff_{50}$ in the median ID_{50} or Ict_{50} subject.
10. Prolongation Time ($T_{prolongation}$) – the number of hours by which duration is increased by administering twice the incapacitating dose.
11. Dose-Onset factor (D_{onset}) – the factor by which onset time (Ton_{50}) is shortened by administering twice the incapacitating dose.
12. Peripheral Effectiveness (HR_{50}) – inverse of the dose required to produce a maximum heart rate (HR) above 100.
13. Relative Central Effectiveness – (HR_{50}/ID_{50}) A ratio that is higher when the centrally effective dose (ID_{50}) is low relative to the dose needed to produce a peripherally effective (HR_{50}) response.

Note that, to call attention to an important source of variability in the onset time, we used the term "dose-onset factor" (D_{onset}). As stated, it represents the decrease in Ton_{50}, (the time at which NF performance first falls below 25% of baseline) when the incapacitating dose (ID_{50}) is doubled. In the case of BZ, for example, doubling the absorbed dose shortens the Ton_{50} from four hours to less than an hour. Doubling it again presumably shortens it to just a few minutes. This would be an important concept for military planners to consider. Our data were insufficient to measure the D_{onset} precisely because we preferred not to administer "double doses" to volunteers. In the few cases in which actual aerosol doses were considerably higher than the intended value, however, the dramatically earlier onset of incapacitation allowed an "educated guess" of the D_{onset}.

Although some of these parameters rely on clinical estimates, based on the few cases in which the dose was at least twice the ID_{50}, we observed that in general both mild and incapacitating effects came on much more rapidly (and lasted much longer) as the dose was increased. This has important implications, since BZ is often described as a drug with a very slow onset. When disseminated as an aerosol in the field, however, the wide range of dose distribution would cause a significant fraction of the target population to receive several times the ID_{50}.

Many readers of this appendix will have concerns about military use as well as the clinical pharmacology of incapacitating agents. Accordingly, before getting into the niceties of laboratory findings and comparisons among drugs a brief discussion of possible military applications seems timely.

In actual use, many among the target population would necessarily receive multiples of the ID_{50} and be unable to function within a few minutes. This would create both an early and dramatic psychological impact as well as a rapid effect on performance. BZ and similar belladonnoids would actually begin to cause casualties in a very short time. Unfortunately, because the "official" onset time is about four hours, the markedly more rapid onset of incapacitation at higher doses can easily be overlooked or ignored by military planners.

The same comments apply to the "prolongation time" ($T_{prolongation}$) which is the increase in duration produced by doubling the dose. In the case of BZ, such subjects were incapacitated about 48 hours longer than those who received only the ID_{50}. By the same token, an individual receiving four times the ID_{50} might be incapacitated for an additional 96 hours. Although we could provide only an approximation (due to the rarity of such cases among our subjects), the $T_{prolongation}$ would certainly have military significance. For example, it would be a guide to the number of days during which physostigmine (or other antidote) would be required and indicate how long it would take for a soldier to return to normal, or near normal, ability to function.

The long duration of incapacitation caused by a massive dose of atropine (1,000 mg), was reported in a sailor in the American Journal of Psychiatry (1946)[2], does not, however, support a simple model for doses above the ID_{50}. Atropine, at the ID_{50} (roughly 150 mcg/kg), results in about 6 hours of incapacitation (the D_{50}). Doses of 1200 mcg/kg (i.e., 8 times the ID_{50}) were routinely administered by Forrer and Miller[3] in their "atropine coma therapy," as described in chapter 5.

These doses seemed to prolong coma by only a few hours. Patients given 1500 mcg/kg at 4 A.M., for example, were described as being "incapacitated" only a few hours longer and were able to participate in occupational therapy the same day. If doubling the ID_{50} dose of atropine lengthens the duration by, say, 3 hours (i.e., if $T_{prolongation}$ = 3h) recovery would be expected in 8h (D_{50} for atropine) plus ~12h (i.e., by midnight).

Forrer and Miller used physostigmine to facilitate recovery, but we found that physostigmine restores normal function only temporarily and, in our studies of various belladonnoids, it did not shorten the overall duration (D_{50}).

Thus, using the estimated $T_{prolongation}$ of 4 hours, the recovery of the sailor who accidentally ingested 1,000 mg (roughly 90 [or $2^{6.8}$] x the ID_{50}) of atropine should have occurred in about 4 + (4 x 6.8) hours, equating to about 30 hours. In fact, he did not recover for 7 days. Thus, the $T_{prolongation}$ model is obviously too simple.

Rather than following a straightforward first-order exponential decrease, the elimination of atropine seems to follow something between a zero-order (linear) and a first-order (logarithmic) rate of decline. Such intermediate rates are seen with other drugs as well. It suggests a multiple compartment distribution with differing elimination rates (as demonstrated for BZ in animals by Dr. Albert Kondritzer at Edgewood Arsenal). Pharmacokinetics is a complex science, a foreign subject to many physicians!

BZ (3-quinuclidinyl benzilate)

When we began work on BZ and other belladonnoid drugs at Edgewood, we were venturing into relatively unexplored research territory. Clinical psychopharmacology, as a quantitative science, was in its infancy. Previous studies of therapeutic agents had been mostly observational[4]. Efficacy and toxicity were of primary concern. The measurement of such variables as onset time, duration and degree of response to a given dose was usually based only on clinical estimates, with simple categories such as mild, moderate and severe to describe effects. This was understandable, since in clinical practice doctors are accustomed to dealing with individual patients and the task is limited to adjusting dosage as needed to obtain a therapeutic response, rather than a detailed profile of effects.

The Army, however, was now attempting for the first time to develop trustworthy estimates of how various doses of a given drug would affect populations, rather than single individuals. This required the establishment of parameters – numbers that would define the most probable quantitative clinical effects across a spectrum of subjects. Commanders would need to know not only the typical but also the probable range of response values for such important attributes as potency, time of onset, duration and other important aspects of drug action. Such precision is rarely called for in civilian settings (except in, e.g., cancer therapy).

The early phases of the program, consequently, involved a certain amount of groping, as it were, for the best methods to use. Measurements needed to be relevant to the intended effects, but changes in these effects over time were also of great importance. This meant finding reliable measurement techniques for each variable and at the same time making sure that each measurement would lend itself to frequent repetition over a period of hours to days. While this was easy to do for such basic vital signs as heart rate, blood pressure, respirations and body temperature, it was a greater challenge to find reliable ways to track intellectual and motor performance.

In subsequent pages, as we trace our drug testing chronologically, the evolution of methodology from year to year will be evident. It actually took more than two years to establish a fully fleshed out, standard battery and to adopt it for routine use in the clinical test setting. Translating clinical laboratory assessment into predictions of results in a military setting required still further innovation.

The first volunteer exposures to BZ began in August of 1960, prior to my arrival in February 1961. Those early studies began with intravenous doses of 0.5 mcg/kg, and progressed gradually to a maximum of 10.0 mcg/kg. Technicians recorded the results in accordance with the preferences of the investigators, some of whom had only a modicum of pharmacological training.

The test schedule during that early period included the measurement of vital signs at frequent intervals; and brief notes describing behavioral changes. Most investigators tested performance infrequently after the first few hours. General observation was the primary basis for clinical assessment, using test scores only to help confirm clinical impressions.

The early investigators did not attempt more than minimal statistical analysis. Nor did I, during my first months on the job, when I devoted most of my attention to observing and interviewing subjects throughout the duration of the drug effects. I soon became familiar with the clinical aspects of BZ, the differences associated with various routes of administration, and the comparative usefulness of available performance measures.

During 1961, we dropped some performance tasks and added others. My co-workers and I tried out a battery of six cognitive measures – the so-called "Texas Battery" developed by Moran and Mefford [5] in 1959. The designers had identified six basic cognitive skills, using factor analysis. To allow repeated administration of their brief (three minute) tests while minimizing practice effects, they created 20 equivalent forms for each cognitive skill.

At first, we used all of them, but at three minutes for each, an 18-minute workload soon proved too burdensome for both subjects and scorers, especially when we administered the entire battery hourly. We tested less often after the first four hours, changing the frequency to every two hours until the end of the tenth hour, and every five hours thereafter until scores returned to baseline. This might be anywhere between 24 and 96 hours, depending on the drug and dose used.

We soon found that Number Facility (NF) and Speed of Closure (SC) were the most reliable and easy to administer subtests. Memory for Faces, a seventh task published by Moran and Mefford, proved interesting but scores varied excessively and we dropped it after a brief trial. A task that required tracing a star, visible only in a mirror, was likewise revealing, but cumbersome, difficult to score and excessively subject to practice effect. The Draw-a-Man test, however, which required the subject to draw a representation of the male figure at specified intervals, had the advantage of so-called "face validity." This meant that even an unsophisticated observer could recognize obvious progressive mental impairment and gradual recovery. For this reason, we decided to retain it.

Paper and pencil tests were fine for measuring cognitive ability and required little physical coordination, other than the ability to read and to manipulate a pencil. We provided ordinary reading glasses to offset the loss of near vision resulting from BZ's anticholinergic effects on the muscles of visual accommodation. Later Dr. Dave Harper (one of our draftee doctors) developed an eye-drop sequence[6] that obviated the need for glasses.

Since each subject's score was calculated as a percentage of his pre-test baseline, we wondered whether differences in intelligence would affect these percentage declines, as produced by the drug. Out of curiosity, we timed a few dozen subjects, without drug, as they completed a popular clinical task, the serial subtraction by sevens from 100 to zero. As expected, those with higher GT scores (the Army equivalent of IQ) performed this task more rapidly, but the correlation was low. Also, when we examined NF percentage impairment at various doses, we found that intelligence made little difference.

In 1960, the highest of three pre-test practice trials served as the baseline value for the Number Facility (NF) test and we continued with this definition in 1961. Subjects continued to improve, however, even while under the influence of BZ and by the time they returned to clinical normalcy, their NF scores were usually 10-20% higher than at the start. It was obvious that this sort of improvement could confound estimates of the true time of recovery.

Previously published civilian studies of drug effects on performance over time did not give this problem much consideration, and usually included only 1-3 practice trials. In some cases, improvement by the time of recovery was indeed evident, but for the investigators it was usually not a matter of great concern since the objectives of their studies were usually limited to showing a statistically significant rather than a precise degree of impairment.

We increased the number of practice trials to 10, distributed over a number of hours. Even this did not prevent some subjects from scoring substantially above their baselines after 3 days on BZ and up to 30 or more trials of NF and SC tests. When two teams of undrugged volunteers competed over a 5-day period, we compared their aggregate team scores. They ended almost in a tie, but their improvement, when plotted graphically showed a leveling off after 20-25 trials. Consequently, we increased the practice trials to 20, and used the average of the five highest as the subject's baseline. Subsequently, scores at the time of clinical recovery were usually close to this number.

To provide a more complete profile of performance skills, we needed to measure psychomotor function as well as scores on paper and pencil tasks. After discarding a small pegboard test used in the 1960 studies, we replaced it with a large flat board that rested on a table and used much larger holes and pegs. This reduced the need for the visual acuity required to place circular blocks into matching holes as rapidly as possible.

A novel electronic device called the Zero Input Tracking Analyzer (ZITA) challenged both mental and physical skills. Norman Walker, a civilian engineer and physicist originally designed it as a training device for bombardiers to improve their skill in guiding "dumb" bombs visually by remote control. It required keeping a "zero input" oscilloscope beam on a reference line, in the face of deviations produced by the subject's own efforts to "steer" with a joystick.

One could make the task even more difficult by introducing a lag into the joystick correction. This made it much like steering a small boat with a manual rudder, a task tending to produce overshoot. The device automatically computed the score by measuring the area of deviation under a one-minute tracing. Practice on this task resulted in continually improving scores, so eventually we eliminated it from the protocol.

We also wanted to add some way to assess time estimation ability, often included in drug studies. Most previous investigators required the individual to estimate when an arbitrary time interval had elapsed, or to produce a specific time interval, such as one minute. Although popular, we thought these tasks were too imprecise for our purposes. It was often simply a one-trial test, given without prior practice, and useful mainly as a diagnostic tool for psychiatrists and neurologists.

We found four types of timing skills in the literature: time estimation, time production, time comparison and time reproduction. The last appealed to us most, since it seemed to lend itself to automated administration and scoring.[7] For example, subjects could easily produce, and reproduce with appropriate correction, an interval of 5 seconds. The average of 25 responses produced reliable scores,[8] using error zones as shown in Figure 2.

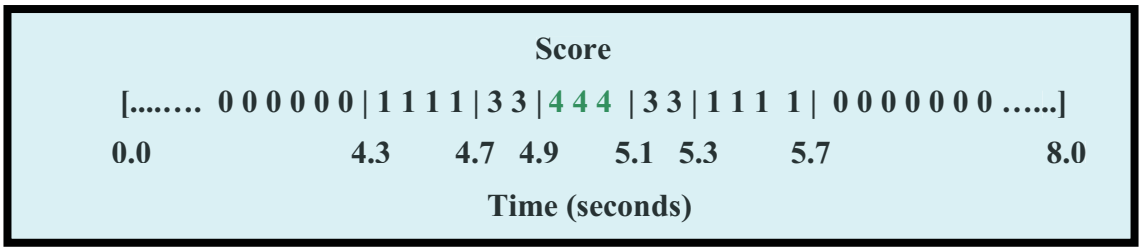


Fig. 2 – Scoring zones (seconds) and points earned for estimates

Volunteers being tested using a redesigned, electronic version of the VITA

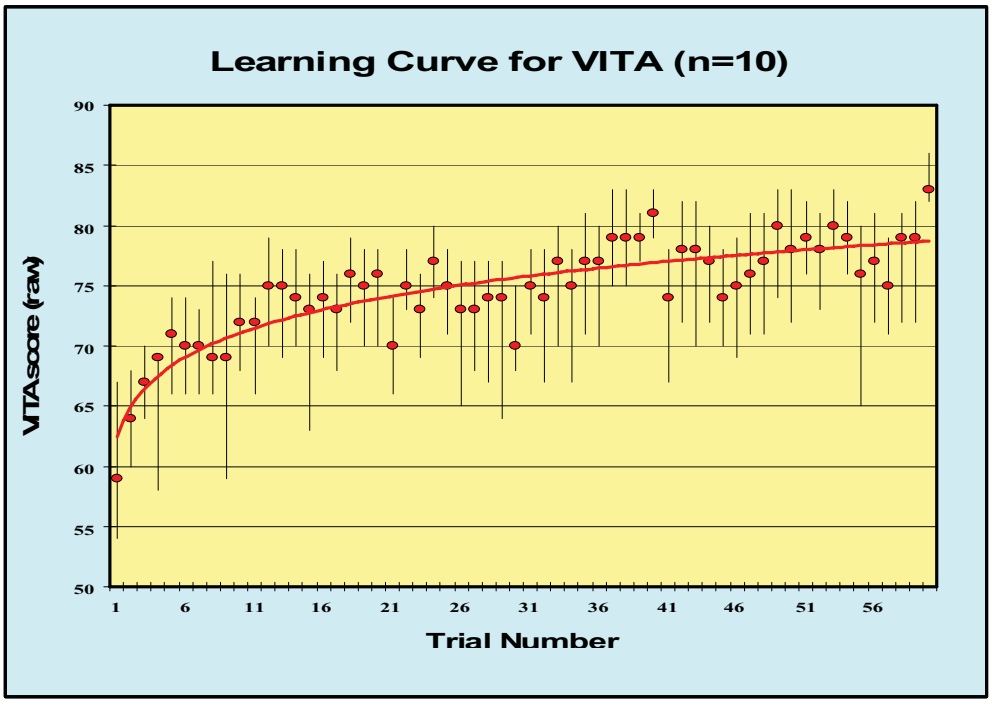


Fig. 3 – Learning curve for VITA, showing that most improvement occurs within 20 trials

An advantage of the VITA was that it did not require equivalent forms. To determine practice effects, we had 10 undrugged volunteers perform the task many times. Averaging their scores showed that learning was rapid, approaching an asymptote after 20 trials. Since it was both sensitive to drug effects, and reliable, we selected it, along with the NF and the SC tests, as one of our preferred cognitive measures.

Throughout 1961, we changed the BZ test protocol frequently and soon became obsessed with trying to represent the intensity of response to various doses of BZ, regardless of route of administration, as a single number. Pincus and Hoagland, at the Woods Hole Laboratory in Massachusetts, had the same goal when studying physiological indicators of adrenocortical function in schizophrenia. By using a number of different changes they created a weighted index that they called the Total Response Index (TRI), finding it to be more useful than any single measure as a reflection of overall response magnitude.

Phil Kysor and I similarly developed a TRI[9] to represent a subject's response to BZ. We combined changes in blood pressure (BP), heart rate (HR) and performance on Number Facility (NF), using a scale from 1- 9 for each variable. It helped us to compare responses to BZ given by various routes of administration. Eventually we could combine intravenous, intramuscular, oral, inhalation and percutaneous responses using the TRI as an indicator of relative effectiveness. Fig. 4 shows "idealized" response curves for various intensities of BZ response.

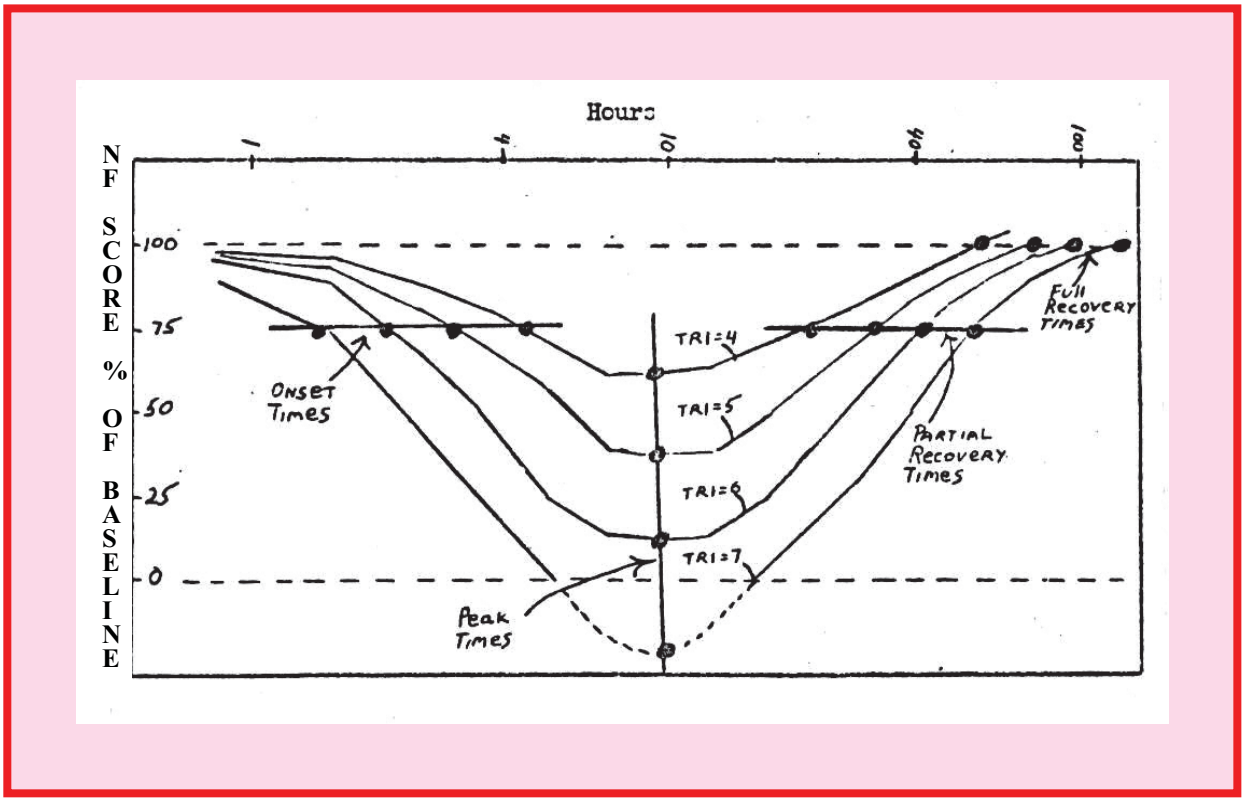


Fig. 4 Idealized performance curves for various TRI's

We conducted 23 separate tests with BZ over the ensuing three years, and will describe them separately in the following sections. Table 1 summarizes their "vital characteristics."

Table 1 – SUMMARY OF 23 INDIVIDUAL BZ STUDIES[10]

#	Type of Study	#	Dates	Route	Dose Range	Comment
1	Familiarization Series	4	May–Jul 60	oral	range finding	minimal Data
2	Oral Dose-Response	13	Sep-Oct 60	oral	4.0-7.5 mcg/kg	range finding
3	IV Dose-Response	29	Sep 60-Mar 61	iv	data minimal	range finding
4	Aerosol Chamber	8	Mar 1961	aerosol	data limited	range finding
5	Percutaneous effect	43	May-Dec 61	pc	range finding	5-10% effective
6	Urinary Assay	5	Jun 1961	IV	low dose	excretion pattern
7	LSD or BZ	3	Jun 1961	oral	low dose study	group interaction
8	Oral Supplementary	8	Jul 1961	oral	high dose	vs. earlier oral
9	Aerosol wind tunnel	7	Aug-Sep 1961	aerosol	varied	munition trial
10	Oral-Aero comparison	2	Sep 1961	compare	medium dose	aero less effective
11	IV THA treatment	5	Oct-Nov 1961	IV	high dose BZ	THA effective
12	Aerosol large particle	5	Nov-Dec 1961	aerosol	varied	large less effective
13	Aerosol dose-response	31	Jun-Dec 1962	aerosol	broad range	ICt_{50} estimated
14	IM dose-response	45	Jan 62-Jun 63	IM	broad range	ID_{50} estimated
15	Military performance	2	Apr 1962	IM	high dose	very effective
16	Oral THA treatment	4	Apr-Jun 1962	oral	high dose BZ	fairly effective
17	Group military skills	4	May 1962	IM	varied	indoor simulation
18	Cumulative effect	16	Jul-Dec 1962	IM	low doses	cumulative 2 mcg/kg
19	BZ and LSD together	1	Aug 1962	IM-oral	low doses	effects minimal
20	Second Dose effect	7+7	Dec 1962	IM	high dose twice	effects different
21	Physostigmine Rx	4	Feb 1963	IM	high dose	highly effective
22	Aerosol Munition Test	8	Jun 1963	Aero	high dose	results more even
23	Utah: “Project Dork”	8	Nov 1964	Aero	range of doses	effectiveness confirmed

DESCRIPTION OF INDIVIDUAL STUDIES

Study # 1 – Approximate Range Finding by Oral Route

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May-Jul 1960	4.0 to 7.5 mcg/kg	4	24 to 72	Ward area	Descriptive Notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Purdue Pegboard, Pursuit Rotor, Tapping Speed, Arithmetic, Color Naming					
Discussion: This was the first study involving volunteers – four members of the laboratory staff who, with minimal baselines, were observed for 48 hours, or until effects appeared to have subsided. No statistical analysis was done with the data, due to the small sample size and the fact that this was essentially a range-finding study, designed to indicate the approximate doses required to produce moderate to severe incapacitation.					

Study # 2 – First Oral Dose-Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May-Jul 1960	4.0 to 7.5 mcg/kg	13	24 to 72	Ward area	More frequent notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Purdue Pegboard, Pursuit Rotor, Tapping Speed, Arithmetic, Color Naming					
Discussion: This was first adequately documented study of the exposure of military volunteers to BZ. More extended baselines were used, as well as scheduled observations at 1, 2, 3, 4, 5, 6, 10, 24, 48 and 72 hours after administration of the drug. Vital signs and neurological status were recorded at approximately the same intervals. The examining physician recorded mental status changes whenever they occurred. The data were less than optimal due to the infrequency of observations after 10 hours, as well as the brevity of written records of behavioral changes.					

Study # 3 – First Intravenous Dose-Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Sep 60 - May 61	1.0 to 10.1 mcg/kg	29	24 to 72	Ward area	More frequent notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Purdue Pegboard, Pursuit Rotor, Tapping Speed, Arithmetic, Color Naming					
Discussion: Using a similar protocol as in the preceding oral series, which took only about two weeks to complete, this study used a much larger number of subjects. Although the frequency of testing and physiological measures was the same, the physician recorded observations only infrequently. As before, the data were less than optimal due to the infrequency of observations after 10 hours and the brevity of the recording of behavioral changes. Based on the changes in scores and other variables, responses to oral dosage was estimated to be about only 80% as great as by the intravenous route, suggesting incomplete absorption and/or greater first-pass metabolism by the liver.					

Study # 4 – First Inhalation Dose-Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May-Jul 1961	4.3 to 26 mcg/kg (est.)	8	24 to 96	Ward area	Scores and Descriptions
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Purdue Pegboard, Pursuit Rotor, Tapping Speed, Arithmetic, Color Naming					
Discussion: Subjects inhaled BZ in a chamber containing specific concentrations of the agent. Measurement of the retained dose was difficult due to a lack of standardization of the breathing pattern and to errors introduced by sampling the concentration of BZ in the chamber rather than direct measurement of amount of agent removed from the chamber. Correlation of intensity of responses to estimated retained dose was much lower than for the oral and (especially) the intravenous route, making the interpretation of the data uncertain, although it was clear that incapacitation occurred in the higher range. The inhalation route, under the conditions of administration, appeared to be about 65% of that by the intravenous route, based on approximately 80% retention by the lungs and 80% absorption of the retained dose. Except in one subject who received the equivalent of 26 mcg//kg i.m., no dose exceeded the equivalent of 17 mcg/kg i.m.					

Study # 5 – Percutaneous Dose-Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May-Dec 1961	1.9 to 60 mcg/kg	43	24 to 96	Ward area	Physiological Measures; Notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: No formal measures used					
Discussion: An effort to see if the skin was permeable to BZ. We used benzyl alcohol as the vehicle in 31 cases and Cresol/N-ethylmorpholine in 12 cases. We limited the frequency of examination since most subjects showed no significant changes except at the highest dosage. Noticeable effects appeared mostly after a delay of 24 hours, suggesting that the percutaneous route is relatively ineffective. Estimated Intensity of response was only 5-10% of that observed by the intravenous route, but duration of effects was similar (after the 24-hour delay).					

Study # 6 – Urinary Assay Study

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Jun 1961	4.0 mcg/kg	4	24 to 48	Ward area	Physiological Measures; Assay
Physiological Measures: BP, HR, urinary assay					
Performance Measures: No formal measures used					
Discussion: We gave low dose BZ, since the purpose was primarily to measure the amount of BZ excreted intact in the urine, and to test the reliability and sensitivity of the urinary assay method, developed by Kondritzer[11]. Animal studies had indicated that only a small fraction of injected BZ was recoverable from urine. Human excretion results likewise showed the fraction of intact drug in the urine to be quite small with most of the BZ consisting of its metabolites. Clinical measures consisted only of general observation and periodic vital signs. Behavioral changes were mild. (The potency of the BZ used in these early studies was found to be less than 90% of the stated value. We were provided with a purer batch for subsequent studies.)					

Study # 7 – Group Interaction Study (BZ, LSD, atropine placebo)

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Jun 1961	BZ 3.0, LSD 1.0 mcg/kg	3	24 to 48	Ward area	Physiol. meas. Perf. Scores Observation of Group Behavior
Physiological Measures: BP, HR					
Performance Measures: NF, SC, gas masking, tent pitching, compass-map problems, other military skills					
Discussion: An initial effort to study group behavior when different drugs were present. In a three session double-blind design, each man in rotation received a small dose of BZ, LSD or atropine and the effect on their interactions and performance of simple military tasks was observed, but not scored. It was possible to distinguish which drug each subject had received by clinical examination. This was a pilot study, intended primarily to test the feasibility of using military tasks in the presence of different drugs.					

Study # 8 –Supplementary Study of Low Dose by Oral Route

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Jul 1961	4.0 mcg/kg	4	24 to 36	Ward area	Descriptive Notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Texas Battery (six cognitive sub-tests)					
Discussion: In view of indications that the purity of previously used BZ was found to be only about 90%, an additional four subjects were given 4 mcg/kg by the oral route. The purpose was to compare the effects of a new batch at the dose previously found to produce mild effects. The quality of data was variable. Only in two of the four cases were the quantity and depth of recorded behavioral information data adequate, and observations were not detailed or highly informative.					

Study # 9 –Supplemental Inhalation Dose-Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Aug-Sep 1961	0.8 – 9.5 mcg/kg (est.)	7	24 to 72	Ward area	Scores and Descriptions
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Texas Battery (6 sub-tests)					
Discussion: Grenades containing a burning mix of BZ were ignited in a wind tunnel and seven subjects inhaled the smoke. Estimation of doses retained was approximate and in general, the quality of data was highly variable and deficient in some respects. This was not a well controlled series and we considered it substandard.					

Study # 10 – Oral vs. Inhalation Comparison Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May-Jul 1961	6.0 mcg/kg	2	24 to 72	Ward area	Physiological Measures & Notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Texas Battery					
Discussion: Dosage accuracy and documentation of response intensity were satisfactory in only two subjects in the preceding series. One of them had reacted more severely than expected to an estimated inhalation dose equivalent to 6.0 mcg/kg) administered in a wind tunnel. Details of the results are not known, but the examiners concluded that this individual had not over-reacted to the previously administered aerosol dose, since his previous response to BZ by the oral route had been within the expected range of intensity. They concluded that excessively deep inhalation in the grenade/wind tunnel was responsible for the apparent over-reaction.					

Study # 11 – Study of Tetrahydroaminoacridine (THA) Treatment Effectiveness

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Nov-Dec 1961	5.0 mcg/kg	5	24 to 48	Ward area	Scores and Descriptive Notes
Physiological Measures: BP, HR, neurological and mental status exams					
Performance Measures: Texas Battery, Zero-Input Tracking Analyzer (ZITA), Variable Interval Time Analyzer (VITA)					
Journal reports by Bell and Gershon[12] indicated that tetrahydroaminoacridine (THA), a cholinesterase inhibitor, was effective in reversing delirium induced by Ditran (JB-329) as a form of psychiatric treatment. It is interesting that their use of Ditran for this purpose was similar to the atropine coma treatment method reported more than a decade earlier by Forrer, Miller[13] et al. In our study, five subjects were given 5.0 mcg/kg of oral BZ on two occasions, 8-14 days apart. 60 mcg/kg of THA was administered iv four hours after the time of the second BZ dose. We observed definite partial reversal of impairment soon after injection, but it was brief. An unexpected observation was the general tendency by the subjects to become impaired more rapidly and intensely by BZ on the second occasion – a finding that was later confirmed in a more careful study.					

Study # 12 – Large Particle Inhalation Dose/Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Nov-Dec 1961	5.0 – 17.0 mcg/kg (est.)	5	24 to 72	Ward area	Scores and Descriptions
Physiological Measures: BP, HR, T, R, neurological and mental status exams					
Performance Measures: Texas Battery (6 sub-tests), ZITA, VITA					
Using particles averaging 2-4 microns in diameter (as opposed to 0.6 – 0.8 microns, used in previous chamber and wind tunnel studies), we undertook this study to compare effectiveness as a function of particle size. We used a retention apparatus to measure retained aerosol doses, subtracting amount of recovered BZ from amount administered, thought to represent a significant improvement in the dose measurement method. Since only 5 volunteers were tested, statistically meaningful comparisons were impossible, but clinically it appeared that the larger particles were substantially less effective. Data collected were still incomplete and discontinuous, with the exception of the two subjects receiving the highest doses, whose reactions were particularly well documented. IV equivalent doses were by this time judged to be about 80% of the retained doses (i.e., 20% of doses retained by lungs was not absorbed).					

Studies of BZ from mid-1960 to the end of 1961 were diverse in both methodology and objectives. One hundred and twenty-three subjects took part in 12 studies, most of them receiving low doses. For example, 41 of 43 tested by the percutaneous route (i.e., 40% of the total number of volunteers who participated) showed only mild or no discernible effects. In the other studies, the majority received doses of 4.0 mcg/kg or less.

In 1960-1961, not only various routes of administration were examined but many different performance measures, pilot studies of assay techniques, effectiveness of treatment with THA, group interaction, military task performance and comparison of response to a second dose (as well as comparison of inhalation to oral route and effectiveness of particle size) were studied. However, the number of subjects used in each study and completeness of documentation were both insufficient to permit meaningful statistical comparisons.

It was evident by mid-1961 that an upgrade was necessary. We needed, for example, to improve the safety of the ward environment, to further standardize the protocol in terms of baselines, frequency and consistency of testing and to ensure more complete documentation of behavioral changes. Psychology technicians, less well trained in medical procedures and seemingly not as interested in careful documentation, were part of this problem. Persistent requests for procurement of registered nurses in order to raise the level of professionalism were finally approved in late 1961 and the first three nurses began work at the beginning of 1962. Their arrival made a great difference.

Study # 13 Small Particle Inhalation Dose/Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May-Jul 1961	3.6-13.6 mcg/kg (est. iv equiv.)	31	48 to 96	Ward or Padded Room	Scores and Descriptions
Physiological Measures: BP, HR, T, R, Pupil Size (PS), neurological and mental status exams					
Performance Measures: Number Facility (NF), Speed of Closure (SC), ZITA, VITA, Draw-A-Man (DAM)					
Employing the retention apparatus method to measure dosage and having nurses available for the first time, this study was much improved in terms of quality and completeness. After testing 31 subjects at estimated i.v. equivalent doses ranging from 3.8 to 13.6 mcg/kg (retained dose of 0.6-micron particles), it was possible to apply statistical techniques to the results and to estimate the incapacitating dose within fairly narrow 95% confidence limits. Variability in breathing patterns and errors of measurement of the retained dose appeared to account for greater variation in response intensity than that observed following intravenous or oral administration.					

Study # 14 Intramuscular Dose/Response Series

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May 1961 - Jul 1961	1.0 – 8.0 mcg/kg	45	48 to 96	Padded Room, new ward	more complete
Physiological Measures: BP, HR, T, R, PS, neurological and mental status exams					
Performance Measures: Number Facility (NF), Speed of Closure (SC), ZITA, VITA, DAM, Behavior Checklist (BCL					
Forty-five subjects were included in this series, which was accomplished over a period of 18 months while inhalation and other studies were being conducted. Doses were assigned as follows: [0.5 mcg/kg – 4 subjects], [1.0 mcg/kg – 8 subjects], [2.0 mcg/kg – 8 subjects], [3.0 mcg/kg – 3 subjects], [4.0 mcg/kg – 5 subjects], [6.0 mcg/kg – 6 subjects], [7.0 mcg/kg – 6 subjects], [8.0 mcg/kg – 7 subjects]. Methodology and completeness of documentation were much more comprehensive.					

Study # 15 Pilot Individual Military Performance Study

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Apr 1962	8.0 mcg/kg	2	72 to 96	2-man sized padded room	Clinical and Military
Physiological Measures: BP, HR, T, R, PS					
Performance Measures: Indoor military skills as well as NF, SC, VITA					
We tested a variety of military skills in this pilot study. Motion picture documentation of performance was provided and used to produce a film (*Soldier's Predicament*).[14] The aim of this pilot study was to examine the relationship between performance of military tasks such as rifle assembly and map reading, to cognitive measures such as NF, SC and VITA. As expected, the performance ability of well-trained soldiers was grossly inadequate and completely impossible during periods of incapacitation, as indicated by their cognitive test scores. The relevance of laboratory measures to simulated military performance was reinforced by these results.					

At about the same time (1962), we succeeded in having a room modified, with installation of padding on walls and floor as well as an adjacent observation station. This was most welcome, since it greatly increased the safety of the volunteers and made continuous observation more practical.

With improved staffing, housing for the volunteers during tests, and better baselines, studies after 1961 were highly improved in quality, with much more complete testing, observation, and recording of data. We were able to apply meaningful statistical techniques to the results. The dose series was still based on an arithmetic progression from doses low enough to be considered essentially "placebo" to doses that were predictably fully incapacitating (we later used 40% increments between successive BZ and other belladonnoid dose levels – a logarithmic series that was statistically more efficient). A "Standard BZ Protocol" was formally established for the first time during this test series. Some of the quantitative results are presented in the figures below. Figs. 5 and 6 summarize heart rate and performance (NF) changes after an incapacitating dose of BZ.

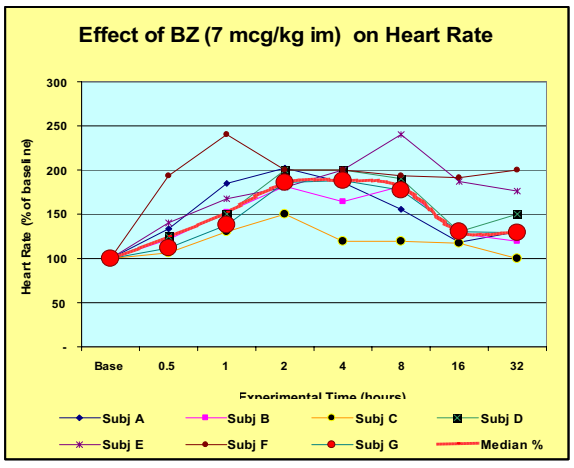


Fig. 5 BZ: Serial heart rates after 7.0 mcg/k i.m.

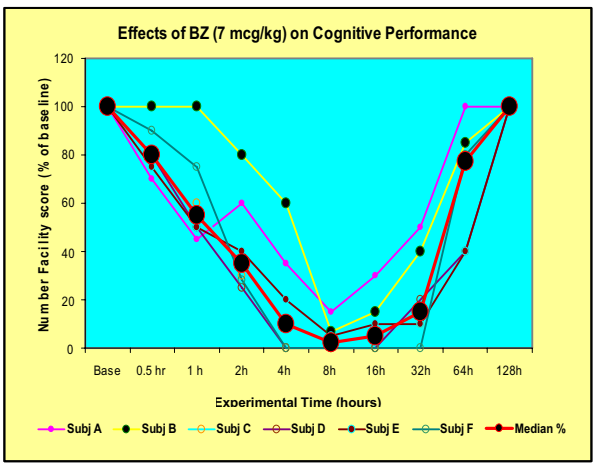


Fig. 6 BZ: Cognitive performance after 7.0 mcg/kg i.m.

Study #16 Second Study of Effectiveness of Tetrahydroaminoacridine (THA)

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Apr-Jun 1962	8.0 mcg/kg + THA	2	72 to 96	2-man sized padded room	Good, esp. first 24 hr.
Physiological Measures: BP, HR, T, R, PS					
Performance Measures: NF, SC, ZITA, VITA, Behavior Checklist (BCL), Symptom Checklist (SCL)					
To confirm earlier pilot observations of the value of THA in reversing BZ effects, we gave 4 subjects a strongly incapacitating dose (8.0 mcg/kg im) of BZ, followed immediately by treatment with oral THA (200 mg in divided doses). Another man received 360 mg of THA in a continuous intravenous drip over an 8-hour period. The results were compared with those of a group of 7 individuals given the same dose of BZ without treatment. Results confirmed the efficacy of THA as an antidote but minor changes in liver function, although temporary, persuaded us to abandon its further use.					

Study # 17 Group Military Performance Study

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
May 1962	6.0 - 8.0 mcg/kg	4	72	Simulated military outpost	Video Observation
Physiological Measures: None (Clinical staff watched on monitor – purposely stayed outside the "outpost").					
Performance Measures: Indoor military skills: masking, radio and telephone communication, map-work, behavior rating					
This study was intended to be as realistic as possible, with the volunteers working as a group for 72 hours in a 16 x 20 foot enclosure. Two men received 4.0 and 8.0 mcg/kg i.m., respectively; a third received a low dose by inhalation; the group leader received placebo (having been tested earlier with 8.0 mcg/kg i.m.). He showed the least impairment observed at this dose and, interestingly, less impairment than average with LSD. By design, medical personnel had no direct contact with the men during the entire 72 hours. The "outpost" contained (among other items) two bunks, table, chairs, military field radio, field telephone, maps, water bag, rations sufficient for three days, first aid kit and a fire alarm. Non-medical personnel handled communications. In spite of periodic use of bright lights by camera operators filming the action,[15] the men became oblivious to their presence and were caught up in the simulation. The clinical team monitored the events via closed circuit television, prepared to intervene if medical problems developed. The volunteer team worked together on a task that involved coded messages and also spontaneously cared for the most affected subject, calming him and preventing falls.					

Study # 18 Cumulative Effects of Intramuscular Doses

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Jul-Dec 1962	0.5-2.0 mcg/kg i.m.	15	48 to 96	Multi-cubicle padded ward	Comprehensive
Physiological Measures: BP, HR, T, R, PS, neurological and mental status exams					
Performance Measures: Number Facility (NF), Speed of Closure (SC), ZITA, VITA, DAM, Behavior Checklist (BCL)					
Daily small doses of 0.5-2.0 mcg/kg were administered to ascertain how much BZ could be given daily without causing a progressive increase in impairment. Four men were given 0.5 mcg/kg i.m. daily for six days without cumulative effects, but mild headaches and fatigue were reported at the end of the series. When 1.0 mcg/kg was given to 8 men for periods of 2-5 days, mild effects were observed daily, but no accumulation was evident. At 2.0 mcg/kg, however, increased effects were seen on the second day, culminating with near incapacitation on the third day, at which time daily doses were discontinued. Thus, it appears that 1.0 mcg/kg daily is the maximum tolerable dosage.					

Study # 19 Pilot Study of BZ and LSD Given Together

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Jul 1962	BZ 2.0, LSD 0.5 mcg/kg	1	48	Padded ward area	Comprehensive
Physiological Measures: BP, HR, T, R, PS					
Performance Measures: NF, SC, VITA					
This was the first documented study of exposure of a military volunteer to a threshold dose of both i.m. BZ and oral LSD, given together. It included a careful baseline for each measurement used. Clinical observations were scheduled at 1, 2, 3, 4, 5, 6, 10, 24, 48 and 72 hours after administration of drug. Vital signs and neurological status were recorded at approximately the same intervals. The examining physician frequently documented mental status. These data were less than optimal due to the relative infrequency of observations and the sparseness of behavioral descriptions. Even in combination, the doses used were too small to cause more than minimal effects.					

Study # 20 Effects of BZ when Given a Second Time

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Dec 1962	6.0 mcg/kg i.m.	7	72	Multi-cubicle padded ward	Comprehensive
Physiological Measures: BP, HR, T, R, PS, neurological and mental status exams					
Performance Measures: Number Facility (NF), Speed of Closure (SC), ZITA, VITA, DAM, Behavior Checklist (BCL)					
Because "second-dose" effects had been noticed in an earlier oral study, we conducted a more formal examination of this phenomenon with 7 subjects who, 2-4 weeks earlier, had been exposed to inhalation doses of 4.8-10.0 mcg/kg (estimated i.m. equivalent) of BZ. The subjects all developed NF score decrements close to the incapacitating level from the inhaled doses. Second-dose effects incidentally noticed in earlier series (acceleration of onset, heightened peak effect, and acceleration of recovery) were clearly demonstrated in this study. The peak responses of these subjects to BZ were as expected, putting to rest our concern about the poor relationship between inhalation dose and response in earlier groups of subjects (the earlier group had received lower inhalation doses and had milder responses. Accordingly, they were given comparably lower oral doses). The defect in both this and the earlier study was the use of two different routes of administration, preventing exact matching of first and second doses. Nevertheless, the more rapid onset and recovery in both series, when the second dose was administered, clearly established the validity of a "second-dose effect," observed with both moderate and high (incapacitating) doses.					

Since 2-4 weeks had elapsed between the two doses in the above # 20 study (compared to 8-14 days in a prior similar group), it was difficult to attribute the acceleration of onset to residual BZ from the first dose. Rather, it seemed that the initial dose in each group had stimulated enzyme induction, causing both more rapid distribution of the drug and more rapid clearance. Presumably, this would implicate two different transport systems. The acceleration was particularly interesting because it had occasionally been reported in Parkinson Disease patients given daily doses of atropine or scopolamine (belladonnoids similar to BZ, although much shorter-acting).

Previously published clinical observations of daily atropine and scopolamine effects usually did not include precise recording time of onset and recovery from each dose. At least one journal report, however, did note that a certain degree of "tolerance" to atropine developed in the course of daily use for several months or years.[16] This may or may not be based on a mechanism similar to the "second-dose" effect that we observed with BZ. Conceivably, this might have military implications if the target population had previously been exposed to an attack with BZ on one or more occasions. The practical significance of the slightly earlier onset and recovery, however (Fig.12), seems to be relatively minor.

The usefulness of the anticholinesterase tetrahydroaminoacridine (THA) in partially reversing delirium, both in Ostfeld's studies of Ditran (JB-329)[17] and our own pilot study of its efficacy in BZ subjects, suggested that perhaps other centrally active anticholinesterases, such as physostigmine, might be similarly useful. Such a possibility is usually not addressed in pharmacology textbooks. In the 1960s, the authors of various chapters on atropine usually stated, in fact, that no antidote for central atropine toxicity (i.e., delirium) was available, and that supportive treatment was the only recourse. Reports in the psychiatric literature of physostigmine's antidotal properties, e.g. in 1950 by Forrer and Miller, were evidently overlooked or ignored. We were also unfamiliar with these reports when we first tried physostigmine. Nor were we aware of Kleinwachter's report in the German medical literature (1864)[18], which described the ability of calabar extract to reverse delirium from belladonna intoxication – an unexpected finding by Goodman during his literature search.

An alternative to THA was welcome, since both Ostfeld's group and our own had noted changes in liver function following the use of THA, even though these indications of liver toxicity cleared rapidly after discontinuation of the drug's use. Physostigmine, fortunately, did not manifest such changes.

Study # 21 Physostigmine Treatment Pilot Study

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Feb 1962	7.0 mcg/kg	7	72	Multi-cubicle padded ward	Good throughout
Physiological Measures: BP, HR, T, R, PS					
Performance Measures: NF, SC, VITA, Behavior Checklist (BCL), Symptom Checklist (SCL)					
We gave a total of between 32 and 230 mg of physostigmine in doses not exceeding 4 mg/hr to 7 subjects, after incapacitation was produced by intramuscular doses of 7.0 mcg/kg of BZ. A double-blind crossover procedure was initiated. Four of the 7 men were willing to receive a second dose of BZ, and the results were as expected. "Blake," described in Chapter 10, had an unusually long period of incapacitation when given placebo treatment. His partner, in contrast, was able to function fairly well when given active intramuscular or oral doses with the same frequency, returning to baseline within 72 hours. In the crossover, two weeks later, "Blake" who had been markedly incapacitated following his first exposure (with placebo treatment) was treated with actual physostigmine at 40-minute intervals following his second exposure to the same dose of BZ. Little benefit appeared during the first 8 hours, while BZ effects were rising to their peak. Thereafter, he returned dramatically to 80-90% on NF testing and was clearly oriented. As long as physostigmine doses were maintained he was consistently able to score well on NF, eat, drink and sleep normally and even played pool without difficulty. As anticipated, his partner, who received placebo physostigmine, was unable to function during the same period. His recovery followed its usual time course, ending at 72 hours (Fig. 8).					

The failure of physostigmine to reverse BZ effects during the first 8 hours (Fig. 8) is interesting and unexplained. It reminds one of the Berry and Davies findings (in 1970 at the British labs in Porton Down)[1] which showed that the reversible anticholinesterase pyridostigmine was paradoxically effective as a prophylactic agent in the event of nerve gas exposure (see ref.[19]).

[1]Fred Sidell and Margaret Filbert noted the findings of Berry and Davies and conducted extensive studies at Edgewood Arsenal to confirm their results. They subsequently succeeded in getting FDA approval for pyridostigmine – the first such approval under the Animal Rule, which permits studies in animals as a basis for demonstrating a drug's effectiveness as a prophylactic or treatment agent. The rule applies, however, only to toxicity resulting from chemical, biological, radiological or nuclear substances, when safety and efficacy cannot reasonably be assured in humans. The Animal Rule was only recently enacted, in July 2000.

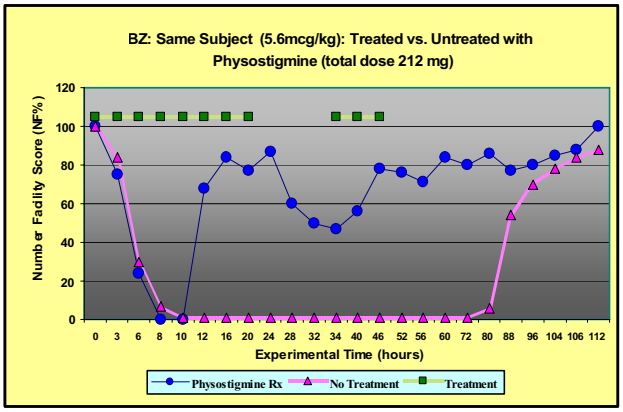


Fig. 8 BZ: Comparison of performance scores in physostigmine treated vs. untreated (same subject)

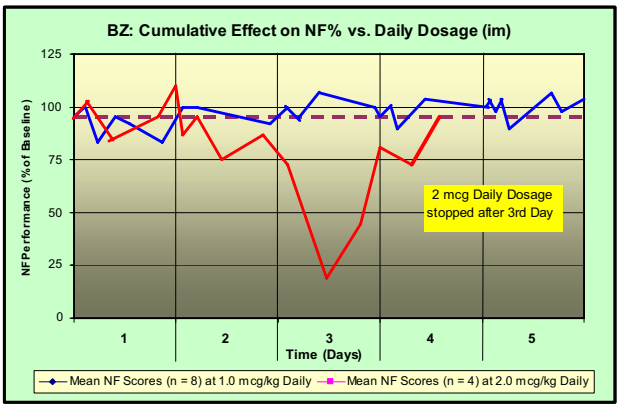


Fig. 9 BZ: Cumulative effects occur by 3rd day with 2.0 mcg/kg but not with 1 mcg/kg

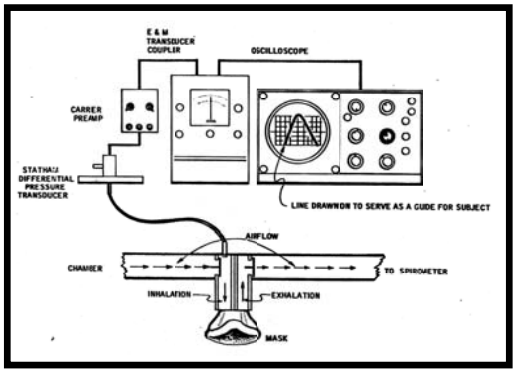


Fig. 10 System to guide self-regulated breathing

The explanation was that temporary attachment by pyridostigmine to the cholinesterase enzyme would competitively inhibit the attachment of the anticholinesterase nerve gas to the cholinesterase molecule. The result of this pre-emption by reversible pyridostigmine would promote metabolism and clearance of the temporarily blocked out irreversible nerve agent. By the same token, if BZ initially floods central cholinoceptive sites during its buildup in the central nervous system, it might reduce physostigmine's acetylcholine-sparing action during the first few hours. After equilibration in the CNS compartment, however, excess BZ might no longer be present, allowing acetylcholine freed by physostigmine's attachment to anticholinesterase to reach cholinoceptive sites more readily. Thus, in the absence of excess BZ, accumulation of acetylcholine in the synapse might then be sufficient to over-ride the BZ blockade, restoring normal transmission. The fact that BZ-induced impairment returns when physostigmine is no longer present suggests that BZ continues to cling to the receptor sites and is not easily displaced. It would be interesting to study changes in BZ excretion patterns when physostigmine is continuously present.

Fig. 8 illustrates the changes in NF scores with intermittent physostigmine treatment. Fig. 9 shows that 2.0 mcg/kg of oral BZ given daily for 3 days produces increasing performance impairment, but 1.0 mcg/kg daily given daily for 5 days produces no change in performance scores. Fig. 10 presents the method developed to control respiratory depth and frequency.[20]

Study #22 – Inhalation Study Using Controlled Respiration

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Jun 1963	Medium to High	8	72 to 96	Multi-cubicle padded ward	Comprehensive.
Physiological Measures: BP, HR, T, R, PS, neurological exams					
Performance Measures: NF, VITA, BCL, SCL					
In this study, a new method of controlling breathing patters was introduced, in which subjects attended to a crayon curve on the glass of an oscilloscope and practiced tracking it as the beam swept across the screen at a rate of 15 per minute (i.e., 4 seconds per sweep). This provided a more consistent relationship between inhalation dose and expected response. A diagram of the setup is shown in Fig. 10 (above).					

Study # 23 *Project Dork* Aerosol Munition Test[21]

Dates	Dose Range	# S's	# of Hours Observed	Setting	Documentation
Nov 1964	Medium to High	8	72 to 96	Inflatable MUST units	Comprehensive.

Physiological Measures: BP, HR, T, R, PS, neurological, mental status exams

Performance Measures: NF, VITA, BCL, SCL, performance in simulated military scenarios

Project Dork, conducted at Dugway Proving Grounds in Utah, was described in detail in chapter 15. Subjects inhaled BZ, disseminated by modified Venturi jets as an aerosol cloud, using an elaborate technique for dosage control. The men stood on a flatbed trailer, which moved back and forth along a fixed-radius arc to track the BZ cloud. They used the previously described oscilloscopic self-regulated, breathing apparatus. Cumulative dosage was measured continuously using spectrophotometric devices. Two groups of volunteers participated: the first at a distance of 500 yards and the second at 1,000 yards from the source.

The target dose at both distances was the ICt_{50}, estimated to be approximately 100, based on prior studies in the Edgewood medical facility. The results showed that this dose was achieved (using 15 instead of 10 liters/min), 2 of the 4 men in each group receiving slightly more than the ICt_{50} and the others receiving somewhat less. We estimated the ICt_{50} using the Total Response Index (TRI) and regression statistics. Because of the fortuitous distribution of dose values, the ICt_{50} could be estimated fairly reliably for each group of four men. The results were remarkably similar (Table 2).

Summary of Calculations Used in Estimating Ict_{50} for Aerosolized BZ

		Group D-1 (500 yards)				Group D-2 (1000 yards)			
	Subject's Initials:	**JS**	**DC**	**RL**	**JA**	**AA**	**JM**	**DM**	**JG**
A	Sampler Ct values (Avg of 2)	81	77	69	54	72	79	54	54
B	Minute Volume (liters)	12.4	16.8	13.8	11.9	13.9	18.8	14.8	22.1
C	B/15.0	0.8	1.1	0.9	0.8	0.9	1.3	1.0	1.5
D	Body weight (kg)	72.7	75	65.9	83.3	65.9	89.9	72.7	76.3
E	75/D	1	1	1.1	0.9	1.1	0.8	1	0.9
F	Corrected Ct (A x C x E)	68	86.3	72.2	44.1	75.5	81.7	54.9	72.2
G	Total Response Index (TRI	4.4	7.1	5.6	4.2	4.5	5.2	5.93	6.5
H	Estim. iv equiv. dose (mcg/kg)	4.6	7.5	5.9	4.4	4.8	5.4	6.3	6.8
I	Ct/iv ratio (F/H)	15	11.5	12.2	10	15.8	15.7	9.3	10.9
	Average Ct/iv ratio	**12.195**				**12.934**			

ID_{50} (iv equivalent) for Group D-1 = 6.2 mcg/kg **Ict_{50} = 6.2 x 12.2 = 75 mg/m^3**	**ID_{50} (iv equivalent) for Group D-2 = 6.2 mcg/kg** **Estimated Ict_{50} = 6.2 x 12.9 = 78 mg/m^3**

Table 2. Summary of calculations used to estimate the ICt_{50} (at 15 liters/min instead of 10) for aerosolized BZ

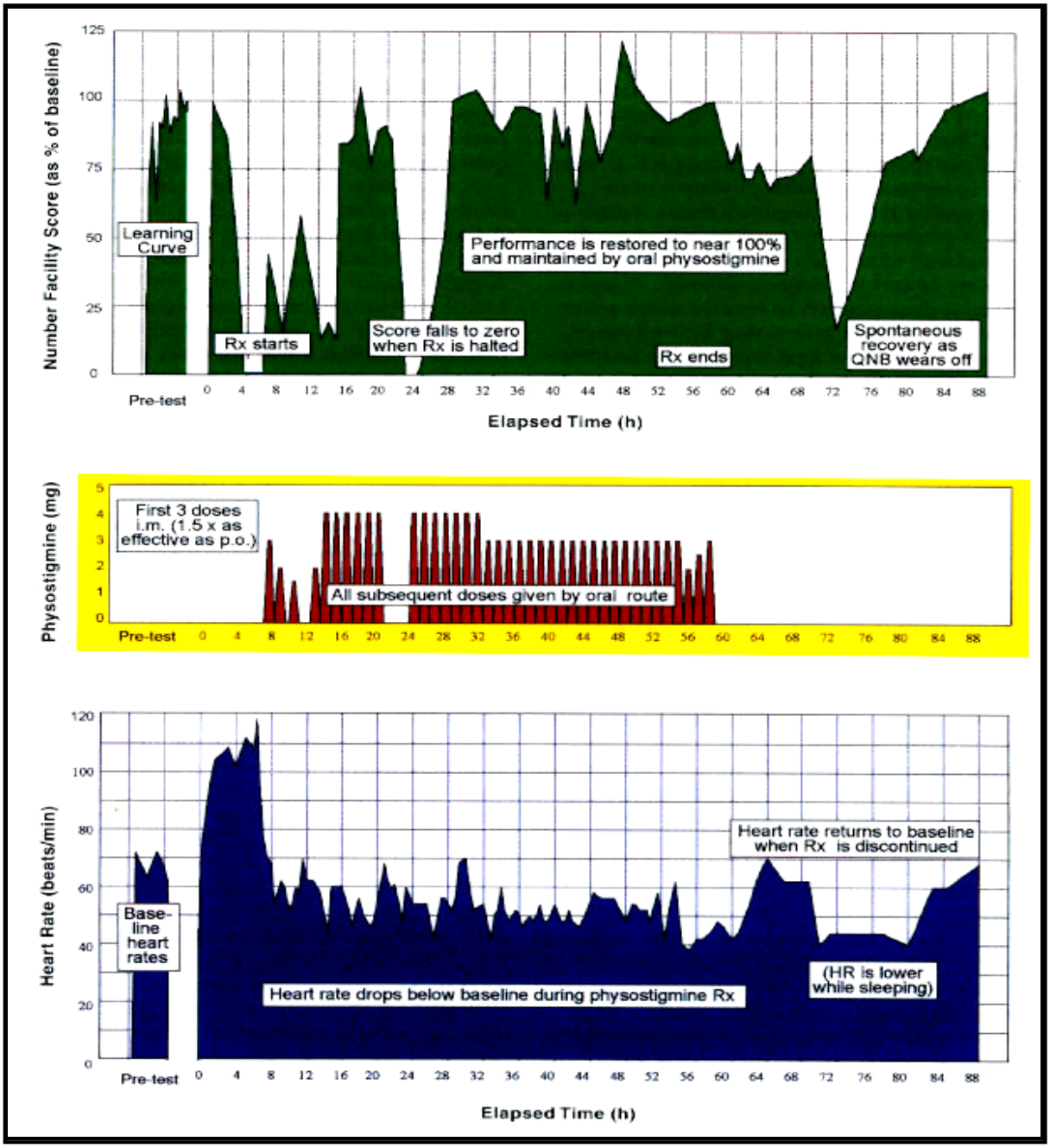


Fig. 11 This subject was one of 8 volunteers who participated in Project Dork, previously described in Chapter 14. Performance scores dropped rapidly when physostigmine was withheld, but returned to near normal when resumed. Heart rate responded similarly. Total amount of physostigmine given was roughly 100 mg (expressed as oral dose equivalent). Note that physostigmine by injection is approximately 50% more effective than by the oral route (i.e., 2 mg i.m. ~ 3 mg p.o.)

Response Criterion: TRI = 6.0
Sample Size = 116 (all routes combined)

Mean Dose (mcg/kg)	Range (mcg/kg)	Response
1.7	**1.0 - 2.0**	**0/12**
3.1	**2.0 - 3.6**	**0/12**
4.1	**3.9 – 4.3**	**1/12**
4.5	**4.3 – 4.5**	**1/10**
5.4	**4.5 – 5.3**	**1/12**
5.7	**5.4 – 6.0**	**6/12**
6.5	**6.0 – 7.0**	**8/12**
7.6	**7.0 – 8.0**	**10/12**
9.2	**8.0 – 12.0**	**9/10**

Table 3 – Fraction of subjects incapacitated at each of 9 doses.

Regression Equation:

Probit Y = -2.26 + 9.2 Log X

9.2 = the probit slope (this is very steep)
Standard error (S.E.M) of the slope = 1.75

%	Mcg/kg	95% confidence limits	
1	3.442	2.656	4.460
16	4.803	4.230	5.435
30	5.403	4.918	5.935
50	6.160	5.656	6.710
84	7.901	6.777	9.211
99	9.730	7.673	12.337

Table 4. Probit Solution for BZ incapacitation

Calculation of the incapacitating dose (ID_{50}) was an important objective in our investigation of BZ and other drugs as well. The method used is a form of "quantal" analysis, in which a particular criterion is selected and the number in each group meeting or exceeding that criterion is expressed as a fraction (as in "Response" column)

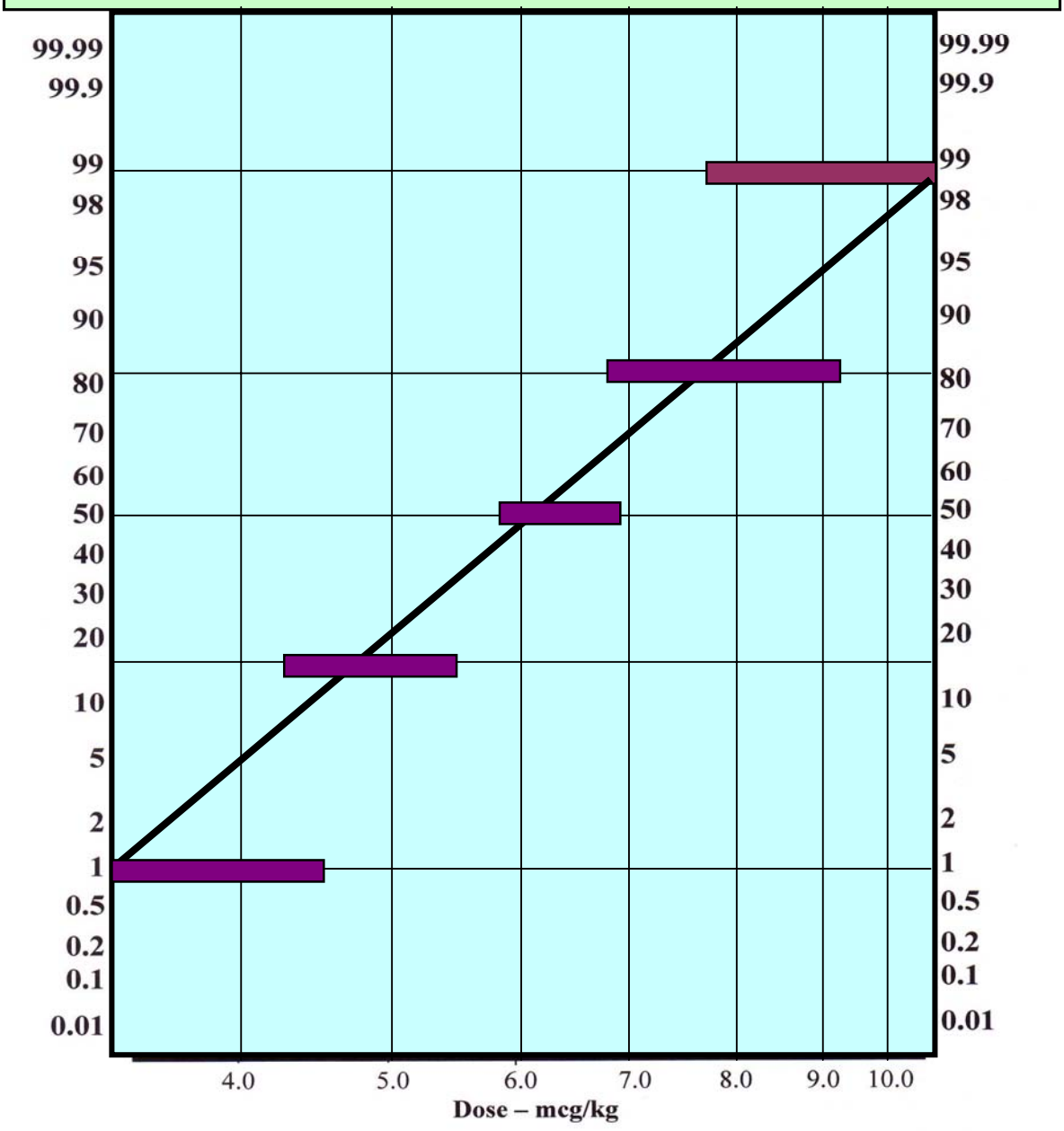
Tables 4 and 5 are based on 116 subjects, each of whom received BZ. Only cases in which NF performance was measured with sufficient frequency and appropriate baselines, and in which the dose (e.g., by inhalation) could be expressed in terms of its intramuscular equivalent were included.

We used the Bliss method to compute a probit regression line (Fig. 12). With 116 cases, divided into approximately equal sized groups and extending to both ends of the range of effectiveness, a highly reliable estimate of the ID_{50} was achievable. In this sample, this value is 6.16 and the 95% confidence limit range is 5.66 – 6.71, a narrow range indeed. Even the ID_1 and the ID_{99} (sometimes of greater interest) are bracketed within remarkable narrow limits The ID_1 = 3.42 (range 2.66 – 4.46) and the ID_{99} = 7.63 (range 9.73 – 12.34)

By comparing this analysis with estimates of the LD_{50} (and assuming a similar slope for lethality) one can predict the probable overlap (if any) between the incapacitating and lethal dose distributions (Fig. 13).

Fig. 12 BZ: Probit dose/response regression

X-axis = log (i.m. dose) in mcg/kg y-axis = % Probability
Horizontal bars = 95% confidence limits ID_{50} = 6.2 mcg/kg +/- 0.6 mcg/kg



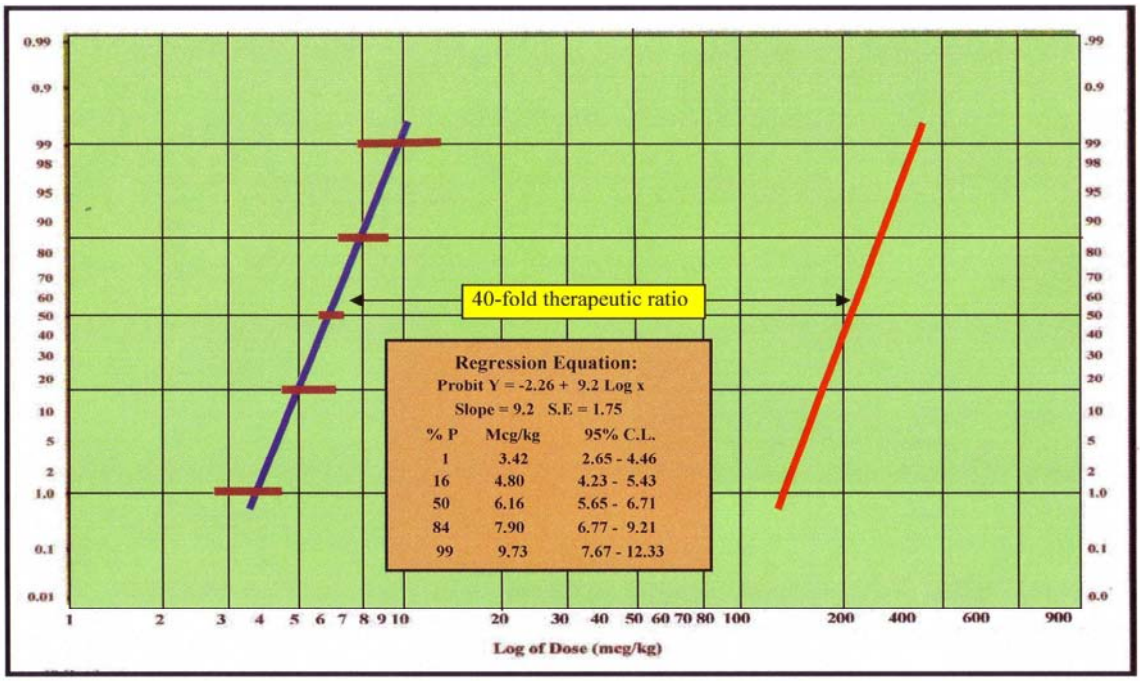


Fig 13 Lack of overlap of ID_{50} probit regression with hypothetical LD_{50} regression

How safe would BZ be in actual use? Although the LD_{50} for BZ is estimated to be at least 40x the ID_{50}, Klotz et al. have argued in "Beware the Siren's Song" that there is no safe incapacitating agent because of the inevitable overlap between ID_{50} and LD_{50} dose distributions.[22] A copy of their theoretical model (Fig 14) indicates that about 10% of those exposed to an ID_{50} aerosol dose would fall into the lower end of the lethal range (they cite the Moscow incident as an example). Their model, however, (without empirical evidence) uses Gaussian curves that extend across five or more orders of magnitude, Their "two receptor" model relies on the supposition that the percent of the population incapacitated would parallel the percent of receptors occupied by the drug, which in turn would parallel the dose received. These assumptions are unwarranted in view of the complexity of nervous system response to drugs, the type of receptor, nature of inhibition (competitive vs. non-competitive) and the slope of the dose-response regression line. In the case of BZ the slope is very steep (Fig.13) and there is no overlap with the lethal dose (assuming a similar slope for lethality).

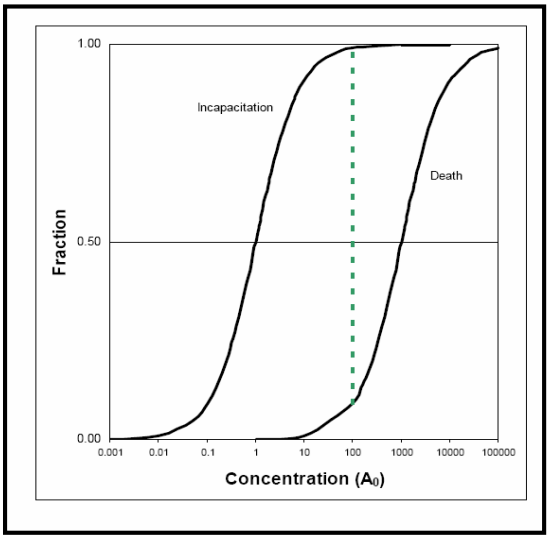


Fig. 14 Relationships among dose, incapacitation and lethality in a two-receptor model at equilibrium. (Klotz et al.)

As shown (Fig.13), there is a ten-fold difference between the ID_{99} and the LD_1 , negating the idea of unavoidable lethality when a BZ dose is restricted to the ID_{50}.

Studies with BZ did not cease in 1964, although the Dork project was our last major BZ experiment, since we believed we had completed the evaluations considered necessary to characterize its actions and effectiveness under various conditions.

When George Aghajanian and Fred Sidell decided to investigate the usefulness of antidotes other than physostigmine, scopolamine became the belladonnoid of choice, since its duration of action was short and both nursing and volunteer time required to conduct treatment studies were limited to a single day of observations.

Since any true (RBC) anticholinesterase drug should, in theory, provide the acetylcholine-sparing action necessary to compete effectively for cholinoceptive receptor sites, they also carried out a trial with VX (against EA 3443)[23]. Ironically, the use of a lethal agent to treat the effects of an incapacitating agent proved highly effective, although never recommended for use in mainstream medical practice. This is unfortunate, since a single sub-lethal dose of VX could provide reversal of belladonnoid intoxication for much longer than physostigmine. In the hands of a knowledgeable practitioner, it could be highly useful, especially when a small number of medical personnel must treat a large number of delirious victims exposed to long-lasting agents such as BZ, EA 3443 and EA 3167.

EA 3443

The second glycolate chosen for thorough evaluation was EA 3443 (Fig. 15). It proved to have characteristics very similar to BZ with an almost identical onset time and duration[24]. It was at least 50% more potent, however, and had greater relative central potency. Our studies of EA 3443 were more systematic than those we had done with BZ. We had the advantage of more than a year of protocol development – a gradual process that became more sophisticated as experience with BZ increased.

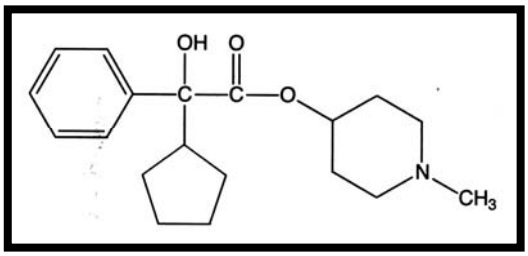


Fig. 15 EA 3443

The dose design is shown in Table 7. We tested 75 subjects: 38 by the intramuscular route (dose range: 0.6-8.0 mcg/kg), 17 by inhalation (using a Ct dose range of 28-333) and 20 by the percutaneous route (dose range 2.3-60 mcg/kg).

Hours	Days	# Subjects
51	2	6
73	3	16
96	4	21
120	5	8
168	7	10
205	9	14

Table 6. EA 3443: Number of subjects observed for various numbers of days

Duration of observation (Table 6) for each subject was lengthy and required a total more than 300 subject days of testing, considering that each subject (in groups of 2-4 as a rule) occupied a test cubicle for an average of five days. Vital signs, including pupil size, heart rate, blood pressure and performance on NF and VITA, were measured at 1, 2, 3, 4, 6, 8, 10, 12, 16 and every four hours thereafter until recovery. The nurse entered full descriptions of behavior as often as possible, and completed the Behavior Checklist (BCL) at frequent intervals.

Subjects often had difficulty reading cognitive test forms due to a paralysis of accommodation. Initially, we provided reading glasses but in 1964, Dr. Dave Harper developed an ingenious solution. He used an anticholinesterase ointment containing 0.25% diisopropylflourophosphate (DFP) to overcome the belladonnoid effects. Although the DFP ointment worked, it frequently caused a painful spasm on application, so he preceded it with topical Cyclogel (a belladonnoid used by ophthalmologists to cause brief mydriasis). This buffered the DFP and permitted a smooth induction of normal vision.

Number of Subjects	Dosage of EA 3443 by Route im (mcg/kg)	Inhalation (mg min/m^3)	# of Hrs Observed
Intramuscular			
38	0.6-8.0		51-120
Inhalation			
4	4.1 - 5.3	28.0 - 71.0	72
5	6.6 - 10.8	54.0 - 98.0	97
4	13.9 - 16.4	118.0 - 136.0	117
4	21.2 - 28.8	255.0 - 333.0	168
Percutaneous			
6	2.3 - 12.0		150
8	30		194
6	60		216
Total			
75 subjects			

Table 7. Compiled totals of subjects tested with EA 3443 by number of subjects, dose, route of administration and number of hours observed

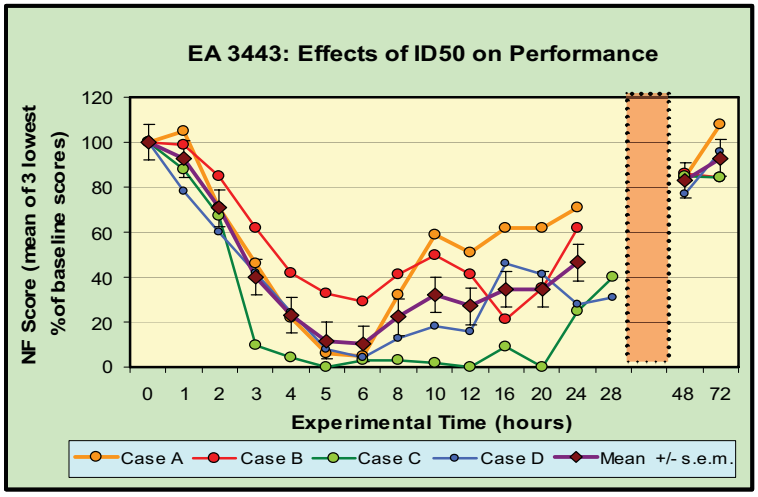


Fig. 16. The time course of changes in performance after EA 3443 is administered by the intramuscular route is very similar to that of BZ, with peak effects at 5-7 hours, and recovery at 50-70 hours. It also possesses a slightly higher central/peripheral index.

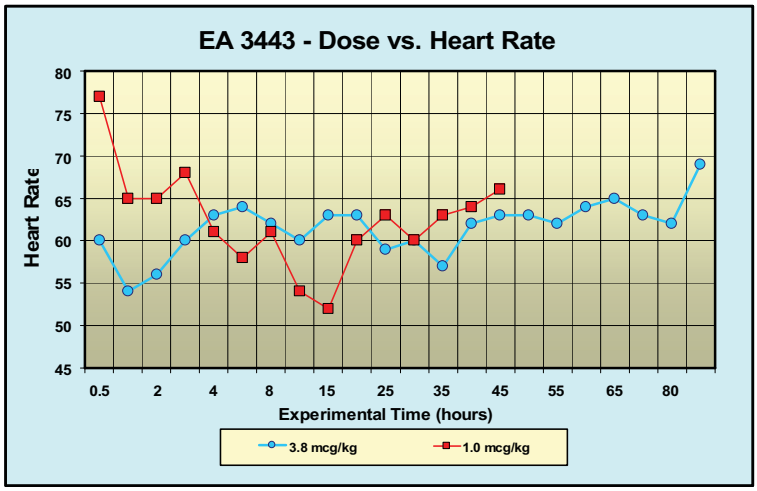


Fig. 17. Unlike BZ, EA 3443 effects on heart rate are minimal. In this chart, the low dose of 1.0 mcg/kg appears to cause a heart rate decrease at 15 hours. The higher initial rate may be an artifact, not seen in the HR at the much larger dose, which remains essentially level. It is probable that low doses normally cause a reduction in rate, as is seen with scopolamine, and is attributable to a dominant effect on medullary centers.

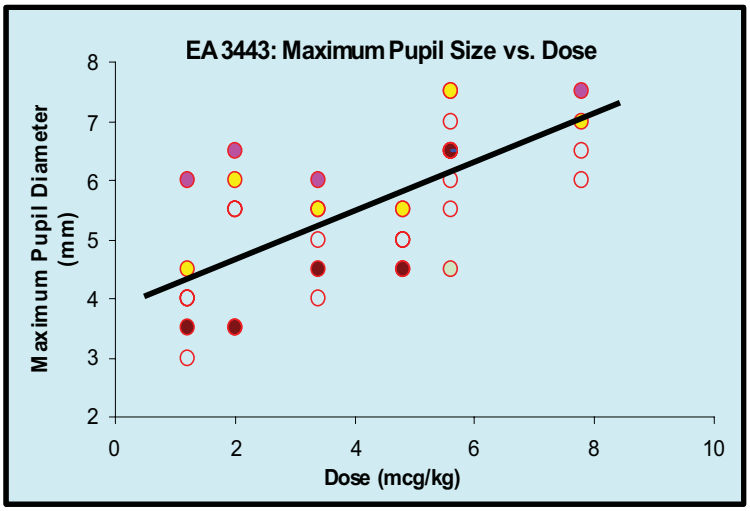


Fig. 18. Enlargement of the pupil (without DFP treatment) occurs only after doses that exceed the ID_{50}. An increase from 4 mm to 7 mm occurs at doses between 6 and 8 mcg/kg.. Pupillary changes persist as long as do the central effects, but the mechanism is often considered to be primarily peripheral in origin. EA 3443 has relatively few peripheral effects below 5 mcg/kg.

Remarkably, at the ID_{50}, EA 3443 produces no systematic changes in blood pressure (Fig. 19).

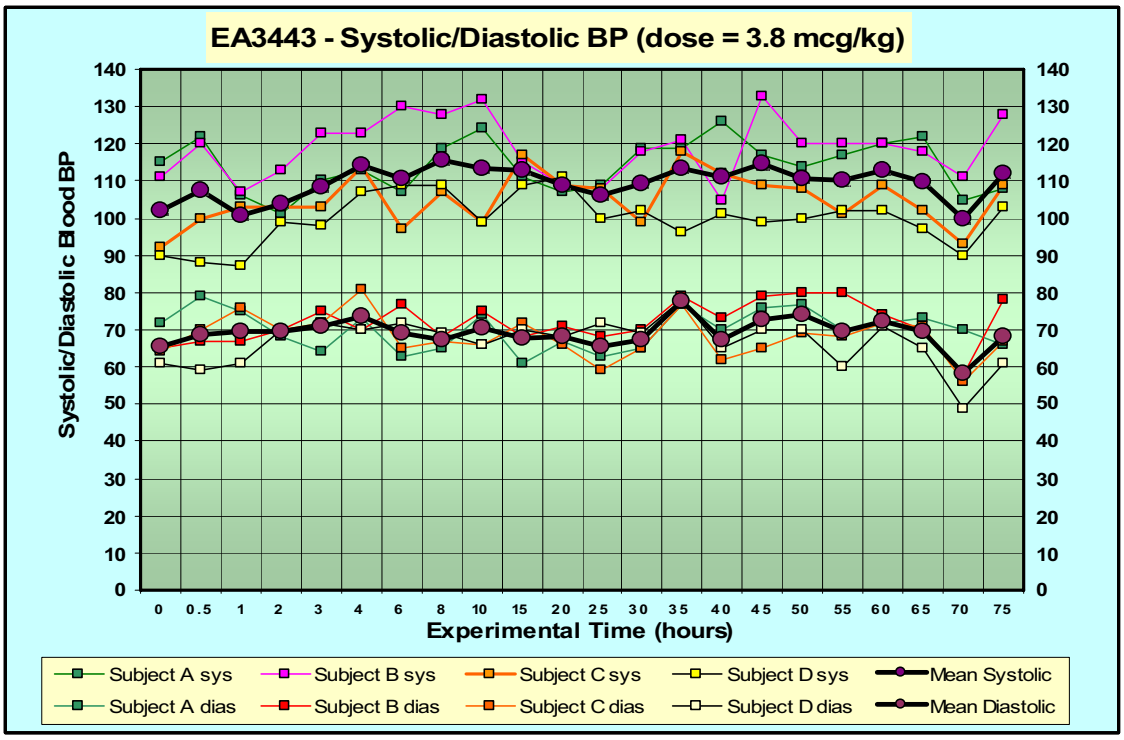


Fig. 19 The lack of any systematic change in either systolic or diastolic blood pressure throughout the duration of EA 3443 action indicates clearly that its effects are primarily central.

Number of Subjects	Dose (mcg/kg)	Food Intake (cal.) mean ± S.E.	Fluid Intake (mL) mean ± S.E.	Sleep Duration (h) ±S.E.
4	0.9	2520 ± 420	1830 ± 266	6.82 ± 1.93
6	1.2	2795 ± 295	1410 ± 298	9.42 ± 1.55
6	1.8	2610 ± 280	1623 ± 226	8.85 ± 1.08
6	2.4	2450 ± 310	1580 ± 102	6.66 ± 2.30
4	3.4	1640 ± 360	1358 ± 254	1.55 ± 0.50

Table 8 EA 3443: Dose-related differences in caloric intake, fluid intake and sleep duration.

In general, caloric and fluid intake both tend to decrease as the dose of EA 3443 is increased (Table 8). Sleep duration per 24 hours increases at lower doses (reflecting its sedative effect) but then declines as delirium takes over. The apparent insomnia during delirium often referred to as the "pseudowakeful state," in which the subject is active and seems to be awake, but is actually asleep in terms of EEG activity.

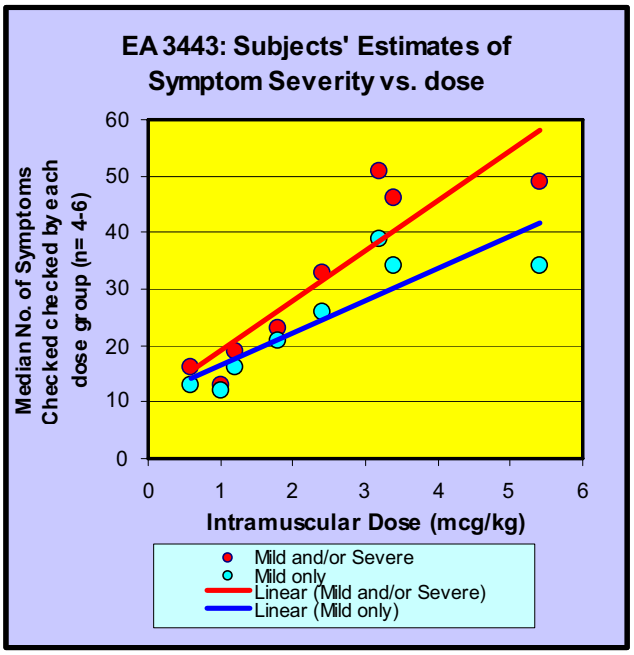


Fig. 20 EA 3443 Symptom severity as a function of dose

A linear relationship between estimates of symptom severity and dose is evident in Fig. 20. Ratings of mild severity alone are compared with combined ratings of mild and severe Either way, the linearity prevails.

Percutaneous studies (Figs. 21 and 22) were accomplished by applying precise amounts of the drug in suitable solvent with a microsyringe. The area of skin covered by the applied solution was then recorded as sketches. Effects of EA 3443 applied in this manner did not develop fully until after 24 hours, due to its slow transit through the skin.

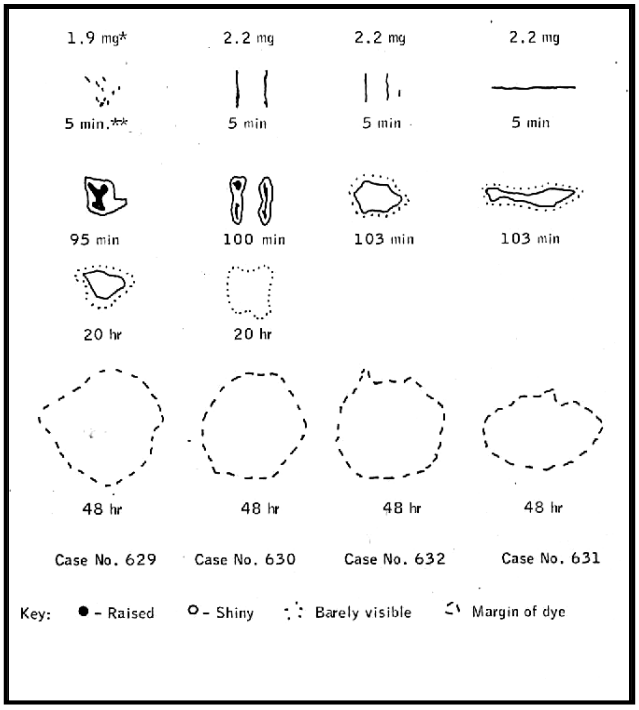


Fig 21 EA 3443 - Actual size and area covered at various times following application of solution.

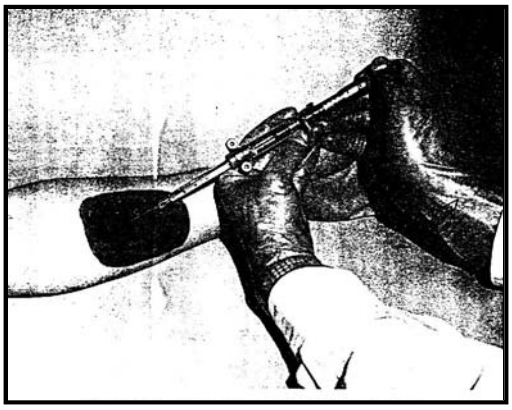


Fig. 22 EA 3443 being applied to the skin

Dermatological applications of glycolates such as EA 3443 were carefully documented. The amount applied and the time elapsed after application are shown (Fig. 21) for each of four cases.

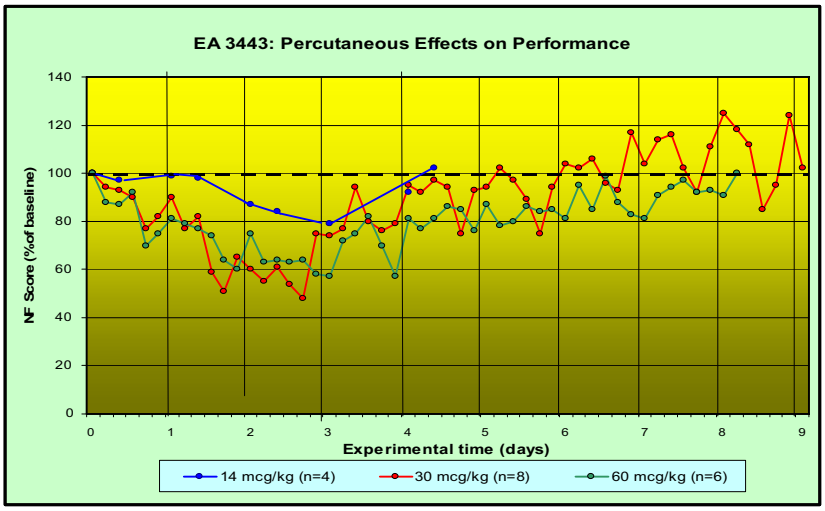


Fig. 23. EA 3443: Effect of 3 different percutaneous doses on NF performance.

Due to the extra time required to pass through the skin, EA 3443 took up to three days to produce maximal effects on NF% performance, and duration was much longer than when given by injection or inhalation.

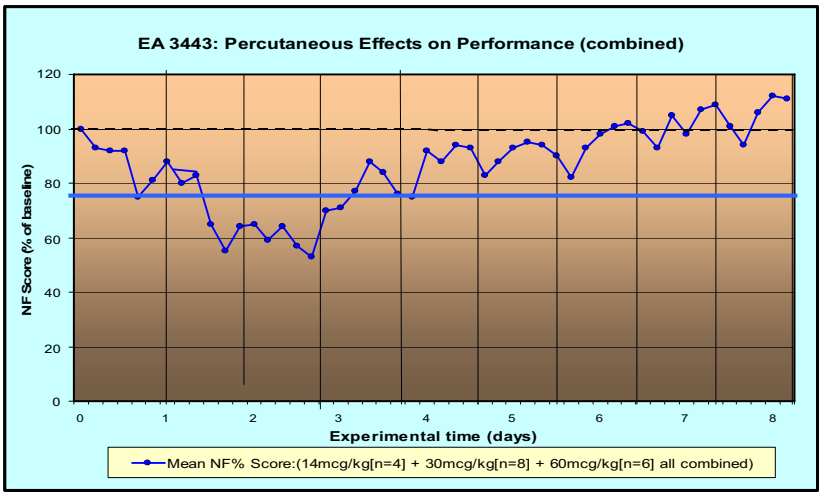


Fig. 24. EA 3443: Effect of combined percutaneous doses on NF performance. The horizontal blue line represents minimal (25%) performance impairment.

Here the dose groups are combined to give a more distinct indication of the time course of effects on performance.

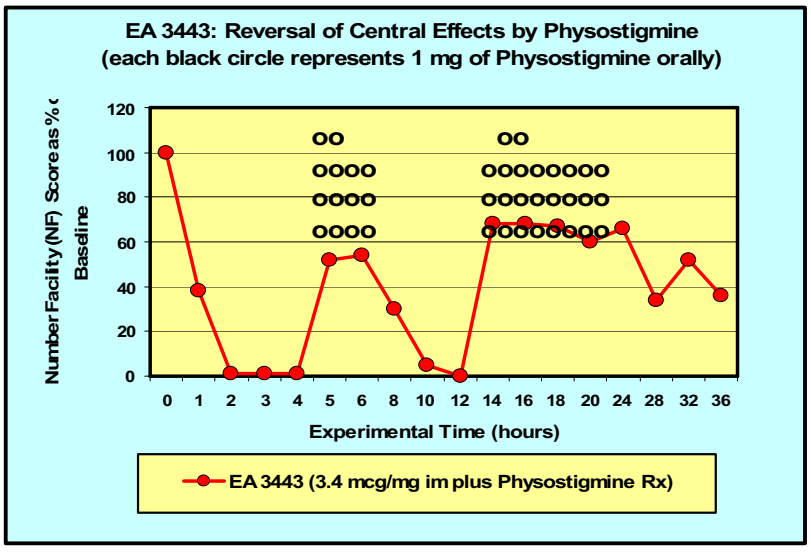


Fig. 25. EA 3443 – Effect of intramuscular physostigmine on NF performance decrement produced by the intramuscular ID_{50}

As with BZ, treatment with physostigmine was highly effective, restoring NF performance scores to about 60% of baseline. More vigorous treatment with higher physostigmine doses was found to have a greater effect.

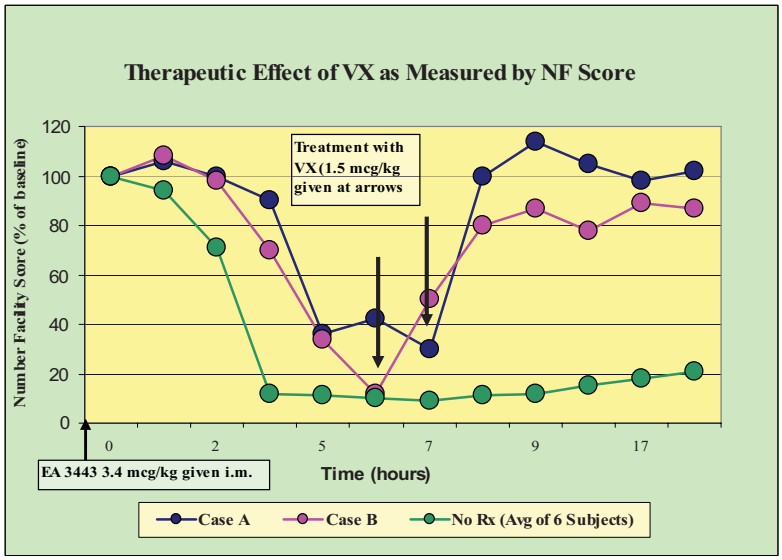


Fig. 26. VX was highly effective as an antidote to EA 3443 induced performance decrements in NF%, leading to virtually full reversal of cognitive impairment with only two doses. This work (by Sidell and Aghajanian)[23] suggests that VX could produce much better and more sustained benefit in known cases of EA 3443-induced incapacitation

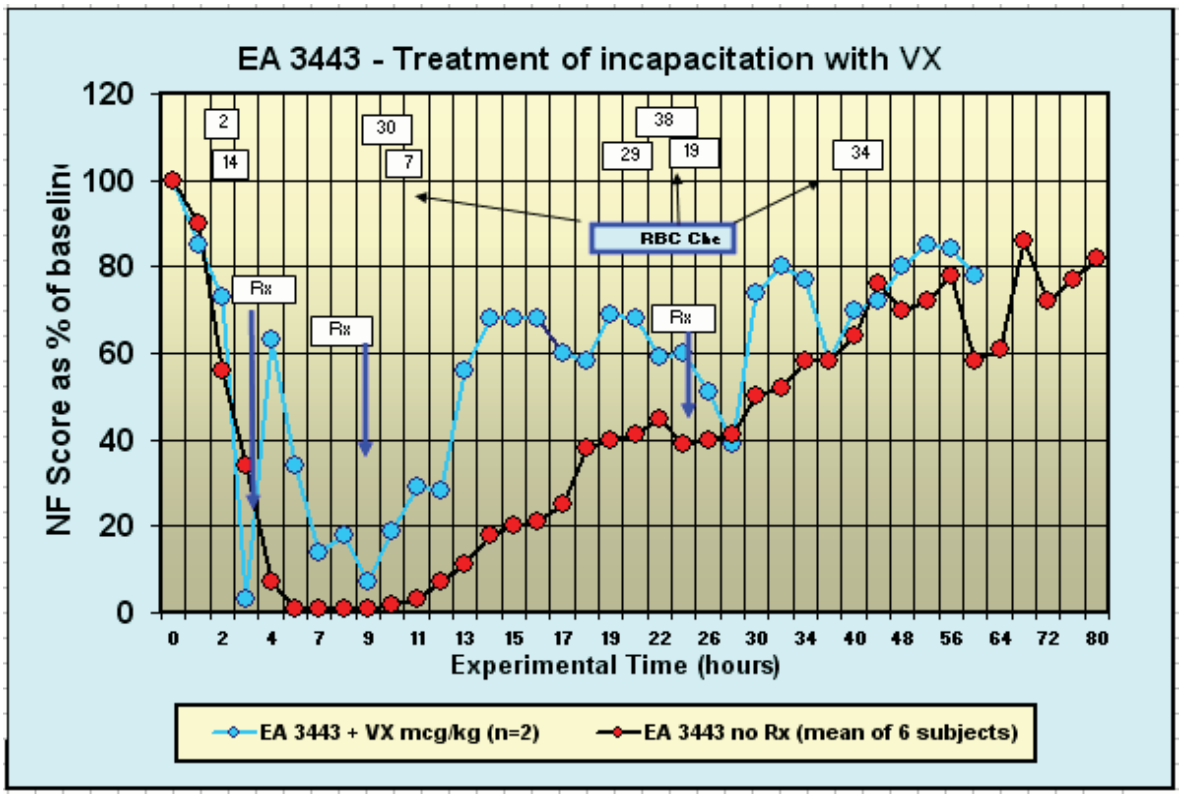


Fig. 27 RBC (true) as well as pseudocholinesterase inhibition was measured several times in this study. A surprisingly large reduction in cholinesterase levels can be well tolerated when EA 3443 is present. Small doses (unspecified) of VX were used here, producing shorter periods of antidotal effect, lasting only a few hours following each treatment.

EA 3580

We began to test this glycolate while studies of EA 3443 were still in progress. Its parameters differ from BZ and EA 3443. It has a lower ID_{50} and greater relative central potency than BZ, but is equal in potency to EA 3443, although it is shorter in duration than the latter. The structure of EA 3580 (Fig. 28) differs from EA 3443 only slightly. Instead of a five-carbon ring it has a four-carbon ring on the alpha carbon of the glycolic acid skeleton. Such small differences in structure, however, can produce major pharmacological differences.[25]

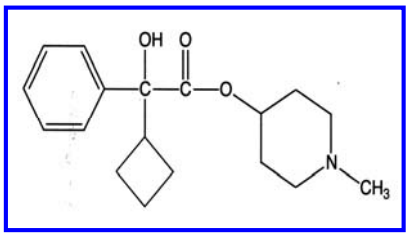


Fig. 28 EA 3580 structure

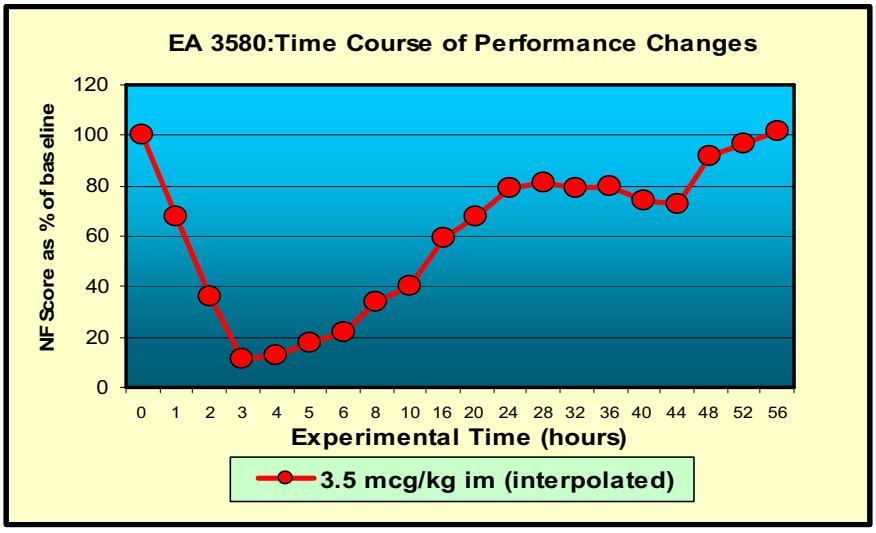


Fig. 29. EA 3580: Performance changes after ID_{50} dose im

The dip in NF scores (Fig. 29) prior to full recovery from the ID_{50} at 56 hours may be due to an underlying diurnal cycle of cognitive efficiency. We found in a group of undrugged subjects that NF scores are highest at about 4-6 P.M. and dip by 15% or more at about 4 A.M.

Table 9 compares the most important parameters for EA3443, EA 3580 and BZ.

Agent	ID_{50} (i.v. or i.m.) mcg/kg	ID_{50} (i.v. or .i.m) mcg/kg	ICt_{50} Mg min/ cubic M	Onset Time Ton_{50} (h)	Partial Re-covery Time $Toff_{50}$ (h)	Duration of Severe effects D_{50} (h)	Prolong ation-Time (h)	Relative Central Potency	Safety Factor
EA 3443	1.2	3.06	54	3 – 4	20–25	16 - 22	38 – 45	2.2	113
EA 3580	1.3	3.5	76	2.0	8.0	6	12	2.0	100
BZ	2.5	5.5	77	4	24	20	40	0.5	40

Table 9. Comparative values for 3 belladonnoids. Prolongation time = increase in duration by 2x ID_{50} Dose-Onset factor (Don_{50}) = increase in speed of onset by 2 x ID_{50} Safety Factor = LD_{50}/ID_{50}

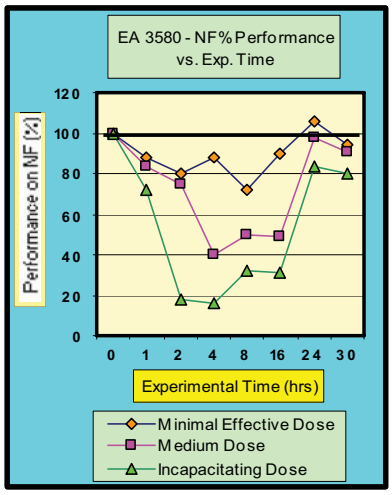


Fig. 30. EA 3580: Number Facility

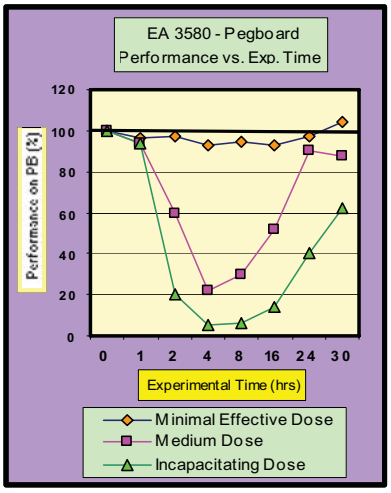


Fig. 31. EA 3580: Pegboard

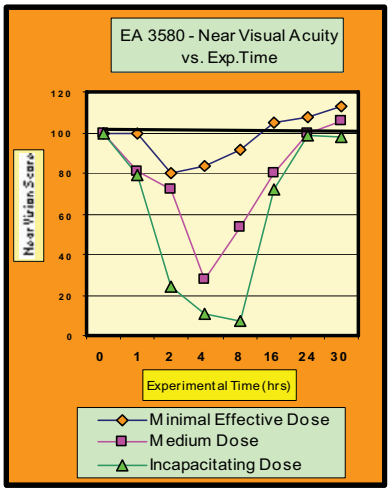


Fig. 32. EA 3580: Visual Near Acuity

Number Facility (Fig. 30), the most consistently used single test of cognitive ability, was affected very similarly to Pegboard performance (Fig. 31), which is a test of psychomotor function. Near (Fig. 32) and Far (Fig. 33) visual acuity were likewise almost identically affected.

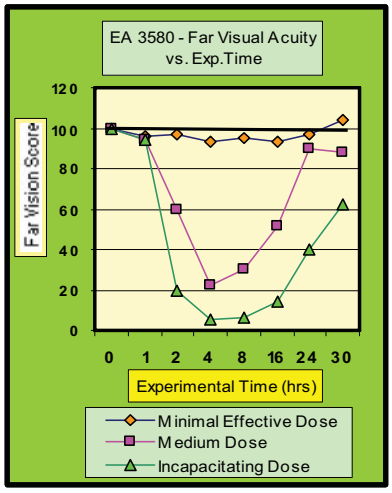


Fig. 33. EA 3580: Visual Far Acuity

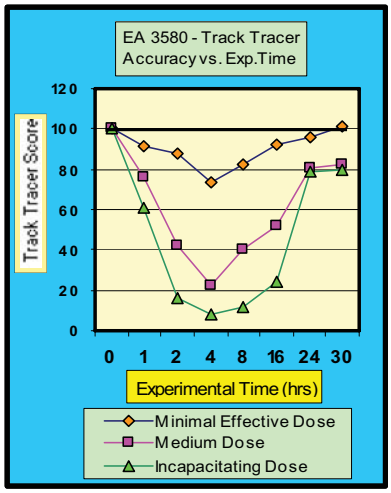


Fig. 34. EA 3580: Track Tracer Accuracy

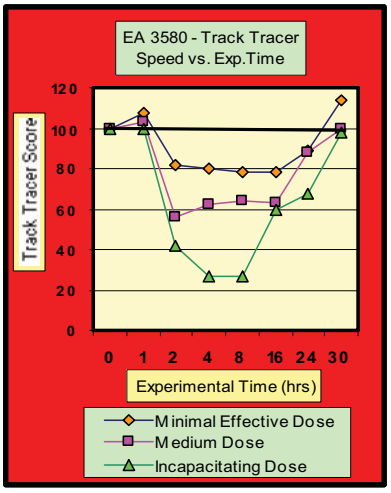


Fig. 34. EA 3580: Track Tracer Speed

In these tests, EA 3580 produced somewhat more impairment in performance of Track Tracing Accuracy (Fig. 34) than in Track Tracing Speed (Fig. 35), suggesting that physical competence may be more resistant than cognitive functions to the effects of anticholinergic drugs with high relative central potency.

In the same study, the six subjects were also tested for 30 hours on several other military and cognitive tests (Figs. 36-41). As with other tasks, scores on a wide variety of performance measures were similar, but some differences were also observable, as shown in the graphs on this and the previous page.

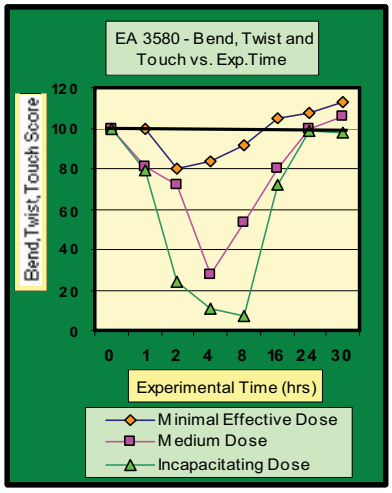


Fig. 36. EA 3580: Bend, Twist and Touch

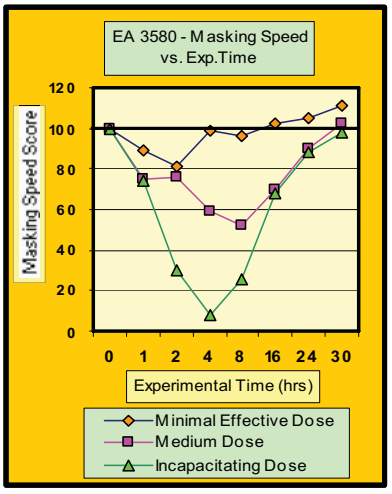


Fig 37. EA 3580: Masking Speed

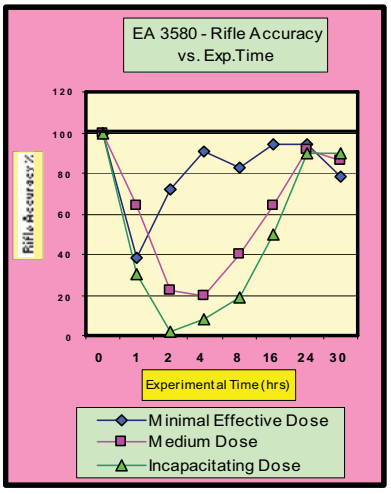


Fig. 38. EA 3580: Rifle Accuracy

Bend, Twist and Touch (Fig. 36) was a physical task that showed changes similar to those observed for cognitive tasks. Masking Speed (Fig. 37) likewise reflected similar effects. As with many tests, some improvement as a result of practice was evident at the time of recovery. Rifle accuracy (Fig. 38) was greatly diminished in the medium and high dose groups but only briefly at the lowest (MED_{50}) dose.

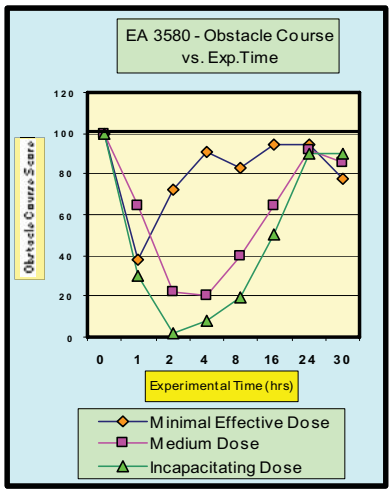


Fig. 39. EA 3580: Obstacle Course

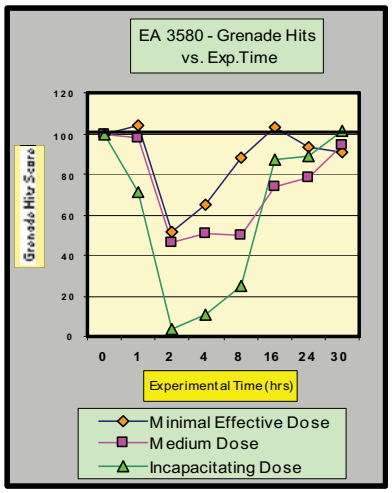


Fig. 40. EA 3580: Grenade Hits

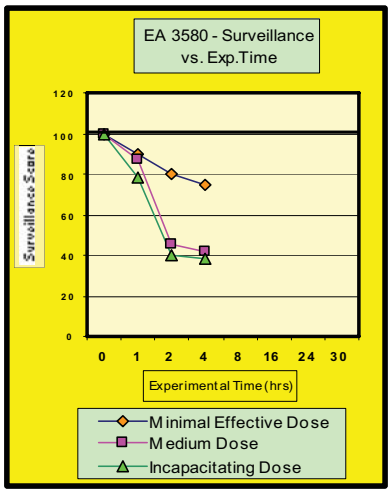


Fig. 41. EA 3580: Surveillance

Obstacle Course Speed (Fig. 39) was degraded as with most of the other tasks. In general, however, with centrally more potent drugs, physical proficiency seems to depend less on "higher" central nervous system functions. Grenade Hits (Fig. 40) showed more variability, probably because the sample of performance was limited to only six grenades. Surveillance (Fig. 41) was tested only for the first few hours.

It is evident that in each of the preceding 12 graphs, the split between the performance curves after different doses increases to a maximum during the period of peak effects. Furthermore, all measures of performance are notably similar in terms of magnitude and time course, even though they tap into tasks that vary from purely cognitive, such as NF, to almost purely physical, such as running an obstacle course. Also, whatever differences may exist in the proficiency with which these skills are carried out under normal conditions, they become increasingly inconsequential as the intensity of drug action increases (this applies to all individuals tested, incidentally, regardless of their initial level of competence in any of these activities).

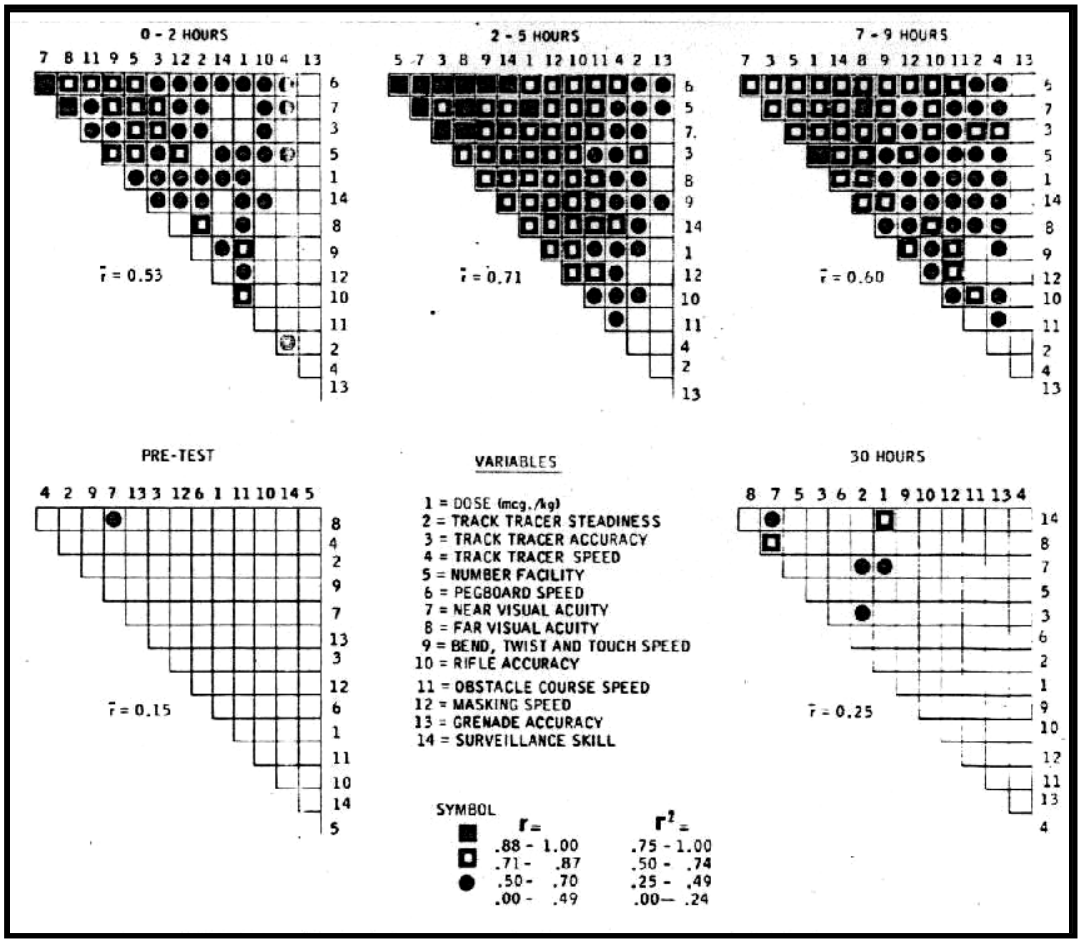


Fig. 42 EA 3580: Intercorrelations among 12 performance tasks after intramuscular ID_{50} (shown by squares of varying density) increase and decrease as drug effects wax and wane.

To demonstrate this statistically, Phil Kysor and I compiled the intercorrelations among the 12 tasks at various experimental times (Fig. 42).[26] Statistically, the matrices shown above simply demonstrate that the variance in scores are progressively accounted for by intensity of drug effects. Thus, one can predict individual impairment in all skill areas by the degree to which drug action affects performance in any single task. This applies, incidentally, to individuals who may be quite dissimilar in various abilities prior to the administration of a belladonnoid drug such as EA 3580.

EA 3167

EA 3167 turned out to be surprisingly long acting, longer even than BZ or 3443, both of which produce about 3 days of incapacitation at the ID_{50}. The MED_{50} was low,[27] close to that of the other two compounds, but a small increase in dose (20%) caused the two subjects tested at that level to require extended physostigmine treatment.

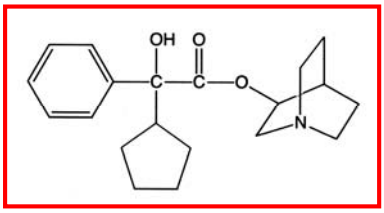


Fig. 43. EA 3167 structure

EA 3167 (Fig. 43) and BZ (Fig. 44) are almost identical in structure, the former having a cyclopentyl group on the alpha carbon of the glycolic acid nucleus, while the latter has a benzyl group This minor difference seems to result in more tenacious occupancy of the muscarinic acetylcholine receptor.

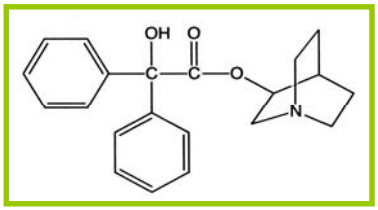


Fig. 44. BZ structure

EA 3167 was the longest-lasting belladonnoid we studied.[28] It is roughly equal in potency to EA 3443 and EA 3580, but has an approximate duration of incapacitating effects (D_{50}) of 120-240 hrs. It has a high central to peripheral (C/P) index of 2.5, which makes it virtually free of peripheral effects at the ID_{50}, and thus, presumably, it has a higher safety margin than most belladonnoids.

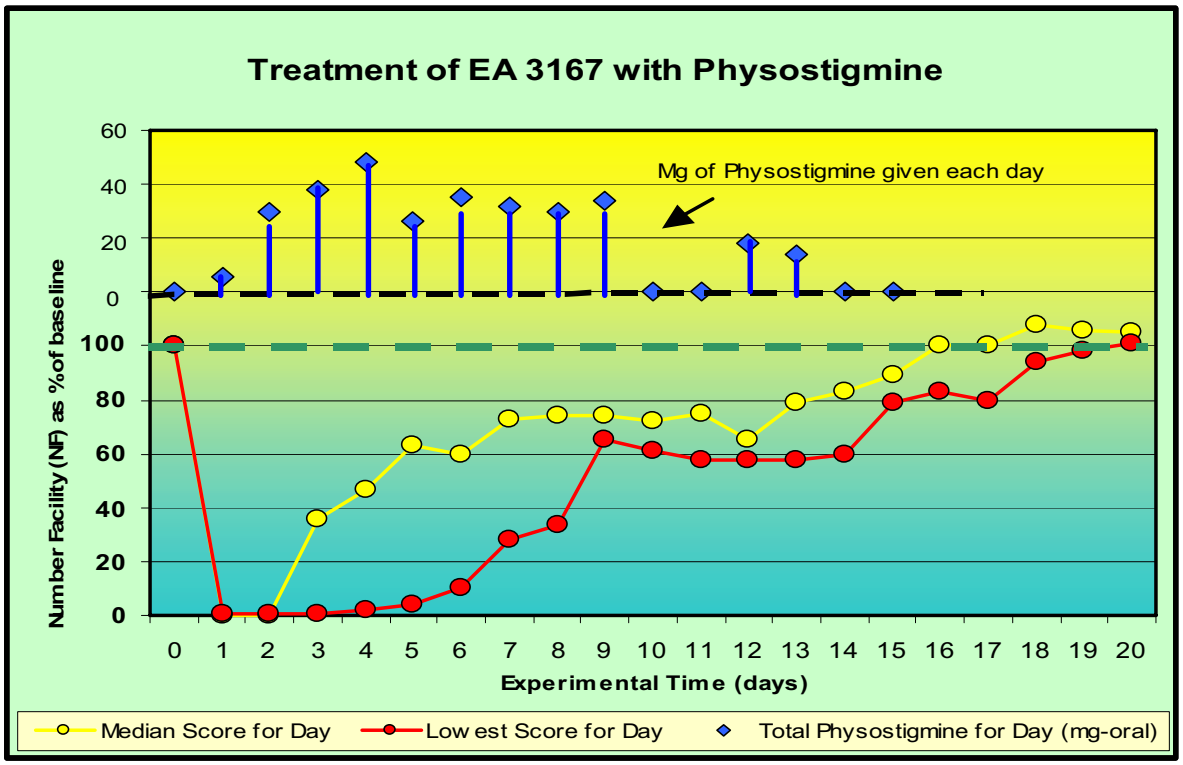


Fig. 44 Use of physostigmine to control prolonged delirium produced by 3.8 mcg/kg im of EA 3167

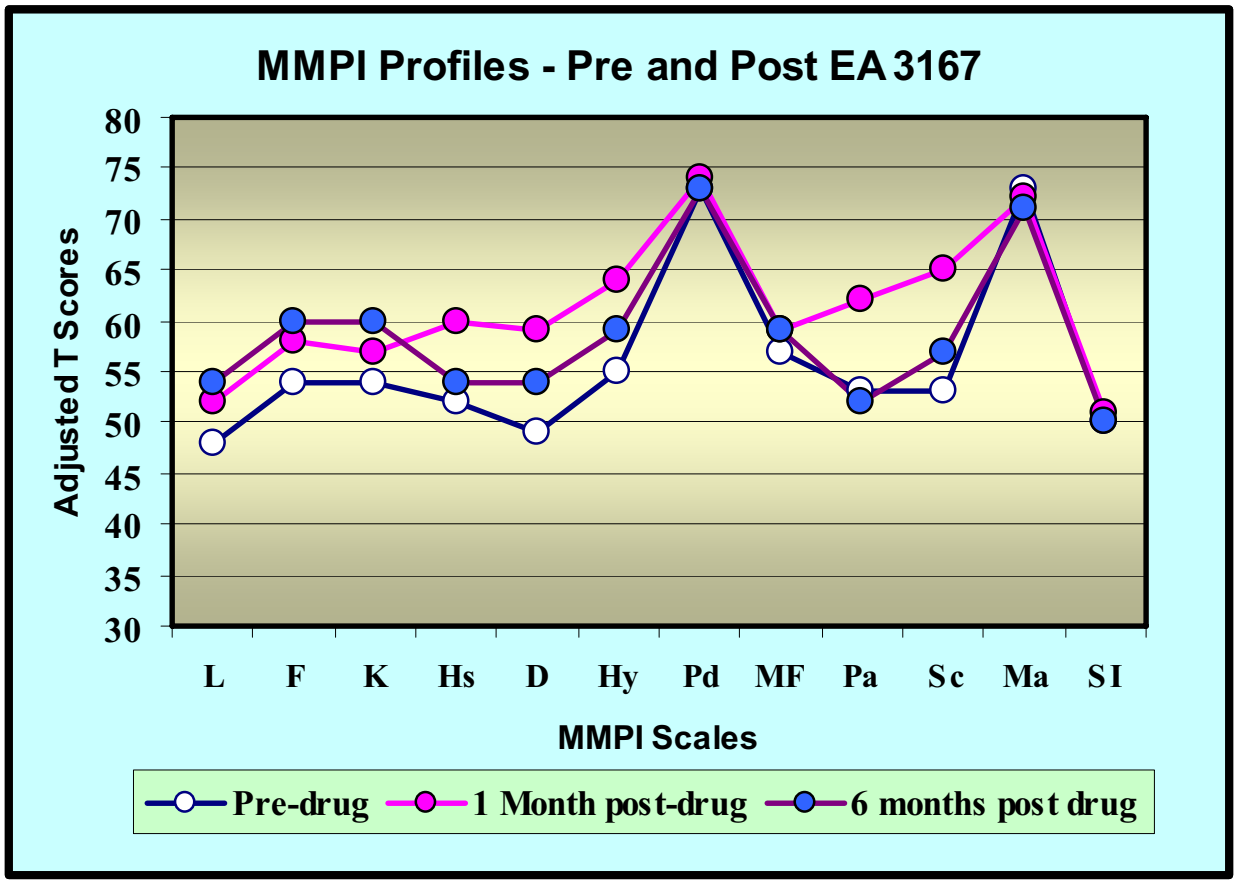


Fig. 45 – EA 3167: Comparison of baseline MMPI profiles with follow-up profiles at 1 month and 6 months.

Follow-up cognitive and MMPI testing of the subjects who received EA 3167, at 1 and 6 months (Fig. 45), showed a small residual increase in the paranoid and schizophrenic subscales at 1 month, but at 6 months the profile had essentially returned to the pre-drug values. Differences in the three "validity" scales that persist may be due to attitudinal factors. Scores for intellectual functions returned to pre-test values during the same period, as shown previously for EA 3443 and EA 3580.[29]

A total of 19 volunteers were tested with EA 3167, most of them at low doses. Other than the two cases mentioned above, none required more than 2-3 days to recover. All post-recovery laboratory studies were normal. In view of its excessively long duration, it seemed best, however, not to do further testing.

The consequences of being on the receiving end of an enemy attack with EA 3167 could be severe. Multiple low dose attacks over a period of several days could produce an insidious build-up of cognitive defects. Distributed attacks would also tend to result in a more homogeneous distribution of dosage, since members of the population would probably change their locations at various times and total exposure would thus tend to be more uniform.

EA 3834

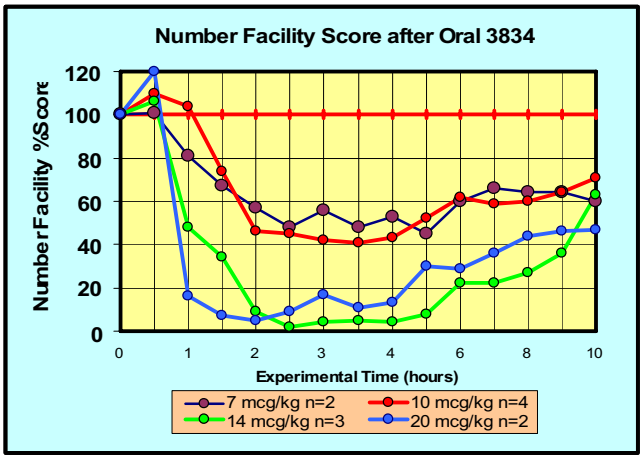


Fig. 46 EA 3834: Effect on NF performance

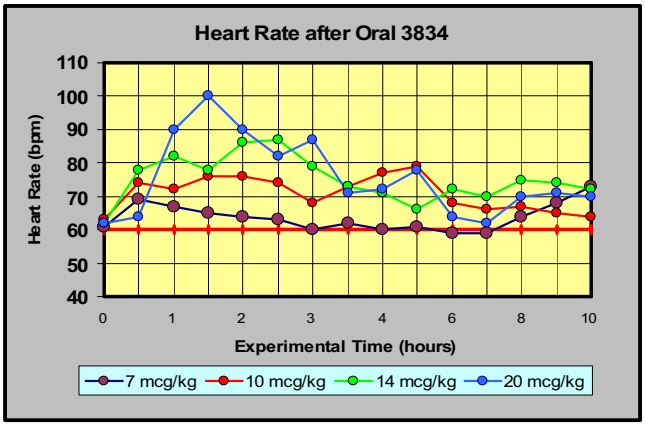


Fig. 48 EA 3834: Effect on heart rate

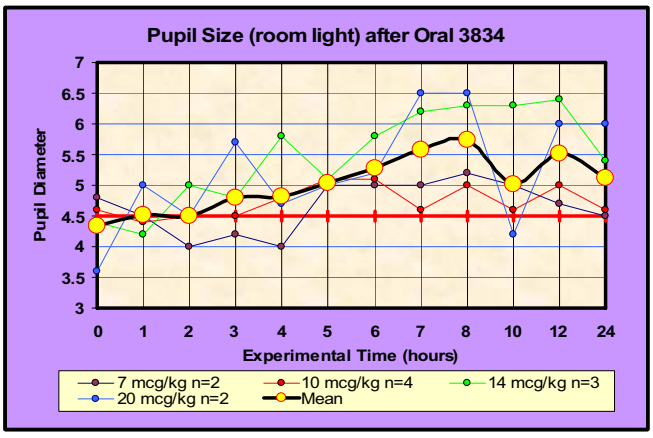


Fig. 49 EA 3834: Effect on pupil size

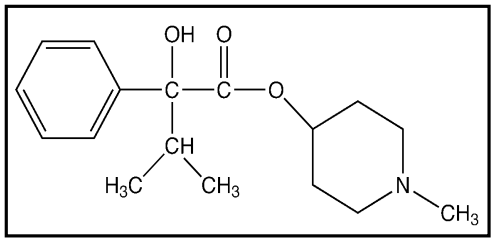


Fig. 47 Structure of EA 3834

This glycolate was one of the last to undergo detailed analysis. It proved to have an interesting combination of properties. It has a rapid onset, and sufficient potency to make it good alternative to the longer-acting belladonnoids such as BZ, EA 3443 and EA 3167. The onset time (Ton_{50}) of EA 3834, even after the predictable delay following oral administration, is only about 45 minutes (Fig. 46). It is interesting that the initial rise in NF scores indicates a slight performance increase at 30 minutes, but this is rapidly followed by a dramatic decline at 1 hour.

Heart rate increase was not very great (Fig. 48), even at and above the ID_{50} (calculated to be about 12 mcg/kg, based on inspection of the NF results shown above). This signifies a high central/peripheral ratio, which is obviously preferable from a toxicity standpoint, especially in a hot climate.

Pupil size shows only a modest increase, and takes 8 hours to peak (Fig. 49). This suggests that most of the enlargement of pupils is central in origin although, as indicated previously, there is some doubt as to the centrality of the mechanism.

(Note: A realistic military scenario with EA 3834 was described in detail in Chapter 17 of the main narrative section of this book.)

302196

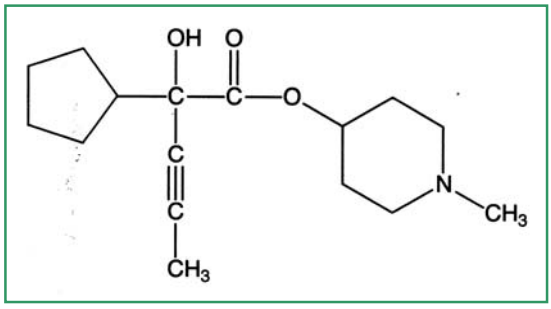


Fig. 50 302196: N-Methyl-4-piperidynyl α-propynyl-cyclopentyl glycolate

The belladonnoid glycolate 302196 (Fig. 50) differs from EA 3580 and EA 3443 in that it has a triple bond side chain on the alpha carbon of the glycolic acid skeleton, instead of a cyclopentyl or cyclobutyl side chain group as well as a cyclopentyl instead of a benzyl group at the same carbon.

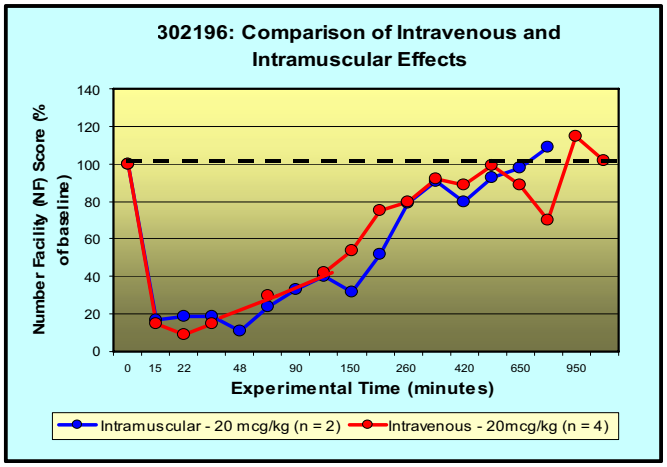


Fig. 51 302196: Effects on NF performance (i.v. vs. I.m. routes):

The ID_{50} of 302196 produces essentially the same effect on performance, whether given by the intramuscular or the intravenous route (Fig. 51). Peak effects occur early, with a Ton_{50} of abut 10 minutes. Partial recovery occurs at less than 4 hours and full recovery at about 10 hours. By both routes, the onset is very rapid and short-lived.

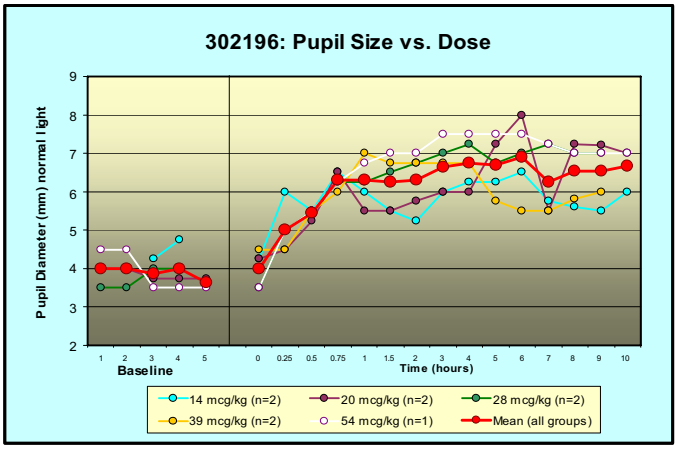


Fig. 52 302196: Effect on pupil size (i.m. route)

Pupil size increased rapidly to a maximum of about 7 mm at 6 hours (Fig. 52), and tended to persist longer than changes in both cognitive performance and heart rate. The probable dominance of the central component of pupillary dilation is reinforced by this observation.

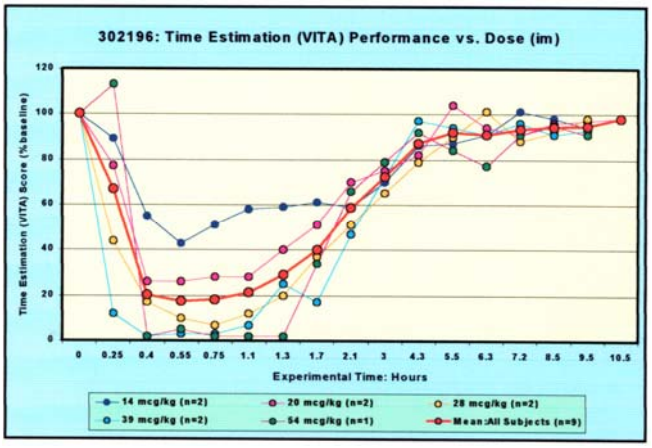


Fig. 53 302196: Effects on VITA scores

At the ID_{50}, 302196 produces impairment of Variable Interval Time Reproduction (VITA) scores (Fig. 53). This decrement is very similar to that shown for Number Facility (Fig. 54). Four dose groups are shown in each graph. The decline in scores is very rapid and recovery occurs early.

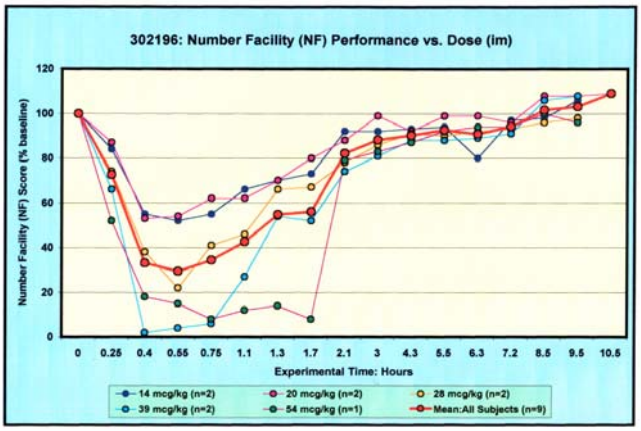


Fig. 54 302196: Effect on NF scores

Although 302196 is not very potent when compared to BZ and other glycolates, its rapid, brief effects bring it closer to the ideal for a tactical agent (Fig. 54). The logistical problems of delivering the larger doses required to produce incapacitation, however, would limit its practicality

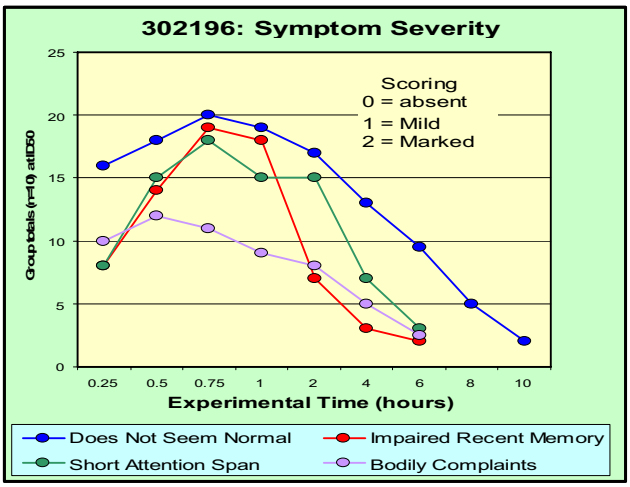


Fig. 55 302196: Effect on specific signs and symptoms

At frequent intervals, the nurses rated the 302196 subjects using the standard checklist (BCL) of observable symptoms. For 10 subjects given the ID_{50}, the ratings were totaled at the times indicated (Fig. 55). Scores for "does not seem normal" do not return to baseline until about 10 hours, but by 6-10 hours, the degree of impairment of recent memory and attention span, as well as the severity of bodily complaints, all appear to have reverted to near the pre-test levels.

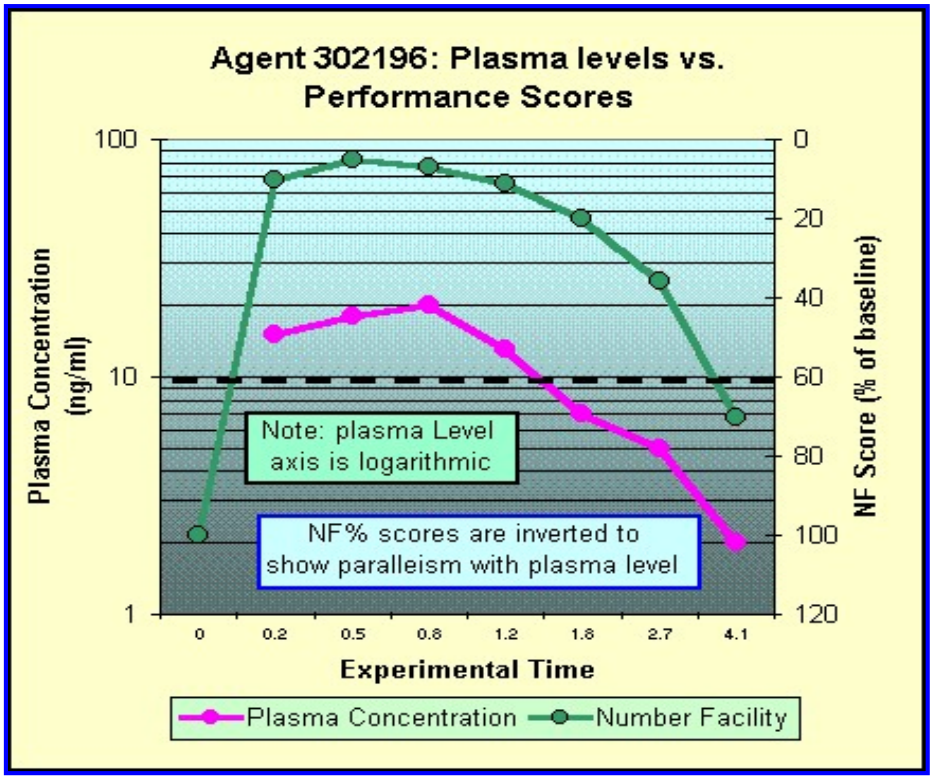


Fig. 56 302196: Correlation between plasma levels and NF performance

By 1965, our laboratory had developed the ability to measure blood levels of 302196. Its relative lack of potency made the test dosage range higher, creating more easily detectable blood concentrations. In this graph (Fig. 56), NF scores (right y-axis) are inverted to make the parallelism between blood level (left y-axis) and performance more apparent.

Atropine, Scopolamine and Ditran

(Note: Although a few glycolates other than the ones discussed in prior sections of this appendix were administered to volunteers in low doses, the data for these agents were insufficient to give more than a general indication of their potency and duration. At the end of the belladonnoid section, rough estimates of parameters such as relative peripheral and central potency are shown graphically.

Quite early in the course of testing BZ and other synthetic glycolates, we realized that no comprehensive studies of scopolamine or atropine over a full range of dosage had been published, even though these venerable belladonnoids had long been accepted as medically safe and effective. Ditran (JB-329), a more recently introduced belladonnoid, had been characterized in clinical reports as a useful drug for certain mental disorders, but many details of its pharmacology in man remained unexamined.

In the 1950s, Edgewood investigators had been interested in atropine primarily as a treatment for anticholinesterase nerve agent poisoning. They found it highly effective in blocking the access of acetylcholine to muscarinic receptors, both in the peripheral nervous system and in the brain. A primary concern was possible undesirable central effects of atropine if administered in the absence of nerve gas. This could easily happen if commanders or individual soldiers falsely suspected or anticipated a nerve agent attack. But the precise dose-response relationships over a broad range of dosage, especially with respect to performance, were still lacking.

Studies by Enoch Callaway (and others) at Edgewood, in the 1950s, demonstrated mild but significant cognitive impairment at total doses of 4 mg, but not 2 mg. This was important in selecting the dose to be provided in syrettes. Atropine syrettes containing 2 mg of atropine are included in each soldier's equipment whenever the possibility of nerve gas exposure appears likely. The contents of the syrette are to be self-injected into the thigh, through the combat clothing. Training exercises promote a soldier's doing this without hesitation. If cholinergic symptoms continue to develop, a second syrette may be used. Higher doses can be given under medical supervision in severe cases of poisoning.

Although used for centuries for various ailments, e.g., as a pre-anesthetic and in the treatment of Parkinsonism, there were no systematic studies covering the range from mild dryness of the mouth at 0.5 mg up to incapacitation and delirium at doses of 10-12 mg. We did not carry out such studies until rather late in our program, since they had a lower priority than the belladonnoids potent enough to have possible use as an incapacitating agent. Nevertheless, there were two reasons to look more closely at atropine. First was our wish to ascertain its MED_{50}, ID_{50}, onset time (Ton_{50}), duration (D_{50}) and relative central potency (HR_{50}/ID_{50}) for purposes of comparison with BZ and other belladonnoids already characterized. We therefore began our dose-response studies, including not only atropine, but scopolamine and Ditran as well, and were later able to publish the results in the open literature (Ketchum et al.[32]).

A second reason for our interest in these drugs, scopolamine in particular, was their short duration of action. This allowed us to study various potential antidotes in a time-efficient manner, with the added assurance that these established compounds were already considered to be safe by the FDA.

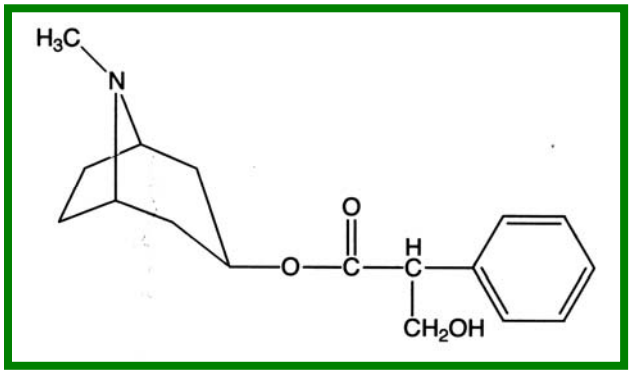


Fig. 57 Atropine: chemical structure

Although not usually classified as a glycolate, the structure of atropine (Fig. 57) can be visualized as such, taking certain liberties with the rules of chemical nomenclature.

Ordinarily, however, it is referred to as a tropane.

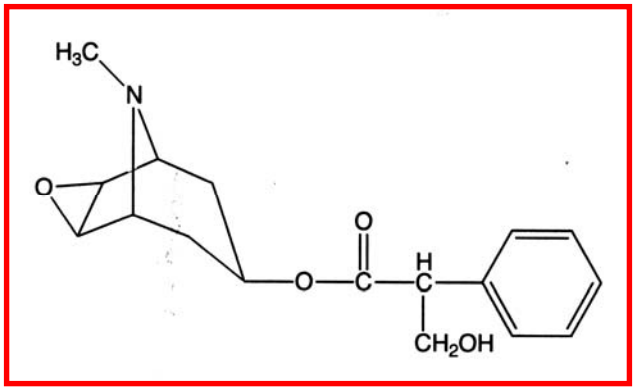


Fig. 58 Scopolamine: chemical structure

Differing from atropine (Fig. 58) by only a single oxygen atom (bridging two carbon atoms in the distinctive seven-carbon ring), scopolamine has much greater ability to enter the central nervous system.

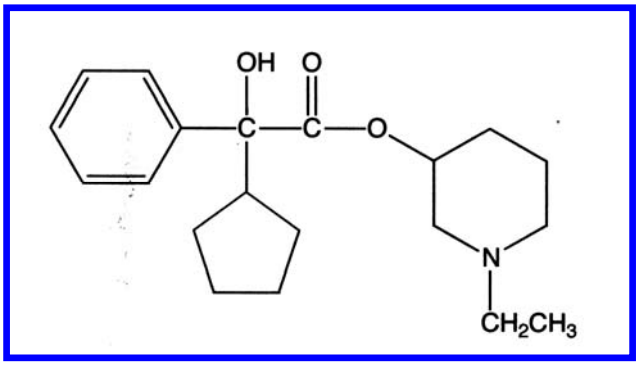


Fig. 59 Ditran (JB-329) structure of main component

This compound (Fig. 59) is clearly recognizable as a substituted glycolic acid ester (actually a 2:1 mixture of two very similar glycolates), but usually the combination is treated as a single agent. It is referred to (inconsistently) as JB-328 or JB-329.

Ditran's pharmacological properties are very similar to atropine in terms of potency and relative central efficacy, but its effects are longer in duration.

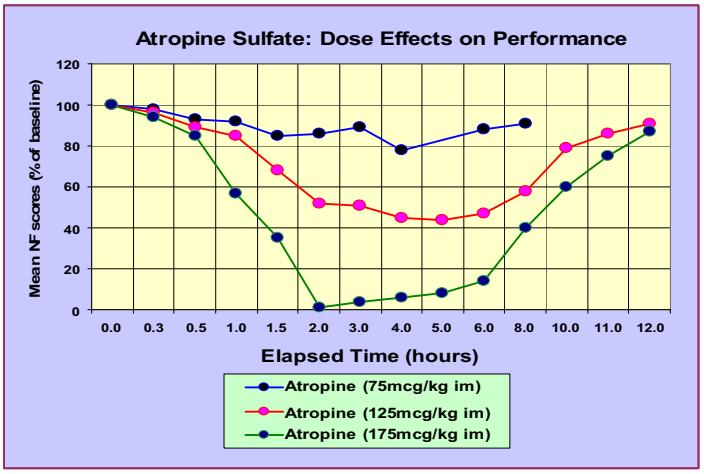


Fig. 60. Atropine: Effects on NF performance

By inspection, atropine's effects on cognitive (NF) performance reach a maximum at about 4 hours (Fig. 60). The estimated MED_{50} is about 90 mcg/kg and the ID_{50} is about 160 mcg/kg. Onset time (Ton_{50}) and duration (D_{50}) at the ID_{50}.are about 1 and 6 hours respectively. The relative central potency of atropine is the lowest of any of the belladonnoids we studied (Fig. 74). Once again, as is the case with BZ vs. EA 3167 and EA 3443 vs. EA 3580, a minor structural change makes a major difference.

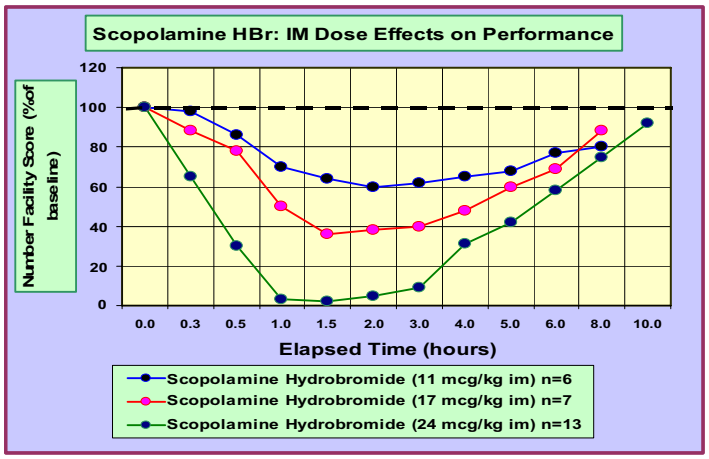


Fig. 61. Scopolamine: Effects on NF performance

Scopolamine's effects on cognitive function are qualitatively similar to those of atropine,[30] but its relative central potency is about 7-8 times as great. This results in an ID_{50} of about 22 mcg/kg and an MED_{50} of about 10 mcg/kg (Fig. 61).

Onset time (Ton_{50}) at the ID_{50} is about 30 minutes. Partial recovery time (75% of baseline) is about 7 hours and full recovery occurs at about 10 hours.

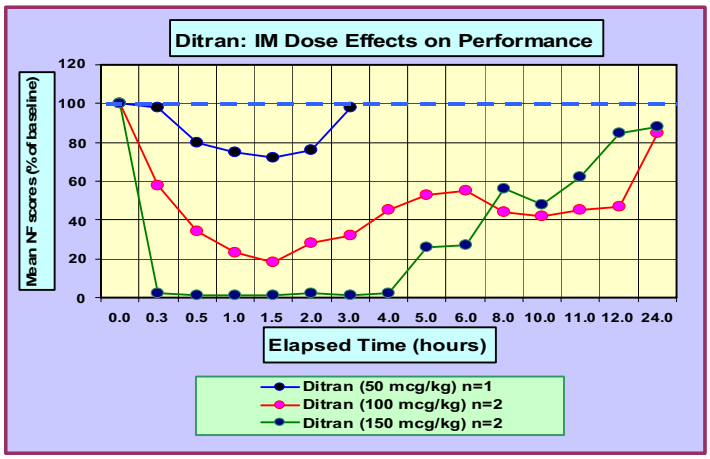


Fig. 62 Ditran: Effects on NF performance

Ditran (JB-329) is somewhat more potent centrally than atropine. Its estimated MED_{50} is about 50 mcg/kg and its ID_{50} is about 125 mcg/kg. It is more rapid in onset than atropine (at the ID_{50}) and duration appears to be more than 10 hours (Fig. 62).

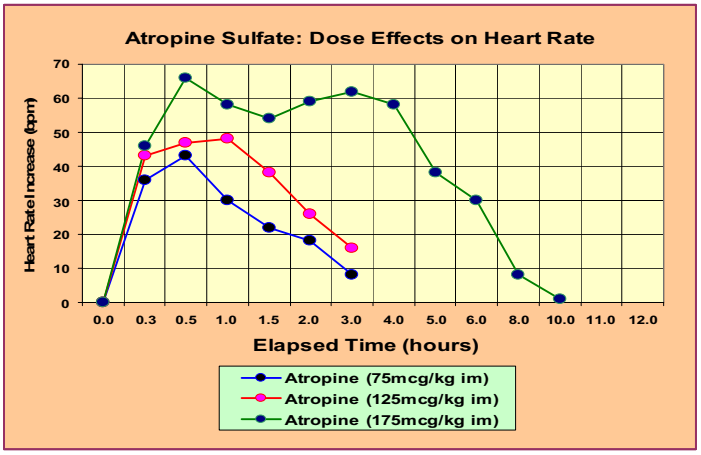


Fig. 63 Atropine: Effects on heart rate

Atropine's peripheral effects on heart rate (Fig. 63) and blood pressure (not shown) are substantial and very rapid in onset, peaking at about 30-60 minutes. In this graph, baseline heart rate is shown as zero. Maximum heart rate at the ID_{50} is thus about 125 (60 + 65). It remains at this level for about 3 hours and returns to normal at about 9 hours. At the ID_{50}, minor changes in the electrocardiogram were noted in a study by Hayes et al.[55]. These changes rapidly revert to normal as HR declines.

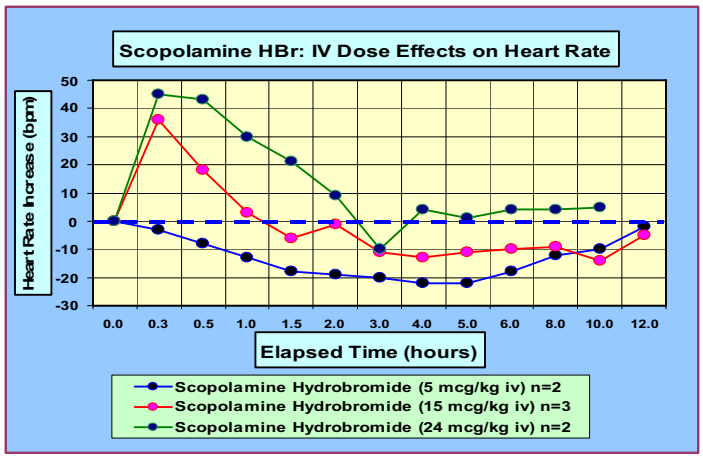


Fig. 64 Scopolamine: Effects on heart rate

Atropine, increases, but scopolamine actually decreases, heart rate at low doses and at higher doses it does not produce elevations as high as atropine at the ID_{50} (Fig. 64). This is probably attributable to medullary mechanisms that tend to reduce heart rate. Similar effects also occur with atropine but they are quickly overwhelmed by atropine's much greater peripheral potency. (Low dose studies of atropine reveal this more clearly.) Note that the duration of scopolamine's effects is very similar to that of atropine.

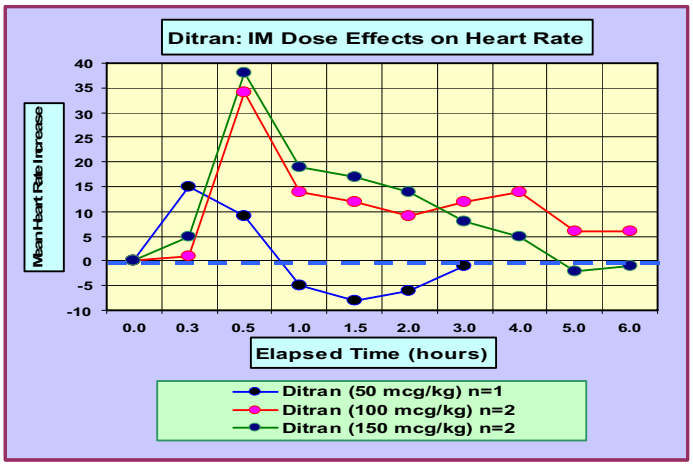


Fig. 65 Ditran: Effects on heart rate

Ditran is intermediate between atropine and scopolamine with respect to heart rate changes, with a slight dip below baseline at the low dose of 50 mcg/kg (Fig. 65). Peak HR elevation occurs at about 30 min, somewhat later than both atropine and scopolamine. The tachycardia is short-lived, with recovery at 5-6 hours. No doubt, the short duration of Ditran was an advantage when used by Ostfeld et al. in their "Ditran coma therapy," which was perhaps inspired by Forrer's "atropine coma therapy" introduced a few years earlier.

Treatment of Atropine, Scopolamine and Ditran Intoxication

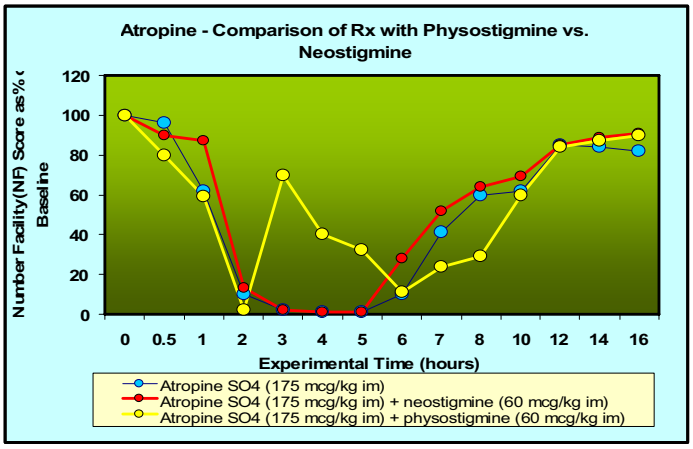


Fig. 66 Atropine: response to physostigmine vs. neostigmine

As with all the belladonnoids we studied, physostigmine is quite effective in reversing performance decrements, but the effect fades in 2-3 hours (Fig. 66). Neostigmine, a quarternary compound which does not cross the blood-brain barrier, became preferred in the 20th century precisely because it is free of central effects. When compared with physostigmine at the same dose (60 mcg/kg), its effectiveness in reversing the cognitive performance impairment produced by atropine is totally absent.

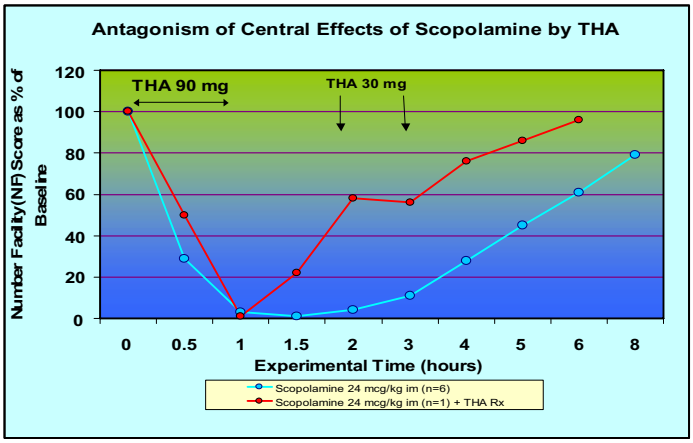


Fig. 67 Scopolamine: Response to tetrahydroaminoacridine

As we soon learned, tetrahydro-aminoacridine (THA) is less effective in some respects than physostigmine in reversing scopolamine induced decrements in NF% scores (Fig. 67) but surprisingly, does seem to shorten the duration of belladonnoid intoxication. This may reflect a greater affinity for the cholinesterase enzyme. THA's tendency to cause temporary liver enzyme abnormalities, however, persuaded us to avoid its further use.

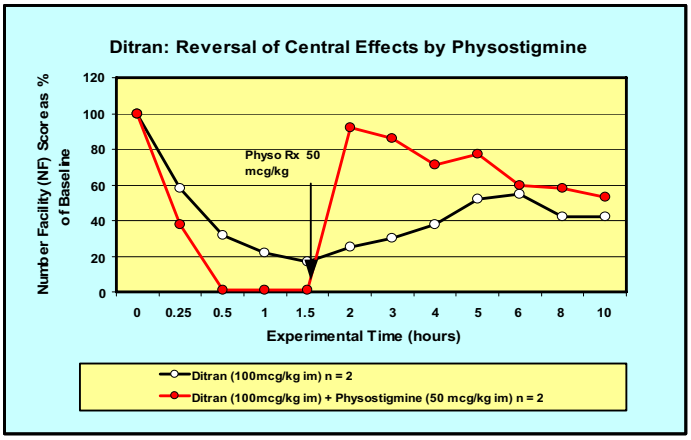


Fig. 68 Scopolamine: Response to tetrahydroaminoacridine

Dramatic reversal of Ditran-induced decrement in NF performance was produced by a single dose of 50 mcg/kg of physostigmine. NF scores rose from zero (during delirium) to almost 100% within 30 minutes (Fig. 68). As with THA, the antidotal effect of physostigmine against Ditran seemed to be more enduring than against other belladonnoids. The reason for this is unknown and clearly requires replication with a larger number of subjects. (n = only 2 in each group in Fig. 68).

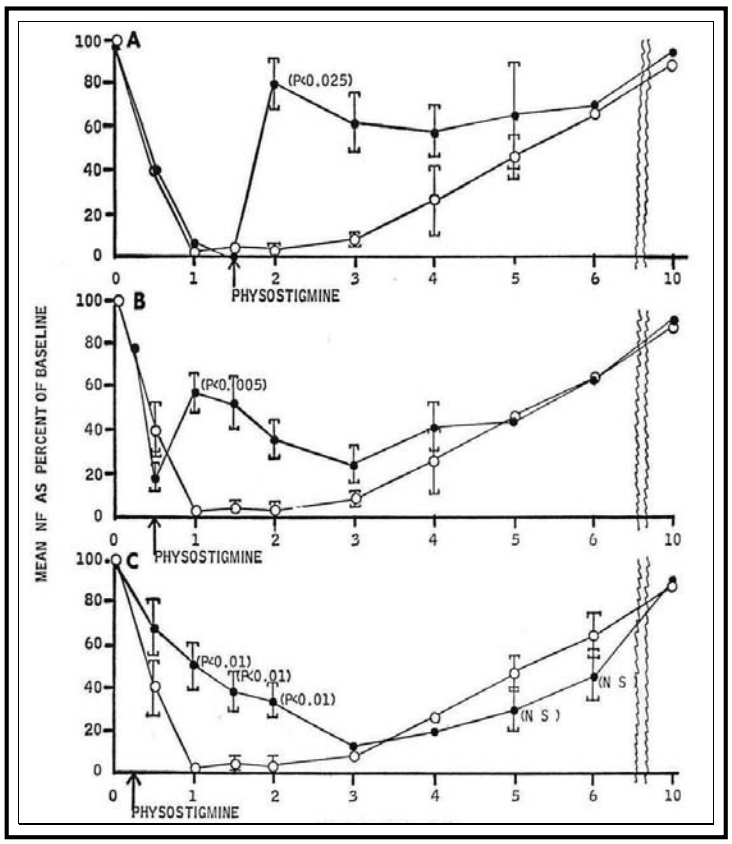


Fig. 69. Scopolamine: Effectiveness of physostigmine treatment (open circles represent placebo effect)

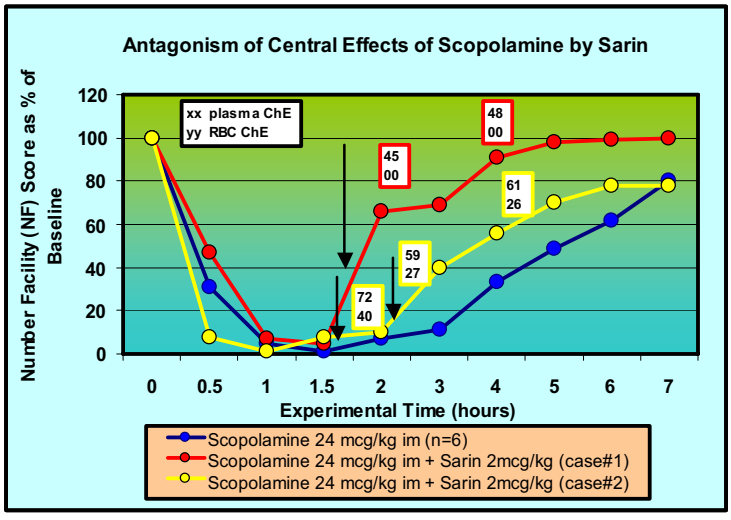


Fig. 70 Scopolamine: Effectiveness of sarin treatment

The above-mentioned relative ineffectiveness of THA during the onset phase of scopolamine also occurred when physostigmine was given before peak effects. We first reported this early lack of effect of physostigmine in 1967, demonstrating its ability to reverse scopolamine delirium under double-blind controlled conditions (Fig. 69). We have, however, yet to hear an explanation of this phenomenon (which also occurs with BZ and other belladonnoids).

As shown here, when given at 30 minutes, physostigmine has little effect, but once the maximum effects of scopolamine are reached, it becomes highly effective as an antagonist. When given at 15 minutes (3rd panel) it is even less effective. Note that during the recovery phase, subjects given physostigmine at 15 min, did not respond as dramatically at first and produced significantly lower scores during the recovery phase. Nevertheless, full recovery was achieved at 10 hours in all three treated groups.

The effectiveness of non-lethal doses of agent sarin, a strong inhibitor of both RBC (true) and plasma (pseudo) cholinesterase, was impressive (Fig. 70). In two subjects who were treated with the same dose of sarin, however, the benefit was greater in one (red) than the other (yellow). Differences in RBC cholinesterase inhibition may explain this disparity. In studies by Drs. Sidell and Aghajanian,[31] levels of plasma cholinesterase were sometimes reduced almost to zero by sarin, without producing clinical signs of toxicity (note reversal in upper legend, which has plasma as "xx" and RBC as "yy").

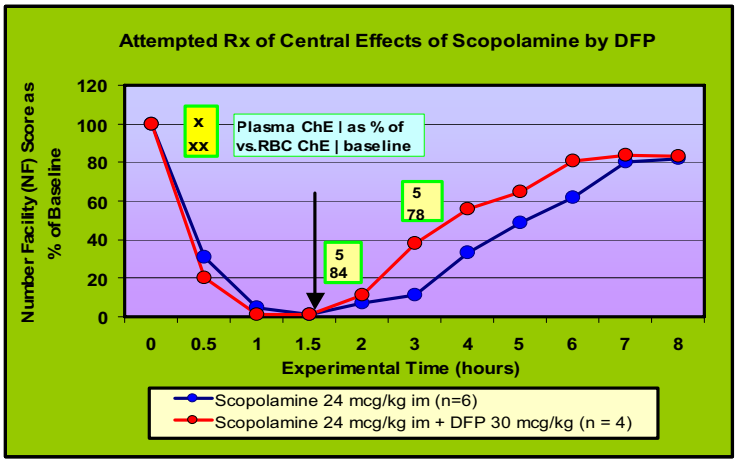


Fig. 71. Scopolamine: Minimal response to DFP treatment

As an inhibitor of plasma (pseudo) cholinesterase, DFP produced only minimal reversal of scopolamine-induced incapacitation.[32] Note the very low plasma ChE levels, with only minor decreases in RBC ChE (Fig. 71). DFP does improve near vision when applied to the eye (David Harper, unpublished data) suggesting that paralysis of the muscles of visual accommodation is probably peripheral in origin. Persistence of pupillary enlargement (in the face of systemic treatment with physostigmine) may be due to physiological or pK factors, causing limited access to the iris.

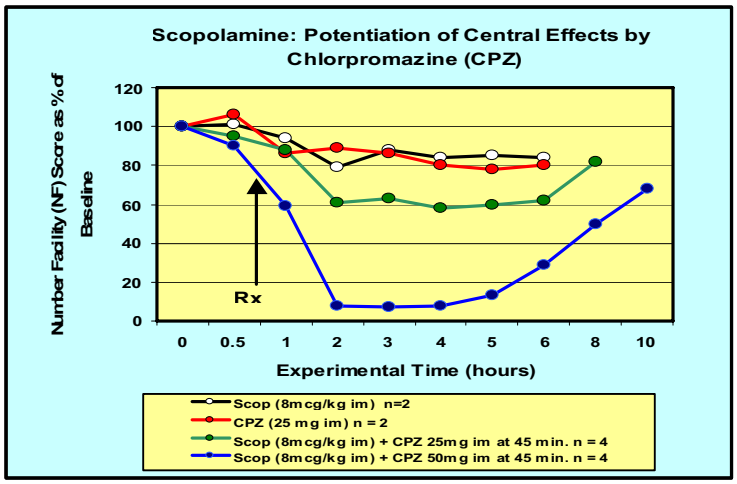


Fig. 72 Scopolamine: Thorazine increases performance decrement

Because chlorpromazine (CPZ, aka Thorazine) had commonly been used clinically to treat belladonna-induced delirium, George Aghajanian[33] tested its effectiveness in reversing cognitive impairment in NF% scores when given in doses of either 25 or 50 mg of Thorazine at 45 minutes (Fig. 72). Decrements in NF% scores were actually increased by chlorpromazine – clearly an adverse effect on cognitive function rather than a beneficial one.

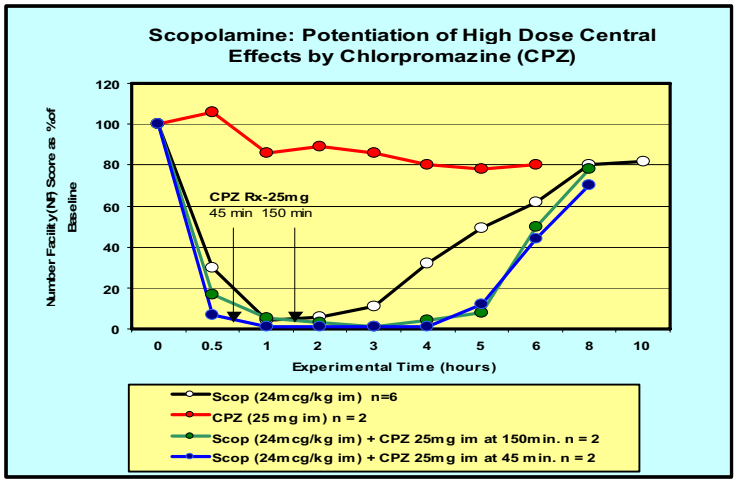


Fig. 73 Scopolamine: Minimal benefit from treatment with Thorazine

Although 25 mg of chlorpromazine alone caused only mild impairment of NF scores, it clearly prolonged the incapacitation produced by 24 mcg/kg of scopolamine – slightly higher than the ID_{50} (Fig. 73). Partial recovery time (the time at which the ID_{50} returns to above 75% of baseline) was not delayed, but duration of severe effects was almost two hours longer. No doubt, CPZ's popularity in the emergency room is related mainly to its ability to decrease delirious hyperactivity (a practical benefit for the attending physician).

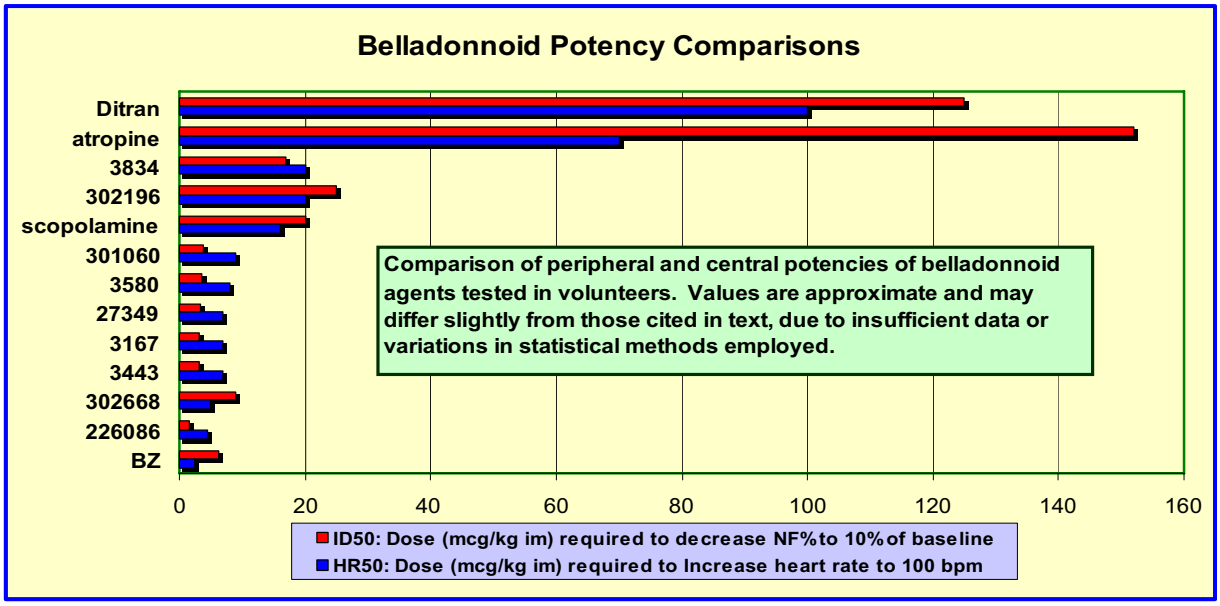


Fig. 74. Relative central potencies of the belladonnoids (including six compounds not described in detail in this appendix due to limited testing and, therefore, insufficient quantitative data).

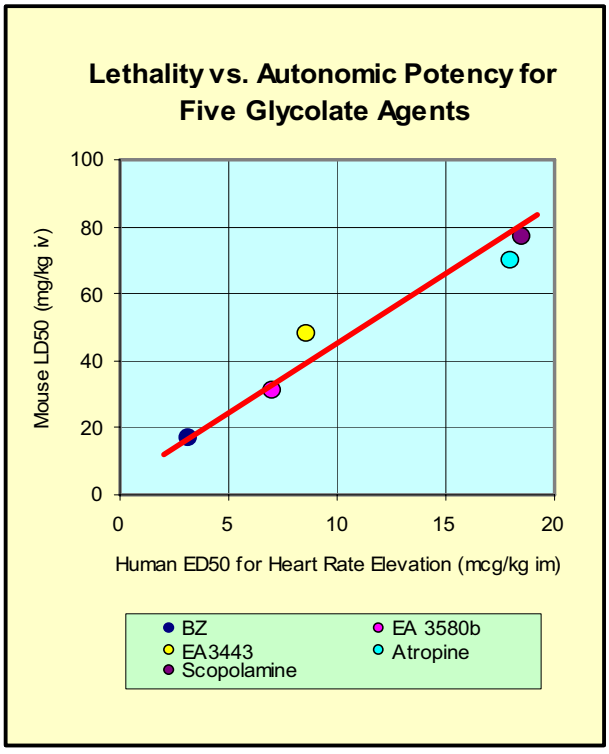


Fig. 75 Human HR_{50} vs. LD_{50} in the mouse

As shown in Fig. 74, belladonnoids vary greatly in both their relative peripheral and central potencies.[34] BZ is approximately 7x as potent as atropine, while 302196 is about 40% less potent than atropine. The peripheral potencies of 27349, 302282, 3443, 302668, 3443, 3580, 226086 and 3167 (Fig. 74) fall between 20% and 60% of BZ's potency in terms of their tendency to produce elevation of heart rate and blood pressure.

Several of these compounds, on the other hand, show greater central potency than BZ (Fig. 74). Higher potency is present in EA 3167, EA 3443, EA 3580 and possibly the less thoroughly studied 302282 and 226086. A high absolute central potency, combined with high central to peripheral potency ratio produces a belladonnoid that has both low dose requirements and a high safety margin (therapeutic index). Such compounds would presumably be safer and more effective than BZ.

Figure 75 indicates the linear relationship between the LD_{50} in the mouse and the HR_{50} (average dose sufficient to raise the human heart rate to 100 beats per minute).[35] Only five belladonnoids are shown because of insufficient data for the other agents. It seems clear, however, that the linear relationship supports the hypothesis that the mechanism of lethality is peripheral (cardiac) in man as well as in other animals. Estimating the lethality of various belladonnoid compounds, however, requires certain assumptions. Although civilian physicians have reported treating organophosphate poisoning safely with very high doses of atropine (more than 3,000 mg in 48 hours in one severely poisoned child[36] and survival of a 1,000 mg dose by an enlisted man,[37]) the lethal

dose, when unopposed by a cholinesterase inhibitor, is not known with certainty. Textbooks of pharmacology generally estimate the LD_{50} to be about 100 mg, sometimes even less. Epidemiological and clinical reports vary wildly – some suggest 10 mg as the lethal dose in a child, but many times this amount in adults. Fortunately, we have the benefit of Goodman's exhaustive compilations, based to a large extent on case reports published in the 19th and early 20th century.

Goodman cautioned that there are statistical problems when relying on such sources, since they may be heavily weighted toward extreme cases – unexpected deaths from low doses, or remarkable recoveries from unusually high doses. He noted that even when large series were used, they suffer from a lack of precise knowledge of the dosage. In four independent series of datura poisoning in India during the latter half of the 19th century, for example, the death rate was 14.9 per cent.[38, 39, 40] One might assume that such cases received comparable standards of medical care in other countries.. But among 35 Hungarian overdose cases treated between 1930 and 1932 all survived.[41] Moreover, among 63 cases collected in Hungary between 1900 and 1905, only 3.2% (i.e., 2 cases) died. Other mortality rates varied from 1.96% of 51 cases to 22.8% of 92 cases. Major differences in diagnosis, severity of intoxication or adequacy of treatment must have been present.

In some larger series, the number of deaths reported was more consistent. Peterson and associates[42] found a mortality rate of 9.46% of 973 cases of belladonna poisoning, while Webster[43] cites a rate of 10.54% among 1063 cases.

In Tables 10 and 11, meta-analyses based on 576 cases gleaned by Goodman from a number of reports, there are only moderate variations in mortality among cases grouped by route of administration or by age. Using chi-square analysis, Goodman found no statistically significant age-related differences in susceptibility to the lethal effects of atropine.

DESCRIPTIVE STATISTICS OF CASES OF INTOXICATION WITH SOLANACEAE (BY ROUTE)

Route	N	Mortality
Opthalmological	88	5.68
Oral medicinal products	126	10.32
Oral plant materials	249	7.63
Parenteral	49	4.08
Percutaneous	45	2.22
Other	19	0.00
TOTALS	**576**	**Mean = 6.94%**

Table 10 Deaths from Solanaceae by route

AGE AND MORTALITY RATE WITH SOLANACEAE

Age in years	N	Mortality %
0-5	98	11.22
6-15	86	5.81
16-40	194	6.70
40-50	86	4.65
51-60	78	5.13
61 and over	34	8.82
TOTAL	**576**	**Combined = 6.94%**

Table 11 Deaths from Solanaceae by age

These statistics tends to belie the notion that children and the elderly, although somewhat more vulnerable, are extremely more likely to succumb to overdose. None of these data clearly establish the $LD_{50,}$ however, which is required to estimate the therapeutic ratio (LD_{50}/ID_{50}) for atropine. This ratio is an important key to making reasonable estimates of lethality for the other belladonnoids, since there are no BZ deaths (for example) from known dosage on which to base such estimates.

Goodman noted that the usual textbook estimates of the lethal dose of atropine (and scopolamine) are undoubtedly too low. With respect to scopolamine, for example, he found 9 cases that survived scopolamine doses of 225-267 mg, 3 cases that survived 324-384 mg and 2 who survived 500 mg.[44]. (Abood also reported personal observation of two recoveries from large oral doses of scopolamine: 350 mg and 500 mg, respectively.) These doses are close to the highest reported lethal range for atropine. Since scopolamine has about 7x the potency of atropine centrally, but roughly equal potency peripherally, one can infer that death from belladonnoid drugs is probably due to a peripheral effect – most likely cardiotoxicity.

When he converted doses in children to equivalent adult doses (based on body weight), Goodman found a dozen cases of children surviving weight-adjusted doses ranging from 112 to 1190 mg. This again suggests that, on a per kilogram basis, children are not appreciably more susceptible to high doses of atropine than adults, challenging the conventional medical opinion that children are especially sensitive to this drug. One source on the Internet stated that 10 mg was the lethal dose in children. Yet, among a group of 13 children who (presumably in error) received 13 mg of atropine in the form of eye drops, all became delirious but all survived (Goodman, E: unpublished monograph, 1962).

Of course, none of these data precisely establish the $LD_{50,}$ which is needed to estimate the therapeutic ratio (LD_{50}/ID_{50}). Nevertheless, extrapolation of the approximate therapeutic ratio for atropine (while also taking into account that lethality among the glycolates is proportional to their peripheral potency) provides the most feasible way to estimate the LD_{50} for the other belladonnoids (none of which have been known to have caused death in humans).

Lethal Dose Estimates for Atropine in an adult population

Percentage Deaths	Lethal Dose (mg)	95% confidence limits (mg)
1	23	13-40
16	127	96-167
30	232	181-297
50	453	335-612
84	1621	963-2729

Table 12 Lethality dose estimates for atropine derived from probit analysis

Using only lethalities among individuals who had received known oral doses of atropine of at least 30 mg (86 cases), Goodman created a table of probabilities of lethality at various dose levels, using probit analysis to produce the values and confidence limits for the LD_1, LD_{16}, LD_{30}, LD_{50} and $LD_{84.}$ (Table 12) It is difficult to be fully confident of the reliability of these values, since there is no guarantee that they are truly representative of the actual distribution of dosage among a population exposed to a cloud of a glycolate agent coming from a single munition. The dispersal of material from a point source (e.g., a single bomblet) would theoretically result in a Gaussian logarithmic distribution of dosage. The additional effects of wind, weather, terrain and many other factors, however, would add further uncertainty and a widening of the range of actual dosage.

Goodman's literature review and analysis appears, however, to provide the best available LD_{50} estimate for atropine, since it is based on the actual outcomes of known doses. He excluded from his analysis the few reported cases in which death occurred after less than 30 mg of atropine (e.g. 3 mg). He assumed that deaths following such low doses were probably the result of complications, including, for example, hyperpyrexia due to an excessively warm environment and/or underlying medical illnesses.

Thus, mortality estimates from belladonnoid poisoning, based on hospitalized cases alone, do not permit reliable estimation of actual mortality in a combat setting. As mentioned, over-heating, especially in warm climates, would be a major consideration. Soldiers wearing heavy gear, in a desert setting, would be particularly vulnerable to death by heatstroke, even after absorbing relatively small doses of a belladonnoid agent. Accordingly, immediate cooling is probably as

important as treatment with physostigmine in preventing such deaths. Some fatalities and serious injuries must also be expected as the result of disorganized behavior. In a heterogeneous civilian population, underlying illnesses, especially cardiac, would also pose additional risks. Prompt treatment, on the other hand, could prevent most belladonnoid-induced deaths. Goodman noted that some of the fatalities following large overdoses did not occur until 18 hours or more after ingestion. This suggests that an antidote, even if delayed by several hours, may still be life-saving.

If the LD_{50} for atropine (route unspecified) is approximately 450mg and if the incapacitating dose (ID_{50}) for intramuscular atropine is approximately 10-12 mg in the average adult, , a safety ratio of about 40 (450mg/10-12mg) would seem to be a conservative estimate. Furthermore, since BZ has a central to peripheral potency ratio greater than that of atropine, an estimate of 40 as the safety factor for BZ is probably quite conservative.

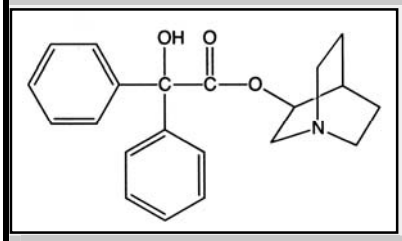
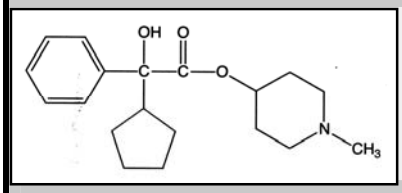
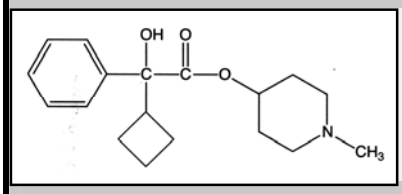
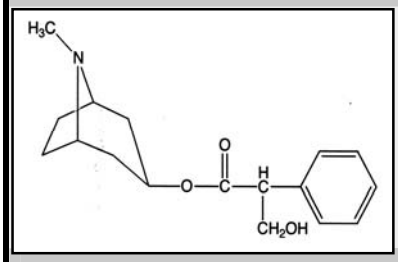
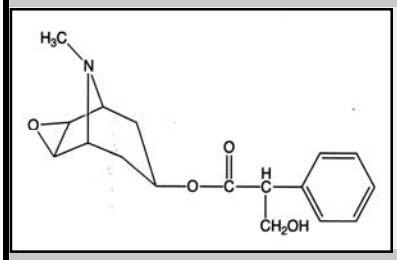
We used an additional analysis to support the estimated LD_{50}/ID_{50} ratio for BZ. Upon reviewing the LD_{50} of several glycolates in the mouse, it appeared that the lethality of each closely paralleled its peripheral (as reflected in heart rate changes) rather than central effects (as reflected in performance decrements).[45] This calls into doubt the opinion, voiced in previous textbooks of pharmacology, that death from belladonnoids such as atropine results from respiratory paralysis – primarily a central nervous system effect.

Based on all the above observations, we concluded that peripheral effects on the heart predict the lethal dose for belladonnoids better than do their central effects. This was apparently the case in animals such as the mouse, for which the LD_{50} had been previously established by direct measurement. EA 3443 and EA 3580, both of which have greater relative central potency in man than BZ, also were found to have higher safety margins in the mouse (and other species).

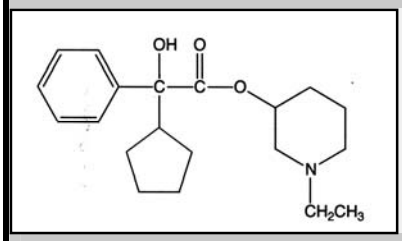
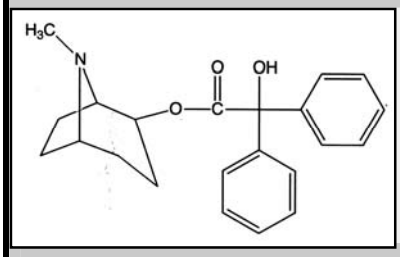
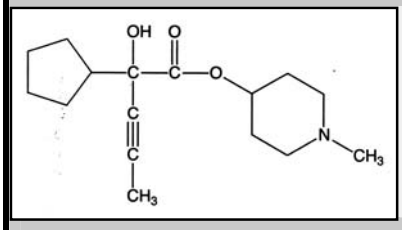
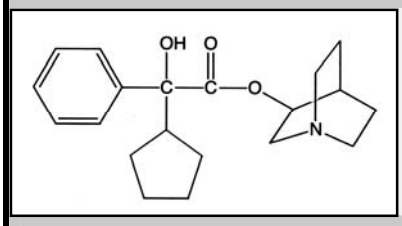
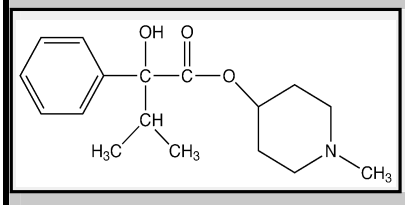
This establishes, by analogy, a high therapeutic ratio for such compounds as 3167, 3443, 3580 as well as the less thoroughly studied 302282 and 226086. A high relative central to peripheral potency, combined with high absolute central potency produces a belladonnoid that has both low dose requirements and a high safety margin (therapeutic index). These compounds, consequently, would seem to be both safer and more effective than BZ.

* * * * *

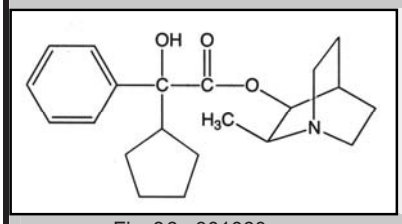
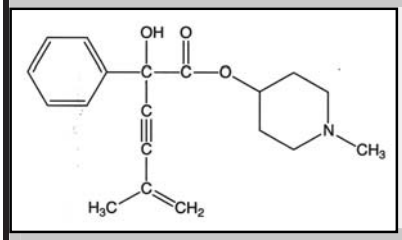
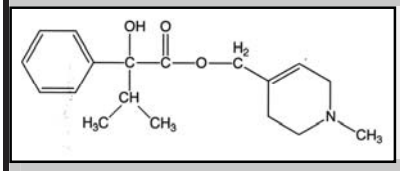
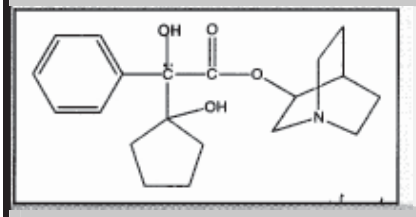
STUCTURES AND NAMES OF BELLADONNOIDS STUDIED

STRUCTURES	NAMES AND PARAMETERS
 Fig. 76 – BZ	**BZ**[46, 47, 48, 49] Chemical name: 3-quinuclidinyl Benzilate (QNB) MED_{50} 2.3 mcg/kg ID_{50} 6.2 mcg/kg LD_{50} ~ 250 mcg/kg D_{50} 48-72 hr C/P ratio ~ 0.5
 Fig. 77 – EA 3443	**EA 3443**[50, 51] Chemical name: N-methyl-4-piperidinyl α-cyclopentylphenylglycolate MED_{50} 1.2 mcg/kg ID_{50} 3.4 mcg/kg LD_{50} ~ 350 mcg/kg D_{50} 16-24 hr C/P ratio ~ 2.0
 Fig. 78 – EA 3580	**EA 3580**[52, 53, 54] Chemical name: N-methyl-4-piperidinyl α-cyclobutylphenylglycolate MED_{50} 1.4 mcg/kg ID_{50} 3.9 mcg/kg LD_{50} ~ 400 mcg/kg D_{50} 16-24 hr C/P ratio ~ 2.0
 Fig. 79 - Atropine	**Atropine**[55, 56] Chemical name: dl-tropyl tropate MED_{50} 63 mcg/kg ID_{50} 152 mcg/kg LD_{50} ~ 6,000 mcg/kg D_{50} 8-12 hr C/P ratio ~ 0.25
 Fig. 80 – Scopolamine	**Scopolamine**[57, 58] Chemical name: 6,7 epoxytropine tropate MED_{50} 9.4 mcg/kg ID_{50} 20.2 mcg/kg $LD/_{50}$ ~ 4,000 mcg/kg D_{50} 5-10 hr C/P ratio ~ 1.6

STUCTURES AND NAMES OF BELLADONNOIDS STUDIED (2)

STRUCTURES	NAMES AND PARAMETERS
 Fig. 81 - Ditran	**Ditran (JB-329)[59, 60]** Chemical name: 1-ethyl-3-piperidinyl-α-cyclopentyl phenylglycolate (a 70-30 mixture of this and its pyrrodinyl analogue) MED_{50} ~ 4.0 mcg/kg ID_{50} ~ 10.0 mcg/kg LD_{50} ~ 700 mcg/kg D_{50} 20-28 hr C/P ratio ~ 0.6
 Fig. 82 – CS 27349	**CS 27349[61]** Chemical name: Benzilic acid, 2α-tropanyl ester MED_{50} 1.2 mcg/kg ID_{50} 3.4 mcg/kg LD_{50} ~ 350 mcg/kg D_{50} 48-72 hr C/P ratio ~ 2.0
 Fig. 83 – 302196	**302196[62]** Chemical name: N-methyl-4-piperidynyl α-propynyl-cyclopentylglycolate MED_{50} ~ 12 mcg/kg ID_{50} ~ 29 mcg/kg LD_{50} ~ 2,000 mcg/kg D_{50} 20-28 hr C/P ratio ~ 0.8
 Fig. 84 – EA 3167	**EA 3167[63, 64]** Chemical name: 3-quinuclidinyl Phenylcyclopentylglycolate MED_{50} 2.8 mcg/kg ID_{50} 4.1 mcg/kg LD_{50} ~ 120 mcg/kg D_{50} 8-12 hr C/P ratio ~ 2.0
 Fig. 85 – EA 3834	**EA 3834[65, 66, 67]** Chemical name: N-methyl-4-piperidinyl α-isopropylphenylglycolate MED_{50} ~ 5.0 mcg/kg ID_{50} ~ 12 mcg/kg LD_{50} ~ 400 mcg/kg D_{50} 12-15 hr C/P ratio ~ 1.2

STUCTURES AND NAMES OF BELLADONNOIDS STUDIED (3)

STRUCTURES	NAMES AND PARAMETERS
 Fig. 86 - 301060	**301060**[68] Chemical name: cis-2-Methyl-3-quinuclidinyl phenylcyclopentylglycolate MED_{50} 3.0 mcg/kg ID_{50} ~ 6.0 mcg/kg LD_{50} ~ 150 mcg/kg D_{50} 48-72 hr C/P ratio ~ 2.0
 Fig.87 – 302282	**302282**[69, 70] Chemical name: N-Methyl-4-piperidyl α-(3-methyl-3-buten-1-ynyl) phenylglycolate MED_{50} 1.2 mcg/kg ID_{50} 3.4 mcg/kg LD_{50} ~ 600 mcg/kg D_{50} ~ 6-10 hr C/P ratio ~ 2.0
 Fig. 88 – 302668	**302668**[71, 72, 73, 74] Chemical name: [1-methyl-1,2,3,6-tetrahydro-4-pyriidinyl) methyl α-isopropylmandelate] MED_{50} 4.0 mcg/kg ID_{50} 8.9 mcg/kg LD_{50} 500 mcg/kg D_{50} 16-24 hr C/P ratio ~ 1.6
 Fig. 89 - 226086	**226086**[75, 76] Chemical name: L-2-α-Tropanyl L-cyclopentylphenylglycolate MED_{50} 1.5 mcg/kg ID_{50} 1~ 2.0 mcg/kg LD_{50} ~ 30 mcg/kg D_{50} 8-12 hr C/P ratio ~ 2.4

Special thanks to Dr. A.T. Shulgin, who provided drawings of the chemical structures as well as verifying the accuracies and (in some cases) providing alternate names for the Edgewood Arsenal belladonnoid compounds shown above.

LSD

The Army's interest in LSD (Fig. 90) was high at first, spurred by Major General Creasy's persuasive presentation to Congress in 1957, as discussed earlier in the book. Before 1961, most of the Army testing was carried out by Van Sim and colleagues.[77]

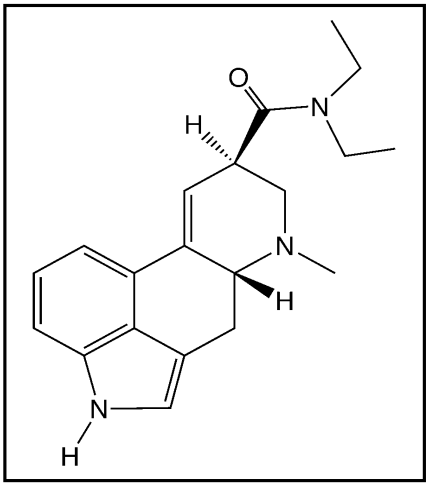


Fig. 90 Structure of LSD

Although a vast literature exists on the subjective effects of LSD,[78, 79, 80, 81] relatively little systematic testing of performance over a range of LSD dosage and throughout the duration of its action had been reported. We therefore undertook studies that would reveal the dose-response relationship with more precision, initially by the oral route and later by intravenous or inhalation routes of administration. A total of approximately 100 subjects were tested between 1961 and 1966, at which time work with LSD was terminated in accordance with new legislation, as well as increasing public concern. Doses of 0.5 mcg/kg were used in a few subjects in 1961, but details of those data were not available while preparing this book. In 1964, however, in the course of testing chess-playing performance, NF scores were obtained at hourly intervals (Fig. 91).

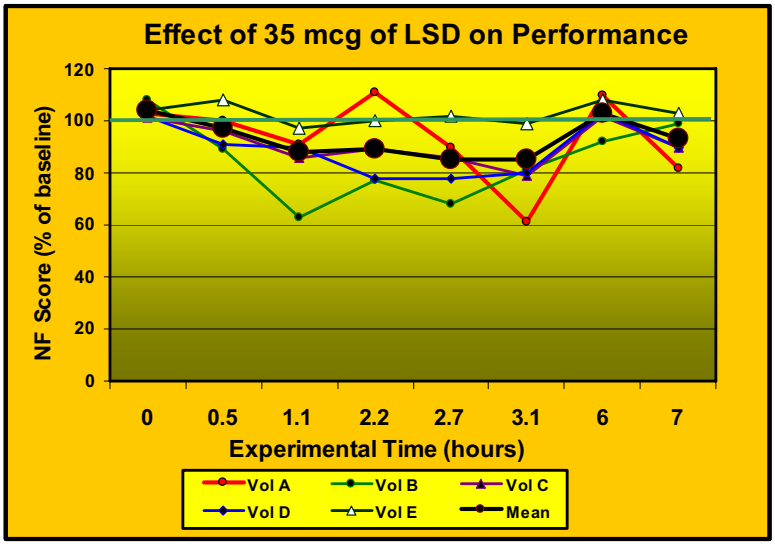


Fig. 91 LSD: Effect on NF scores after 35 mcg by the oral route.

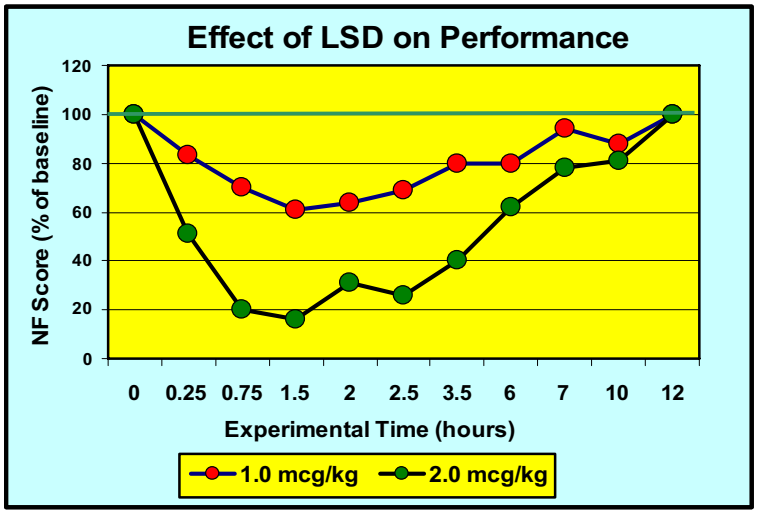


Fig. 92 LSD: Effect on NF performance of oral doses of 1.0 and 2.0 mcg/kg

Fixed oral doses of 35 mcg were used. It is apparent that at this dose, average percent decrement did not exceed 20%. Major Charles Wickstrom had trained the volunteers to play lightning chess and noted only a slight loss of skill at this dose level.[82]

Administration of oral LSD in doses of 1.0 and 2.0 mcg/kg had dose-related effects on NF scores (Fig. 92). Variation in individual response to LSD exceeded variation observed with belladonnoids. On average, however, it is obvious that the larger dose produced scores close to the incapacitating level (ID_{50}), while the 1.0 mcg/kg dose produced scores close to the MED_{50} level (six subjects at each dose). Later, aerosol administration revealed that inhalation effects were only about 30% as great as by the oral route.

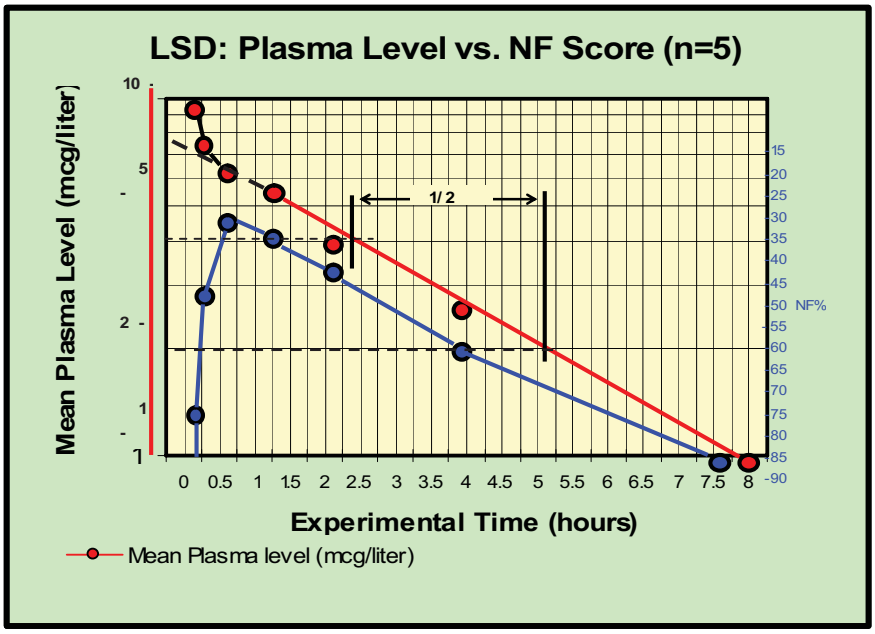


Figure 93 LSD: Estimate of plasma half-life using graphic method (n=5)

In early 1963, George Aghajanian and Oscar Bing developed the first reliable assay method for measuring LSD plasma levels, using spectrophotoflurometry. In their 1964 publication,[83] two axes are used to highlight the parallelism between plasma level of LSD and performance decrement (Fig. 93). A logarithmic y-scale reveals an exponential (first order kinetics) elimination rate. NF scores are on the second y-axis (right), inverted to make the correlation easier to visualize. Following the first 30 minutes, during which the intravenous dose (2 mcg/kg) was equilibrating between the CNS and peripheral compartments, the plasma level declined from about 7 ng/ml to about 4 ng/ml. Thereafter, levels followed a logarithmic decay curve. LSD's plasma half-life, estimated graphically, was approximately 175 min.

Using additional data obtained from subjects given LSD by the inhalation route (n=40), we recently calculated the half-life again (Fig 94). The decrease in the median plasma level between one and two hours was extrapolated to indicate the time at which plasma levels would decline to half the median value at one hour. The approximate half-life by this method is about 160 minutes,[84] in good agreement with the estimate calculated by Aghajanian and Bing. Other investigators have reported other half-life values somewhat higher or lower than these estimates.

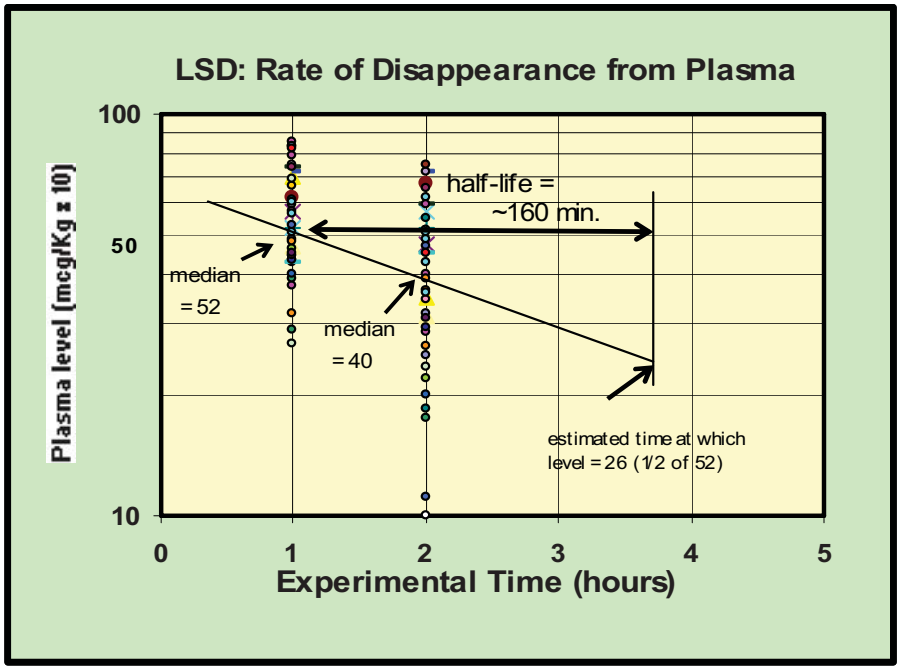


Fig. 94 – LSD: Replication of Aghajanian and Bing's half-life estimate using inhalation plasma levels (n=40)

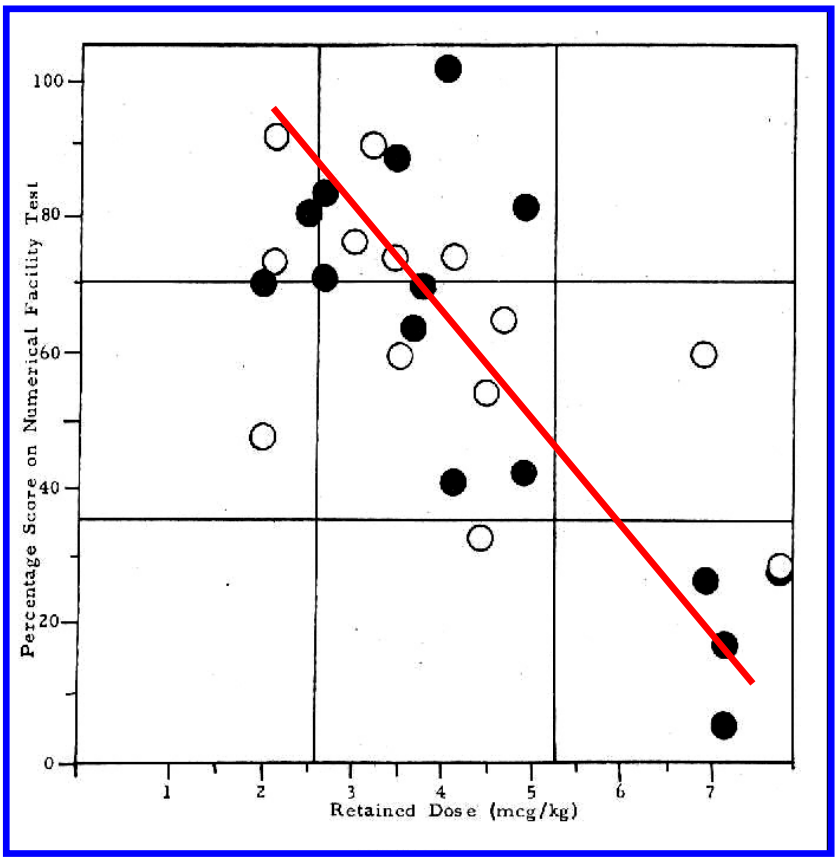


Fig.95 LSD: NF% scores vs. retained inhalation dose

Since LSD would be released as an aerosol if used in a military setting, we devoted considerable effort to estimating its relative potency by the inhalation route.[85] Two forms of the drug: the maleate salt (black circles) and the free base (white) were compared (Fig. 95). There appeared to be no difference between the two salts in their effects on NF performance.

LSD appears to have an extremely high safety margin. Tim Scully reports (personal communication) survival after an accidental overdose of 100 mg in one individual (who thought she was snorting cocaine) and another who consumed 50-75 mg by mouth. Both recovered fully.

Retention of aerosolized LSD, based on more than 50 exposures in 36 volunteers, was roughly equal for the maleate and free base forms of LSD (Fig. 96). The maleate, however, was slightly irritating to the respiratory tract, causing some mild coughing

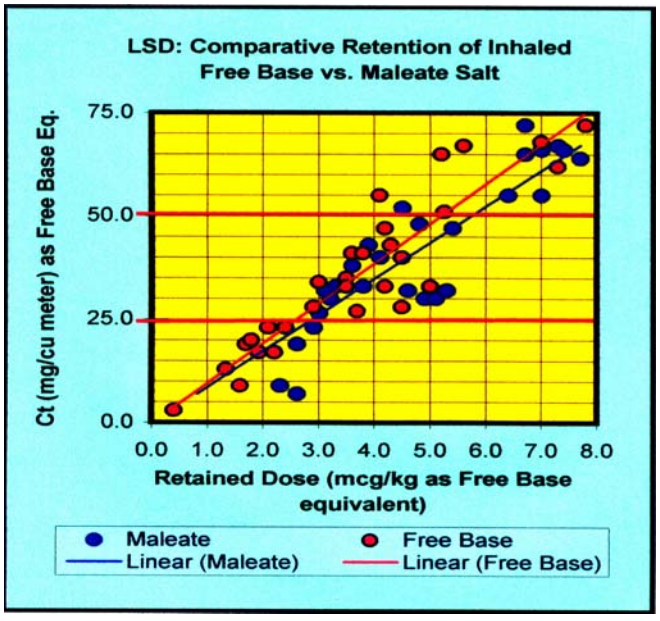


Fig. 96 LSD: Similar retention of maleate and free base

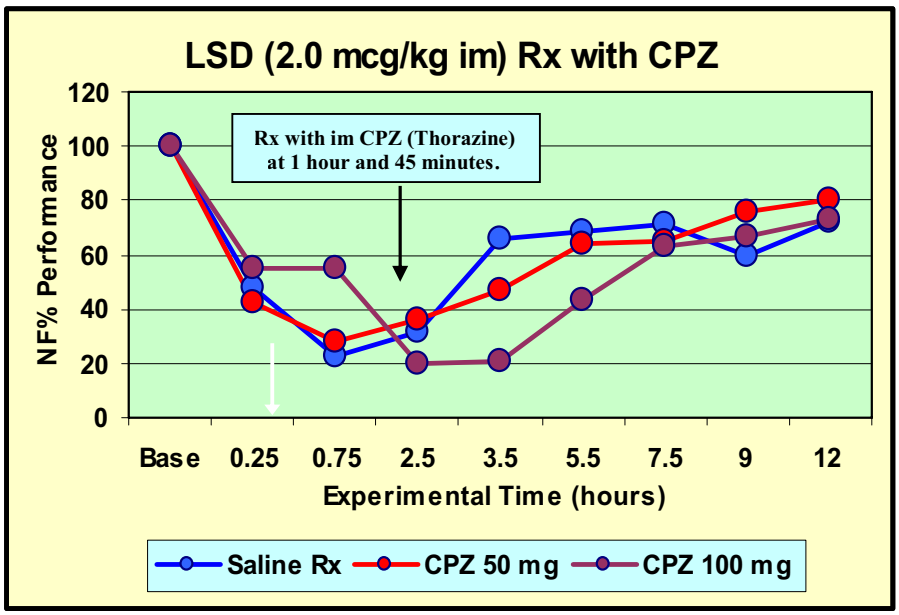


Fig. 97 LSD: Minimal benefit produced by Thorazine treatment

In order to estimate the relative effectiveness of the inhalation route, regression lines were drawn through dose-response values for both the oral route and the inhalation route, and the ratio of the dose values at which the two regression lines crossed the 20% performance line (an arbitrary choice) was calculated (Fig. 98). The ratio of the two slopes indicates that 3.75 times as large an aerosol dose would be needed to equal the effect of LSD given by the oral route, i.e., relative effectiveness equals ~ 28%.

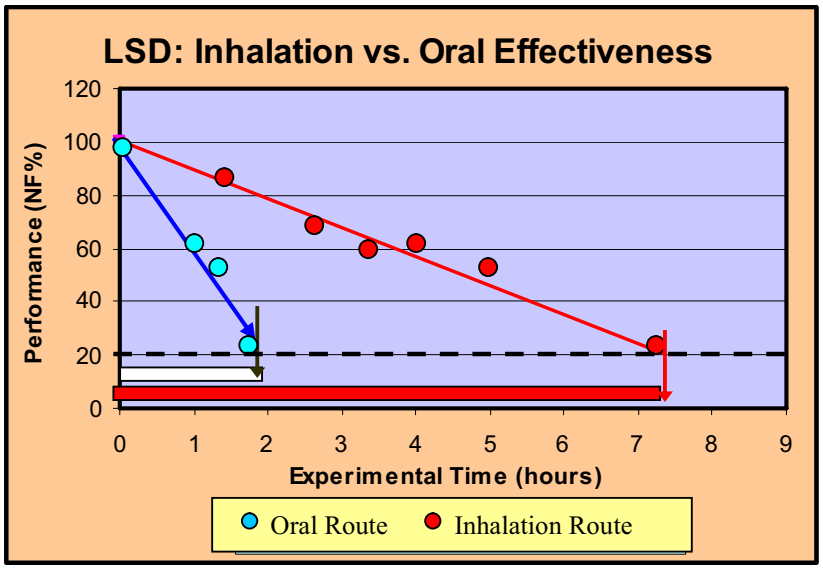


Fig. 98 Graphic method of estimating oral vs. inhalation effectiveness

Thorazine (CPZ) treatment proved to be only minimally effective when given at 1:45 hours after administration of 2.0 mcg/kg of LSD[86] (Fig. 97).

Thorazine was usually the therapy of choice at that time. Later, diazepam (Valium) and other benzodiazepines such as lorazepam (Ativan) became more widely used. These tranquilizers evoked fewer complaints such as "I feel like LSD on the inside and Thorazine on the outside" sometimes voiced by patients treated with chlorpromazine.

.

Dr. Harold Abramson, under a contract with the CIA in 1954, had reached a similar conclusion from a preliminary trial with four subjects. Based on his clinical judgment of response intensity, he estimated the inhalation dose to be only about one-third as effective as the same oral dose. In 1966, he gave me a hand-typed draft CIA report he had never published. The ingenuity of the technique he describes, using a rudimentary aerosol chamber, is evident in the report, which is provided on the following pages.

PRELIMINARY DATA ON LSD AEROSOLS

(1958 draft report by Harold Abramson, M.D. – never published)

Since July 1956, attempts have been made to predict the behavior of man in a chamber containing nebulized LSD. Some modifications in the technique of delivering the aerosol have been made. In general, the same questionnaire technique of scoring the response that has been previously used for LSD was employed. The questionnaire had two categories of questions: (a) 47 questions which are put directly to the subject; (b) nine questions which are rated qualitatively by both subject and observer. A trained group of five adult subjects, all placebo negative reactors, was employed. Table I is a copy of the questionnaire [note: tables and figures were not provided.]

Historical

The first aerosol experiments in this series utilizing quantitative techniques were performed by the writer in 1954. Two types of delivery were employed: (a) powdered LSD diluted with talc, administered by means of a simple inertia device (Fig. 1a); (b) aqueous solutions of LSD administered intranasally by means of the nebulizer illustrated in Fig. 1b. When a talc-LSD powder was administered intranasally, very severe reactions occurred rapidly. With a maximum dose of 256 mcg delivered intranasally in the form of LSD-talc powder, subject J.M. had a most severe reaction, withdrawing to one part of my home in which the experiment took place and refusing to cooperate in his usual fashion. The data on Subject J.M. in this experiment are available. In order to study liquid aerosols, aqueous solutions of LSD-25 were administered intranasally to Subject J.M. The questionnaire was again used to estimate the severity of the reaction. The following technique of comparison was employed.

Two variables, the concentration of LSD-25 in the nebulizer and the inspiration time were varied. Experiments indicated that this technique of changing the response in this type of experiment has some validity. Table II summarizes the experiments. These preliminary experiments indicated to the writer that the response of a well-tested subject was fairly regular since with a given dose of 40,000 mcg-seconds (calculated administration of 56 mcg) severe psychological changes were regularly obtained independent of the time of administration between 4 and 400 seconds. Within the limits of error, there was no important difference between the 4-second and 400-second reaction.

It seemed that the reaction appeared to set in more rapidly and was over more quickly with intranasal administration than orally administered LSD-25, thus approximating an intravenous injection.

Methods

The present experimental project was begun in the summer of 1956. A complete shift in the nature of the project necessitated starting from the beginning with the construction of a chamber, calibration of all equipment, and organizing an aerosol project on a quantitative level both chemically and psychiatrically. It cannot be overemphasized that the study of aerosols without tested placebo negative subjects is apt to be very misleading.

For this reason it is emphasized that all future work, which will form a basis for a psychological reaction to the drug itself, be carried out with only placebo negative subjects. It is well known that people will volunteer as subjects for application of irritant substances to the skin without building up many anxieties in themselves. However, very few people like to breathe in toxic agents.

Aerosol Chamber

The chamber was approximately cubical, volume 8.2 cubic meters, and was built into a larger room of the laboratory at Cold Spring Harbor. The window and door were on the same side. A 75-watt flood light illuminated the interior from without. Aluminum foil covered the ceiling.

Nebulizer

The nebulizer was constructed identically with the De Vilbiss nebulizer illustrated in Fig.1b. However, it was an especially large model with a capacity of 50 mg. This nebulizer was chosen because (a) at least 5 ml was the volume utilized in the initial experiments, and (b) a vertical nebulizer

was deemed more practical even though certain advantages as far as particle size were offered by the horizontal Vaponephrin nebulizer.

All the experiments were conducted at the lowest volume velocity of compressed air that would generate a suitable mist. The volume velocity was 5.7 liters per minute. The flow meter reading was 6 liters per minute. A horizontal glass trap 37.5 inches long connected the nebulizer with the interior of the chamber. The internal diameter of the trap was approximately equal to that of the nebulizer output tube (approximately 5/8" internal diameter). The orifice of the trap was flush with the inside wall of the chamber.

Sampling

Four samplers of the bubbler type calibrated for 20 ml of liquid in each were operated at 13.1 liters per minute for the first minute. After the first minute was completed, the volume velocity for the second minute was 14.1 liters per minute. The four samplers were distributed as follows: three were approximately at the nose-level of a person seated in the chamber; the fourth sampler was suspended from the roof at the geometric center of the chamber quite close to the head of the person seated in the chamber.

Calibration of the Chamber

The dye, phenolsulfonphthalein (PSP), was used to determine concentration and distribution of mist in the air of the chamber by means of the samplers. This also indirectly determined the distribution of aerosol in the chamber. By using very large sheets of cellulose acetate, it was possible to study the distribution of fallout and impingement in the chamber quite accurately, determining PSP colorometrically. The calibration of the chamber was accomplished by means of a checklist and data of the type illustrated in Table III.

Stability of LSD Aerosols

With the use of Siamese fighting fish it was determined that nebulization of LSD-25 with compressed air under our conditions for 10 to 20 minutes did not destroy appreciable quantities of LSD-25. This was also true for the fallout and impingement droplets, although further experiments might be desirable on this point, since the nature of the surface and the intensity of illumination are limited in this study. The effect of tobacco smoke has not been ascertained.

A typical experiment relating to stability is that of April 2, 1957. Five ml of 1% LSD-25 (5.0 mg of LSD, the equivalent of 500 100 mcg oral doses) was nebulized for 10 minutes. On the basis of previous data with PSP, it was estimated that 15 mg of LSD entered the chamber. The samplers were run so that 100 mcg of LSD-25 should have been collected from 218 liters of air. It was concluded from this experiment that, at the end of 10 minutes of nebulization about 0.5 mcg of LSD per liter was present in the air, on the average.

Three large acetate sheets were placed on the walls and floor of the chamber. The material washed from these sheets showed suitable LSD activity by means of bioassay so that it seemed likely that there was little loss of activity during a two-hour fallout under our conditions. Table IV illustrates the type of experiments and the limits of error studying the material obtained in the samplers after nebulizing LSD solutions so that a total of approximately 100 mcg should have been collected (i.e., actual amount inhaled).

Fallout

Theoretically, the extrapolation from PSP to LSD as far as fallout is concerned is complicated slightly by the difference in molecular weights. The rate of evaporation of the small droplets can be very rapid as the surface curvature increases. The smaller the molecular weight of the dissolved molecule, the greater the number of particles for a given number of grams per milliliter. It has been assumed that this error is not significant at this point in our experimental framework.

Present experiments indicate that a good deal of fallout or impingement occurs even though the trap takes out the larger particles. Thus, in an experiment in which 54% of the inside area of the chamber was covered, 23.6% of the dye delivered into the chamber was recovered on the area sampled. Since the area sampled was approximately half of the area of the chamber, it appeared that half of the aerosol delivered into the chamber in 10 minutes had fallen out within three minutes after nebulization for 10 minutes. In other words, considerable fallout from 0 to 13 minutes had occurred.

This confirms other experiments in which half of the estimated ideal concentration of aerosol based on delivery was picked up by the samplers when they were run immediately after 10 minutes of nebulization.

If a curve is plotted on the basis of our data, half of the fallout occurs within the first 10 minutes and most of the rest sometime within the last 110 minutes. The irregular distribution of the red dye is impingement rather than fallout. It is possible that in a larger chamber, fallout would progress more gradually or differently.

The Checklist

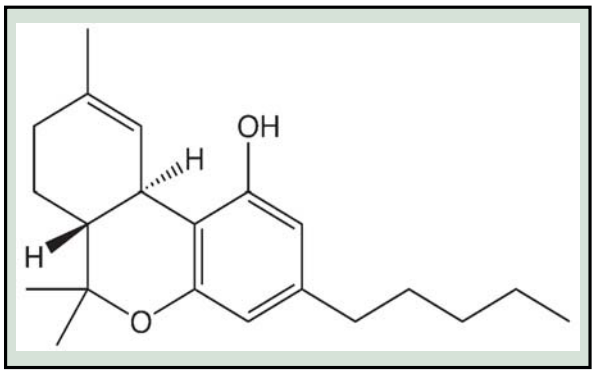
There are certain items of interest in the checklist give in Table III. It is very striking to see the differences in the dye in the different samplers. This difference, for example, in the experiment of 3/13, varied from 0 mg in sampler 1 to 0.09 in sampler 3. This variation in the amount of dye taken up at the different sampling positions has been a consistent finding and is readily confirmed by qualitative observation of the dye itself in the samplers. It is of interest that in one experiment (3/29/57) a large quantity of dye was found on the ceiling. In Item 27, however, the total fallout seems to be fairly consistent.

* * * * *

Unfortunately, the referenced tables were not included with the report. Dr. Abramson told us that he had concluded that the inhalation route was approximately one-third as effective as the oral route. Abramson's ability to arrive at the same conclusion as we did almost ten years later is remarkable, considering that he did not have the benefit of the sophisticated delivery system, including controlled breathing, as we did in our later studies at Edgewood Arsenal.

TETRAHYDROCANNABINOLS

As discussed in the main narrative, the Army's interest in THC type compounds was ambivalent. In the mid-1950s, pilot studies with EA 1476 (red oil)[87] showed it to be potent, but otherwise unacceptable for military use.



Structure of tetrahydrocannabinol

EA 2233, a mixture of 8 stereoisomers of THC (with two methyl groups attached to the heptyl side chain), showed higher potency than THC itself (Fig. 99) in the range of 10-60 mcg/kg by the oral route.[88] Later, after they were separated by Parker Ferguson at Edgewood Arsenal, Dr. Sidell was later able to test two of the individual isomers of EA 2233 but found them to cause both orthostatic hypotension and minimal effects on performance at the very low doses used.[89]

A pilot study with EA 2233, using three performance measures, indicated minimal effects at the doses administered (Fig. 98). Two subjects were tested at each dose level. Only one volunteer, at 60mcg/kg, reported distinct cannabis-like effects. He described a pleasant state in which he was unconcerned with events in the environment and doubted that he would care if a fire broke out.

EA 2233 did not seem to have sufficient potency to be of military interest, since an oral dose of 60mcg/kg caused a maximum decline of only 40% (at most) in number facility performance. Hollister later published a study which showed that the oral effects of ordinary THC were only about one-third that of THC smoked as marijuana..[90] This suggests that effectiveness of EA 2233 in an aerosol might be much greater than by the oral route. In our 1981 study of the effects of smoked marijuana on driving performance,[91, 92, 93] the estimated absorbed dose of THC averaged about 40 mcg/kg, and produced only minimal effects on tests of cognitive performance, such as the BITE (Brief Interval Time Estimation) task, essentially the same as the VITA used at Edgewood. We found a maximum decline of only about 10-20% (Fig.100). This corresponds roughly to the decline in NF produced by 30-40 mcg/kg of oral EA 2233. It would seem that the mixture of all 8 isomers of EA 2233 is not appreciably more effective than ordinary THC, but one or more of the individual isomers may account for most of the performance decrements.

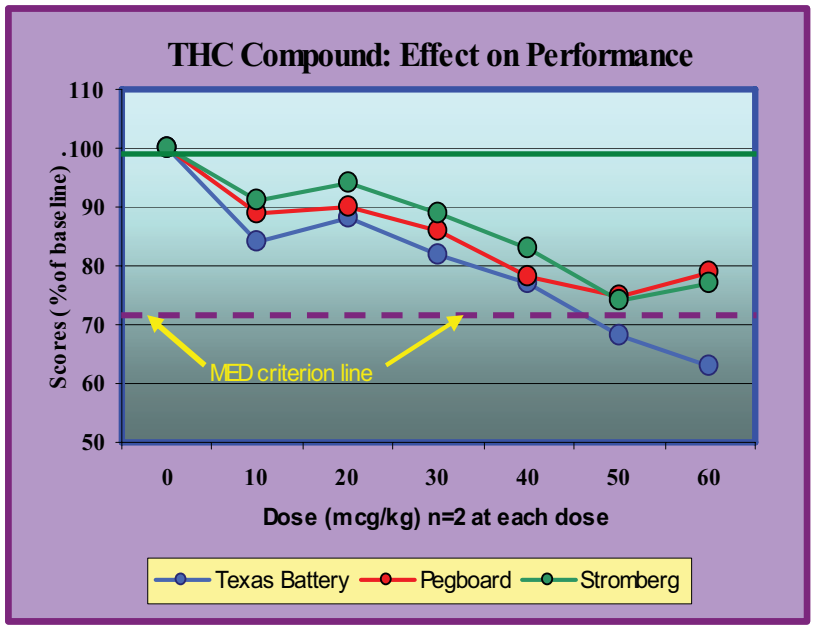


Fig. 100 EA 2233 (THC): Mixture of 8 isomers produces similar dose-related effects on 3 test scores

Problems with hypotensive blood pressure halted single isomer testing in 1965.

ETHYL ALCOHOL

Although not considered to be a potential weapon of chemical warfare, the relative lack of detailed and systematic dose-response studies of ethyl alcohol[94,95] encouraged us to test its effects in normal volunteers. Surprisingly, fairly high doses of alcohol produced only moderate decrements in NF performance. Total doses roughly equal to 9, 11 or 13 oz. of 80 proof vodka, gin or most whiskies caused only a 25-50% decrement in this test of cognitive scores. The MED_{50} (dose producing 2 successive scores below 75%) appears to be roughly 1.5 ml/kg.

Drs. Fred Sidell and John Pless conducted these studies and published their results in Psychopharmacologia in 1970.[96] They found

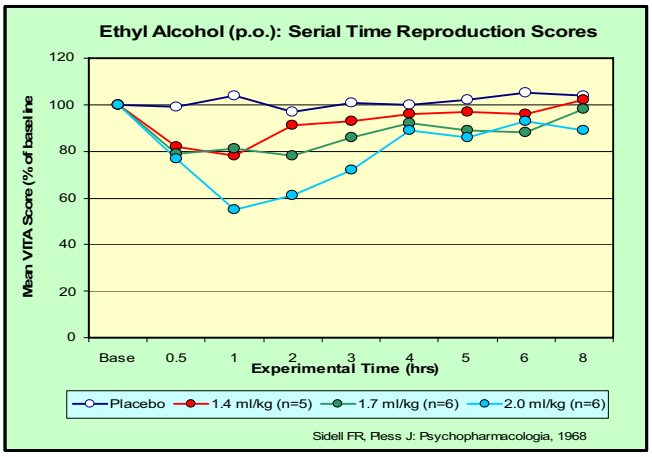


Fig. 101 Alcohol: Effect on time reproduction task (VITA)

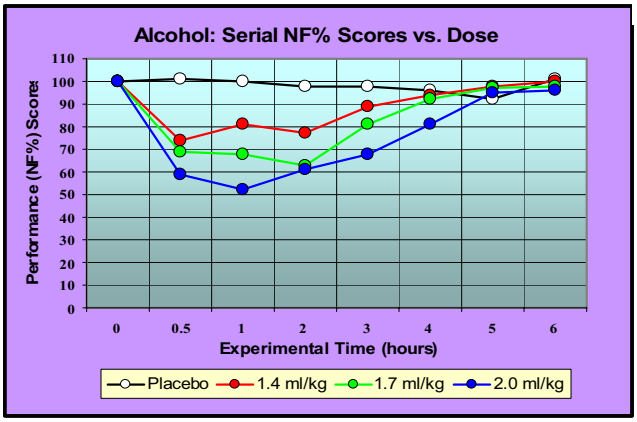


Fig. 102 Alcohol: Effect on arithmetic task (NF)

changes in VITA scores, similar to but slightly less than NF decrements (Fig. 101). In a later study, Hollister and Ketchum[97] found that normal young male volunteers likewise performed quite well on NF and VITA tests after rapid consumption of 7 oz. of 80 proof Vodka (close to the lowest dose used by Sidell and Pless). Both studies showed that the dose of alcohol required to produce major changes in performance is greater than commonly represented in poster guidelines.

It was not surprising that motor skills such as the ZITA (Zero Input Tracking Analyzer), which can be set to be analogous to steering a car or a boat, showed much greater impairment than performance (Fig. 103) on purely cognitive tasks such as NF (Fig. 102) and VITA (Fig. 101). It is interesting that there was no difference in impairment between 1.4 and 1.7 ml/kg. Sidell noted that at the highest dose, recovery took no longer than at the two lower doses. The "SIAM" effect (swift increase in alcohol metabolism) may be the explanation, a phenomenon described by other investigators[98] as a rapidly developing temporary tolerance that occurs during intoxication itself.

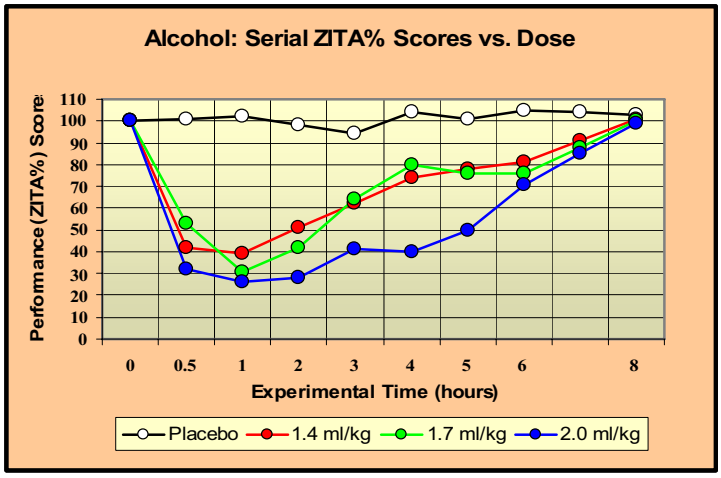


Fig. 103 Alcohol: Effect on tracking task (ZITA)

Numerous investigators have studied the rate at which alcohol is cleared from the blood. Sidell and Pless confirmed some of these earlier findings, noting that blood alcohol levels declined from 14-21 mg% hourly in their non-alcohol-abusing volunteers (with the fastest elimination at the highest doses.). This suggests that the conventional doctrine that each drink of alcohol requires an hour to clear may be overly cautionary. Elimination of a dose of 1.3 ml/kg (Fig. 104) occurred at the rate of about 20mg% hourly in this group of Army volunteers, all of whom had a history of moderate but not excessive drinking.

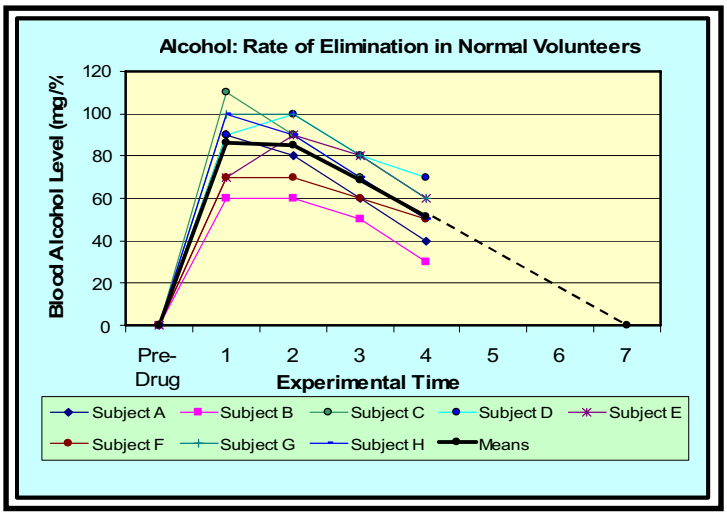


Fig. 104 Alcohol: Estimation of rate of elimination

In 1981, criminologist Victor Reeve, Dr. Leo Hollister and I conducted tests with 40 young male volunteers under a contract with the Department of Justice, Sacramento, CA. With the help of California Highway Patrol officers, and the availability of their high-speed pursuit training course, we combined driving scores with indoor (trailer) measurements of performance on the CTT (a tracking task) and the BITE (as mentioned earlier, a time reproduction task similar to the VITA). On successive weekends each subject consumed placebo alcohol and smoked a NIDA cigarette containing 18mg of THC; 7 oz of 80-proof Vodka and placebo THC; placebo NIDA and placebo alcohol; both alcohol and active THC. Inside, we drew blood samples at hourly intervals between testing blocks and monitored vital signs, symptoms and behavioral changes. Outside, the CHP officers provided a specially equipped car that measured more than a dozen variables. They also conducted roadside sobriety tests, and measured several additional performance items. The results of these tests were exhaustively analyzed statistically in the final publication by Biasotti et al.[99], published four years later.

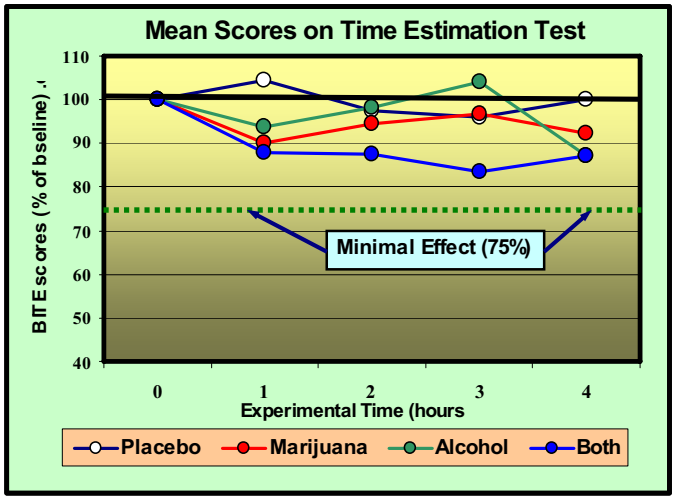


Fig. 105 Alcohol and/or marijuana: effect on Brief Interval Time Estimation task (BITE)

Actual changes in performance were modest (Fig. 105). Alcohol levels of .10% (10 mg%) were expected but, as with the above study by Sidell and Pless, actual levels reached this value in only 2 of 26 subjects. Mean blood level peaked at 0.07% at 1-2 hours. The officers indicated that they would have stopped 10% of placebo subjects, 32% of THC subjects, 50% of alcohol subjects and 60% of those with alcohol plus THC

It was interesting that when scores from all 26 subjects (excluding 4 who were unacceptable for technical or other reasons) were averaged, neither THC nor alcohol alone caused major changes in time estimation. THC subjects were somewhat more impaired on timing than on steering skills. THC and alcohol combined failed to produce average decrements that would have been considered minimal effects (using the Edgewood definition of the MED_{50} as two successive scores below 75% of baseline). Recovery from alcohol scores was attained at 3 hours, followed by a small subsequent drop-off (which may have been due to drowsiness as the alcohol wore off).

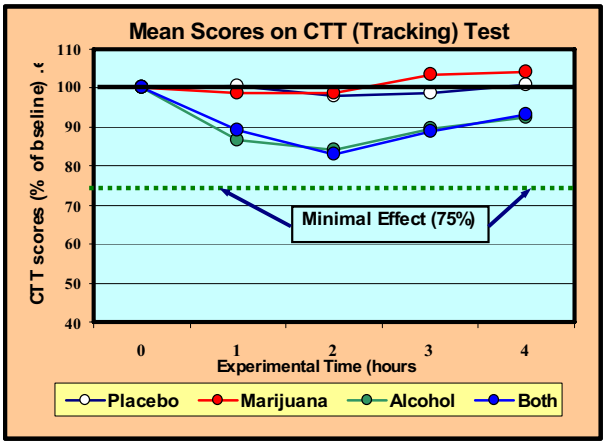


Fig. 106 Marijuana and/or alcohol effects on tracking task (CTT)

THC alone also did not even produce "minimal" effects on the CTT scores, which averaged slightly above placebo scores after 2 hours (Fig 106). When combined with alcohol, THC produced little additional impairment. CHP officers likewise found that THC had relatively minimal effects on driving per se, and in at least two of the driving tasks, scores were actually slightly higher than after placebo. At the dose of THC used, it would be difficult to conclude that smoking small amounts of marijuana after, or concomitantly with, drinking, would cause significantly greater impairment. One presumes, of course, that higher doses of marijuana would adversely affect steering skills.

When subjects consumed 7 oz. of 80 proof alcohol (in orange juice) in 20 minutes, mean blood levels rose only to 0.07% (Fig. 107). This finding was in line with results reported by Sidell and Pless (1971). Only 2 subjects exceeded a level of .10%. The rate of elimination was linear after 2 hours, averaging 15 mg% hourly, somewhat less than reported in many other studies. The mean peak value did not exceed the (then) legal limit of 0.10, even after consuming what most would consider a large dose of alcohol. Similar results have been reported by other investigators.

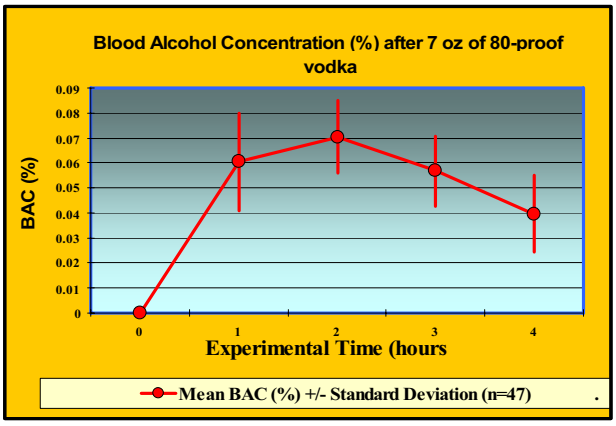


Fig. 107 Alcohol: Mean serial blood levels after 7 oz. of vodka

THC levels, drawn at hourly intervals starting 20 minutes after smoking, were highly variable, as shown by the large standard deviation (which appears quite small when plotted on a logarithmic y-axis). The actual range of all THC values was from 3 to 220 ng/ml (no doubt reflecting major differences in the rate and depth of inhalation). About 25% of subjects had a small but measurable level of THC prior to smoking. (They were required to be moderate but regular users in order for us to avoid introducing non-users to marijuana for the first time.)

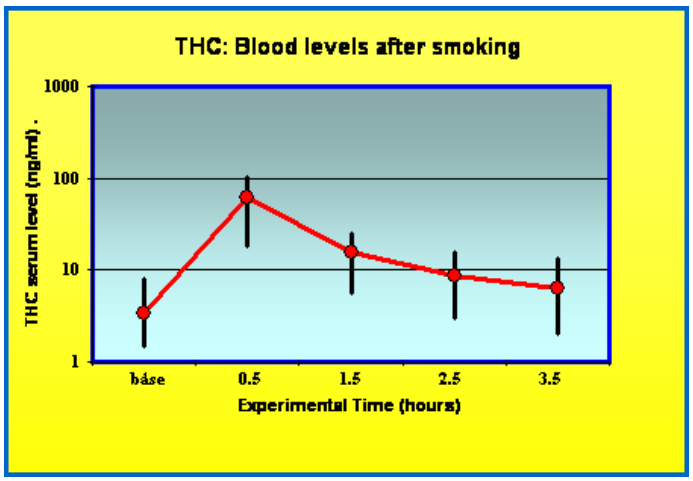


Fig. 108 Marijuana: Serial mean THC blood levels after smoking

The elimination curve of THC is suggestive of first order kinetics in contrast to the zero order (linear) rate at which alcohol is eliminated (Fig. 108). But a simple logarithmic decay curve does not seem adequate to fit the actual decline in plasma level. It is interesting that although peak levels averaged about 80 ng/ml at 30 minutes, they fell rapidly to an average of about 20 ng/ml at 1.5 hours. Thereafter the rate of disappearance slows, possibly indicating some sequestration in fatty tissue.

BUTYROPHENONES

In the 1960s, potent major tranquilizers such as haloperidol (Haldol) and fluphenazine (Prolixin) were new on the psychiatric scene. Many of these synthetic butyrophenones were sufficiently potent to warrant at least preliminary testing in our program. Fluphenazine and 302034 (haloperidol)[100] both impaired NF performance (Figs 109, 110), but this appeared to be due mainly to dysphoria, reduced activity and decreased motivation. This is a typical in normal subjects (in contrast to the therapeutic effect in schizophrenia). Some subjects made only token efforts after receiving these dopamine blocking drugs.

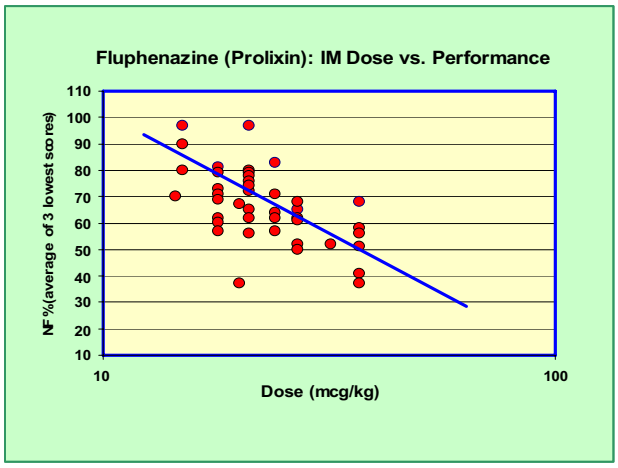


Fig. 109 Fluphenazine: Effect on NF% performance

A side effect, dystonia of the neck muscles, often appeared after the higher doses of 302034 or fluphenazine, usually about 12-16 hours following administration. (This was quickly relieved by 50 mg of i.m. benadryl.) Slopes of the dose-response curves were

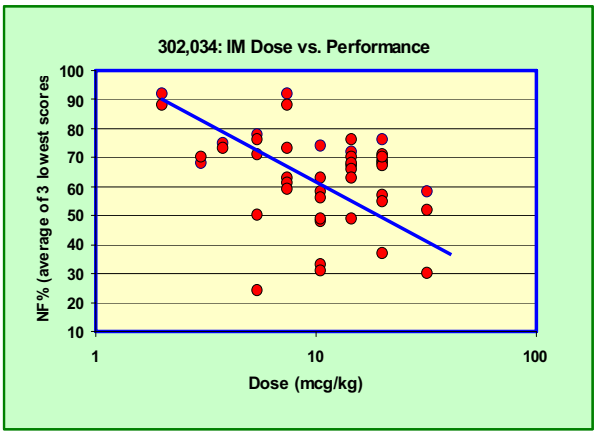


Fig. 110 302034: Effect on NF% performance

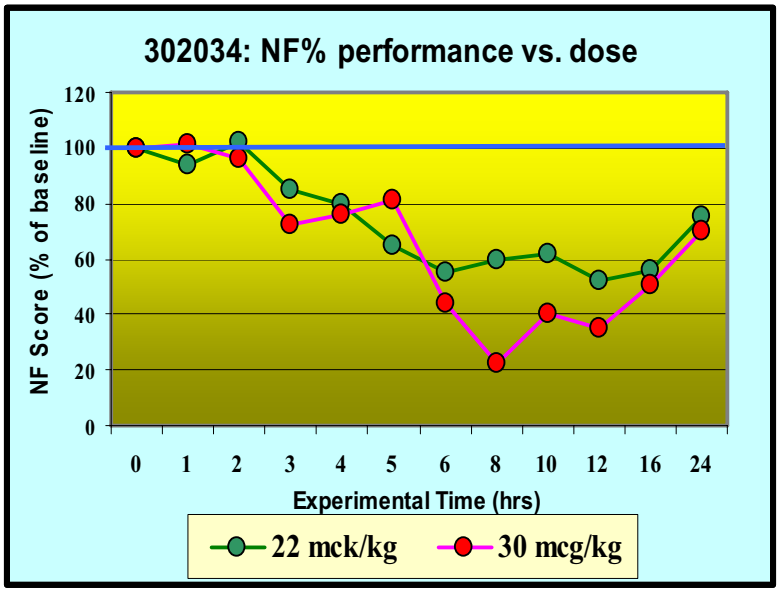


Fig. 111 302034: Time course of NF% performance effects

shallow for both drugs. Fluphenazine was more potent than 302034,.with an MED_{50} of about 5 mcg/kg and an estimated ID_{50} of 100 mcg/kg.

The duration of 302034 effects was roughly equal to that of fluphenazine (Fig. 111). NF performance decrement produced by 302034 was maximal at about 8 to 12 hours. Full recovery (not shown in this chart) did not occur until about 36 hours. Due to a lack of potency, this category of drugs did not seem to warrant further study, especially since indifference in a combat situation might be overcome by the instinct of self-preservation. Also, these subjects were not confused and could probably function on a battlefied if the situation became life-threatening.

VOLUNTEER STATISTICS

As discussed earlier, most of the 6700 volunteers who participated in our program were tested during the 1960s[101]. Approximately 4300 were assigned to Edgewood Arsenal during that period, compared to about 2400 in the preceding and subsequent five years combined (Fig. 112). The number actually exposed to chemical agents during the 1960s was about 1900 (roughly 44%) while a total of about 1300 (54% of those assigned) received an agent during the preceding and following 5 years combined. Overall, slightly less than half of those assigned actually received active agents.

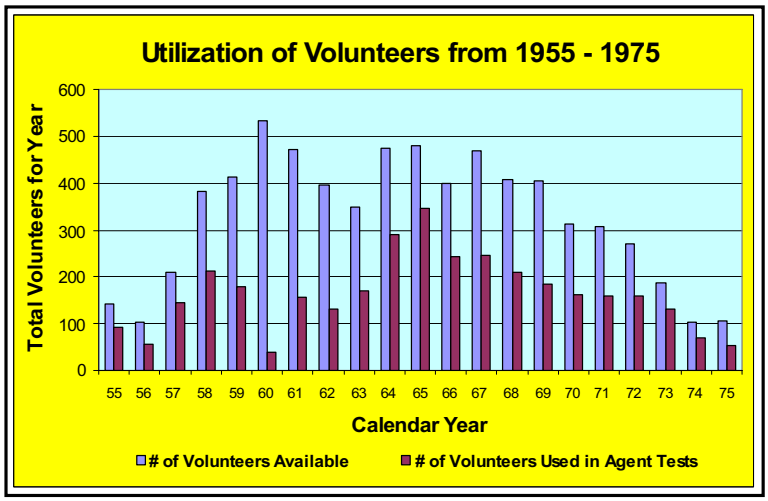


Figure 112 Rise and fall in total volunteers and those used in tests (1955-1975)

1960 was exceptional in that only about 40 (8%) of the 540 assigned (the highest number in a single year) were given chemical agents. The reason for this is not clear. After I arrived in February 1961, the percentage of volunteers tested rose progressively to almost 70% in 1965. This was the peak year, after which percent tested again declined, reaching a low of 50% in 1975.

In 1969, the number of personnel in our laboratory reached its highest level (Fig. 113), with COL Henry Uhrig as chief, and Dr. Van Sim as Chief Scientist (although not in the direct chain of command). Of the five departments established by this reorganization, Clinical Medical Sciences was the largest. It consisted of five branches, and possessed the largest number of personnel, approximately 90 of a total of roughly 250 in the Medical Research Laboratory. The actual number of subjects, however, began to decline – in 1969, only half as many volunteers underwent testing as in 1965.

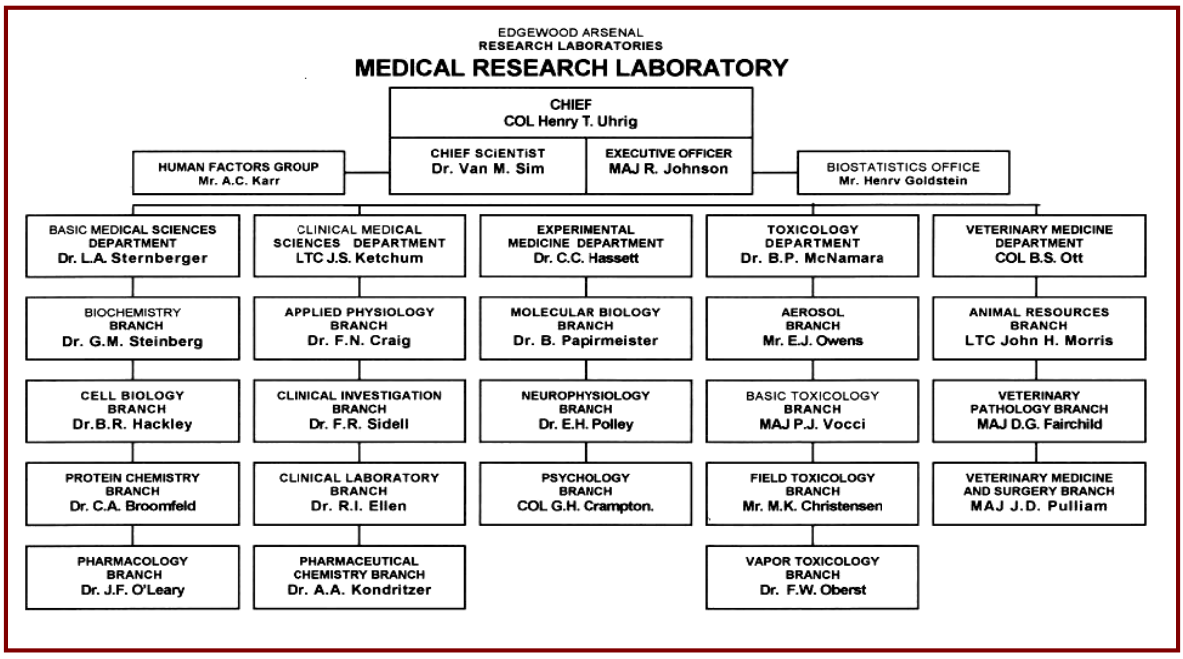


Figure 113 – Organizational chart for the Medical Research Laboratory (1969)

FOLLOW-UP STUDIES

In 1980-81, the Army asked the National Research Council of the National Academy of Sciences to review the medical outcomes of all volunteers tested from 1955-1975.[102,103] Among the belladonnoid drug subjects, observed deaths were actually found to be fewer than the number expected. The policy of selecting only the healthiest candidates to serve as volunteers no doubt accounts, at least in part, for this favorable finding. It is ironic that only in the case of atropine and scopolamine, two drugs accepted in the FDA approved formulary, and in use for centuries, were observed deaths more than the actuarially expected number (Fig. 114). Considering the small numbers, however, the statistical significance of this seeming anomaly is no doubt very low.

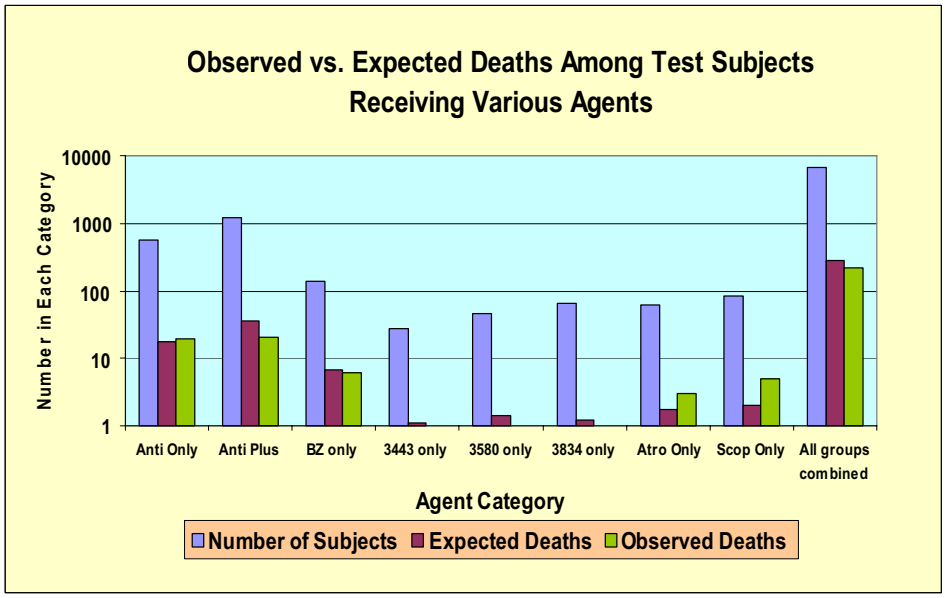


Figure 114 Death rates for various drugs among test subjects vs. controls

When the outcomes of subjects who received only non-glycolate drugs were examined, the results were also rather startling (Fig. 115) Those who had received only LSD, THC or other non-belladonnoid drugs were far less likely to have died than those who had received irritant or irritant plus other drugs. It is eerily tempting to postulate that LSD, in particular, actually may have had a life-prolonging effect, as counter-intuitive as this may seem. One might note that the chemist who synthesized LSD in 1938, Albert Hofmann, is in good health and has already celebrated his one-hundred-and-first birthday!

As skeptics often remind us, almost anything can be proven with statistics. Caution is called for, therefore, in concluding that psychedelic drugs bring with them the unexpected benefit of longer life. But at least, it seems likely that they do not shorten life when administered to normal young men. Proponents of revoking existing prohibitions against this category of drugs may wish to take a measure of encouragement from these findings (chi-square probability of the 2 x 2 table of actual vs. expected LSD and THC mortality expected results = .002847, a statistically significant result!).

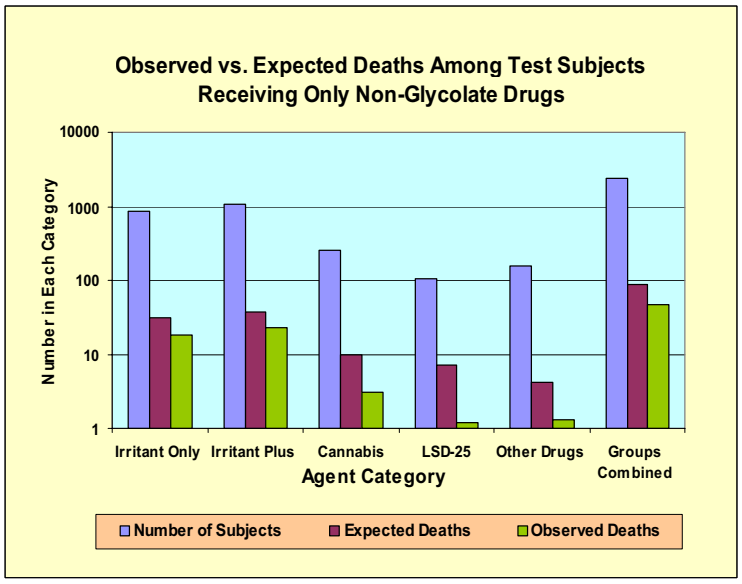


Fig. 115 Expected vs. actual number of long-term follow-up deaths in volunteers receiving only irritants or other drugs such as LSD or THC

THE NUREMBERG CODE[104]

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved so as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the subject there should be made known to him the nature, duration and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests with each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even the remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment, that a continuation of the experiment is likely to result in injury, disability, or death to the subject.

Note: Although often the focus of critics, the description of "informed consent" as stated in Rule 1 does not expressly include (e.g., in the case of drug testing) the necessity of providing the name of the substance being tested. Edgewood physicians did observe the explicit requirements of the rule by describing the purpose of the test, general nature and likely duration of effects to expect, assurance of continuous medical supervision and evidence from previous animal and human studies that the drug was safe. Questions were encouraged and post-test discussions with the physician were routinely included as part of the experimental procedure. All other rules were also complied with.

Congressional Guidelines for Chemical Warfare Objectives (1950)

As a result of its hearing and further study on the problems of research in CBR, this committee offers the following recommendations:

1. There must be a strong and continuous intelligence effort conducted by the United States as a protective measure to keep abreast of foreign developments in the fields of CBR if this country is to have time to develop adequate passive defense and other countermeasures.
2. Surveillance of foreign activities might also give this nation its only inkling of imminent use of CBR against the United States, and therefore is important for this reason too.
3. There is an urgent need for greater public understanding of the dangers and uses of CBR if proper support is to be given to our defenses and countermeasures.
4. In any consideration of international disarmament, a special effort must be made not to overlook the great potential of CBR and the ease of evading detection of CBR activities.
5. There is an urgent need for a higher level of support on a continuing, long run basis in order to develop better detection and protection measures against possible employment of CBR against this country.
6. Civil defense plans of this country should include a more positive effort at providing shelters which are proof against CBR attack, at providing more masks and protective clothing, and in public instruction in defensive measures.
7. More positive and imaginative attention should be given to the problems of detecting and guarding against use of CBR by saboteurs, aimed at disrupting key activities in time of emergency.
8. The committee views CBR as a weapon which is not competitive with nuclear weapons, but complementary to them, designed to do a different job.
9. The committee cannot bring itself to describe any weapon of war as "humane," and makes no moral judgment on the possible use of CBR in warfare. It does recognize that ignoring CBR will not remove the problem of its existence or its possible employment against the United States.
10. It is granted that some forms of CBR offer the prospect and the hope of winning battles without taking human life or destroying homes and factories. If force must be used, this is better than many of the alternatives. But it must also be recognized that even if the U.S. is attacked with the new "gentle" weapons, the consequences of any defeat for our nation would be just as dangerous to our national goals and life.
11. It is also recognized that in the present world situation, with other countries pursuing vigorous programs of CBR development, the best immediate guarantee the U.S. can possess to insure that CBR is not used anywhere against the free world is to have a strong capability in this field, too. This will only come with a stronger program of research.

12. At the present time, CBR research is supported at a level equivalent to only one-thousandth of our total defense budget. In light of its potentialities, this committee recommends that serious consideration be given to the request of Defense officials that this support be at least trebled. Only an increase of such size is likely to speed research to a level of attainment compatible with the efforts of the communist nations.
13. If CBR is to be considered a deterrent force in the U.S. arsenal of weapons, the program of research advocated here will have to be accompanied by an adequate program of manufacture and deployment of CBR munitions.
14. CBR warfare is not particularly expensive as compared with many other modern forms of warfare, particularly when considered as an incremental cost added to already necessary delivery techniques employed for nuclear weapons. This is a further reason why this investment must be given careful consideration.
15. The research being done in CBR has already yielded a variety of peacetime benefits, including antidotes for poisons, new serums to prevent disease, greater understanding of how diseases are spread, new insecticides, and fundamental knowledge of life processes. There is no real separation possible between potential military application of chemical and biological knowledge and peaceful applications. These peaceful applications are required in any case and deserve added support for the national welfare.
16. The United States is in a research and development race, particularly with the Soviet Union, whether it be for peaceful or military purposes. The study by this committee of CBR reinforces our general view of the urgency of the overall race and necessity of full public understanding and support of science and technology everywhere in our nation.

Note: The emphasis on the importance of "full public understanding and support of science and technology everywhere in our nation" (in item 16) is worth underlining. If public knowledge had been maintained over the years by open policies regarding experimental procedures and data, it seems likely that current attitudes toward military research with chemical agents would be more positive.

PERSONNEL WHO SERVED AT EDGEWOOD ARSENAL (1961 - 71)

PHYSICIANS			NURSES	PSYCHOLOGISTS
			Loretta Allen	Richard Allen
George Aghajanian	Larry Gutterman	John Payne	Nancy Bowman	Ernest Clovis
Leon Balter	David Harper	John Pless	June Brenneman	George Crampton
Charles Berdjis	Chevas Haskell	Herb Rakatansky	Frances Casillas	Paul Fiddleman
Dean Berson	Arthur Hayes, Jr.	Mitchell Rosenthal	Addis Chapman	Jim Hart
Oscar Bing	Frederich Hellreich	Daniel Safer	Claire Dunn	Stanley Holgate
Joseph Blair	Brunildo Herrero	Robert Savola	Lois Fisher	Harlan Lindley
Nicholas Bottiglieri	John Josselson	David Sawhill	Billie Fort	Eddie McCarroll
Frank Bower	Stuart Karger	Steve Scher	Lorraine Haskins	Donald Meltzer
Malcolm Bowers	James Ketchum	Hack Schiff	Jenny Hogan	Ronald Smith
Bennett Braun	David Kitzes	Howard Schwartz	Helen Hudson	Edward Stearns
Thomas Chayka	Jack Klapper	Walter Shim	Linda Keister	**OTHERS**
Alfred Cox	John Kuhn	Philip Shiner	Jane King	John Day
Edward Crowell, Jr.	George Leib	Frederick Sidell	Gloria Lyons	Robert Ellin
Samuel Cuccinell	Bernard Levine	Van M. Sim	Josephine Magness	Bill Groff
Ron Daniels	Douglas Lindsey	John Simmonds	Anne May	Ephraim Goodman
Frank Duffy	John Markis	Cal Simons	Linda Newquist	Owen Jones
Kermit Erickson	Claude McClure	Robert Stavinoha	Francis Peck	Charlie Krauss
Richard Fencel	Peter McMichael	Jerry Strong	Carol Riley	Kragg “Phil” Kysor
Walter Giordano	Janice Mendelson	Paul Sussman	Jeanne Shladanguski	Lloyd Matter
Robert Gipstein	Enrique Mendez	Rick Schwartz	Jeanne Talts	Mike McCullough
John Glover	Jack Meshel	Barry Tharp	**SECRETARIES**	Bill McShane
Mark Goldberg	Earl Metz	Arthur Thompson	Elsie Heuer	Millard Mershon
Ron Goldman	Mark Needles	Henry Uhrig	Florence Klatt	Rudy Rivera
William Gordon	Harvey Neitlich	Martin Vancil	Patsy Ross	Carl Stearn
Tony Gottlieb	Paul Omelsku	Henry Yamamura	R. Van Valkenburgh	Dennis Tamplin
Chester Gottlieb	Don Pachuta	Charles Young	Norma Vaught	Allen Mounter

Note: List is not complete, due to the passage of time and the gradual attrition of memory and other sources of .historical data.

SYMPTOM CHECKLIST

(Showing hypothetical example of scores
for a subject given an ID^{50} dose of BZ)

Mentally uncoordinated	2
Unorganized	2
Reflexes were slowed	1
Mouth dry	2
Unable to talk very well	2
Lost sense of balance	1
Eyes were blurry	1
Couldn't focus eyes	2
Speech altered	1
Thirsty	1
Arms and legs weak	1
Dizzy	1
Reached the point of drunkenness	2
Legs felt like rubber	1
Dreaming (hallucinations)	1
Tired	2
Uneasy	1
Partial amnesia	2
No appetite	2
Sleepy	2
Restless	1
Desire to laugh	1
Nauseated	0
Did not feel good	1
Arms were wandering	1
Arms and legs looked red	1
Throat hurt when swallowing	1
Double vision	0
Nervous	1
Felt irritable, impatient	2
Experienced no effects	0
Floating on a cloud	1
Muscles twitched uncontrollably	0
Fun feeling	1
TOTAL	**41**

The volunteer, after recovery, estimates the degree to which each symptom was present. (Form can only be completed when subject is reasonably oriented.) Scoring is [0] if symptom is absent, [1] if present but mild and [2] if marked. Items were chosen from those frequently mentioned in post-test write-ups by a large sample of previous volunteers who had received a belladonnoid drug.
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BEHAVIOR CHECKLIST

(Showing hypothetical example of scores
For a BZ subject at 4 hours experimental time)

Item*	Score
Does not seem quite normal	2
Dry mouth: subjective (1); obvious to the observer (2)	2
Poor coordination	1
Short attention span	2
Spontaneous bodily complaints	1
Disjointed illogical associations	1
Impaired recent memory	1
Misperceptions (illusions)	1
Abnormally drowsy	2
Difficulty speaking (enunciation)	1
Visual hallucinations	1
Restless (1); hyperactive (2)	1
Confused as to time (day, month, year)	1
Confused as to place	0
Does not obey instructions	0
Admits to nausea	1
Auditory hallucinations	0
Retching-vomiting	0
Anxious (tense)	1
Limited verbal response to questions	1
Admits to headache	0
Angry (1); openly hostile (2)	1
Negativistic (contrary)	2
Euphoria (inappropriate -- smiling, laughing)	1
Suspicious (1); paranoid (2)	1
Abnormally talkative	0
TOTAL	**25**

The nurse records observations at scheduled intervals. Scoring: [0] if feature is absent, [1] if present but mild and [2] if marked. Items were chosen from those most frequently mentioned in nursing observations as recorded in the clinical charts of a large sample of volunteers who had previously received a belladonnoid drug. (Items were less relevant to drugs such as LSD.)

Note: This is one version of the BCL: specifically the one used in
Sidell FR, Braun BG: EA 3834:
Effects in man after a single oral dose. *EATR 4597*, 1972

LIST OF REFERENCES

1. Bliss CI. The Statistics of Bioassay. New York, NY: Academic Press; 1952
2. Alexander E, Morris DP, Eslick RL: Atropine poisoning: report of a case with recovery after ingestion of one gram. New Engl. J. Med. 1946;234:258-259
3. Forrer GR: Atropine toxicity in the treatment of schizophrenia. Journal of the Michigan State Medical Society. 1950;49:184-185.
4. Kimura KK: Current information from Hoffman-LaRoche, Inc., on RO2-3308 as of February 1960. Chem Warfare Laboratories Special Publication 2-29, 1960.
5. Moran LJ, Kimble JO, Mefferd RB: Repetitive psychometric measures: equating alternate forms. Psychol Rept. 14:335, 1964.
6. Aghajanian GK, Kitzes DL, Harper DG, Bottiglieri NG: EA 3580A: Estimate of minimal effective dose in man. Edgewood Arsenal, MD. CRDL Technical Memorandum 2-12. 1965
7. Ketchum JS, Kysor KP: Effects of secobarbital on time estimation performance. Edgewood Arsenal, MD. Unpublished manuscript, 1962.
8. Simmonds JS: "VITA" time estimation apparatus: control data on 10 normal volunteers. Edgewood Arsenal Technical Memorandum 114-119, 1967.
9. Ketchum JS, Kysor KP: A model for predicting the effect of anticholinergic compounds on cognitive performance. In Berdjis, C (ed.): Proceedings of a Contractors Conference on Behavioral Sciences. Edgewood Arsenal Special Publication No. 100-11, 90-102, 1965.
10. Ketchum JS: The human assessment of BZ. CRDL Technical Memorandum No. 20-29. U.S. Army Report, 1963.
11. Zvirblis P, Kondritzer AA: Adsorption of H^3BZ and C^{14}atropine to the mitochondrial fraction of the rat brain. Edgewood Arsenal Technical Report 4042, 1966.
12. Bell C, Gershon S, Carroll B, Holan G: Behavioural antagonism to a new psychotomimetic: JB-329. Arch Intern Pharmacodyn Ther. 147:9-25, 1964.
13. Miller JJ, Schwarz H, Forrer GR: Atropine coma therapy. Oral presentation to Michigan State Medical Society, 1957.
14. Ketchum JS: Soldier's Predicament. Sound-color film. Graphics Arts Department, Chemical Research and Development Laboratories, Edgewood Arsenal, MD:1963.
15. Ketchum JS: The Longest Weekend. Sound-color 16mm film. Graphics Arts Department, Chemical Research and Development Laboratories, Edgewood Arsenal, MD. 1962.
16. Forrer GR, Miller JJ: Atropine coma: a somatic therapy in psychiatry. Am. J. Psychiat; 115:455-458, 1958.
17. Abood LG, Ostfeld AM, Biel J: A new group of psychotomimetic agents. Proc. Soc. Exp. Biol. Med. 97:483-486, 1958.
18. Kleinwachter I: Observations concerning the effectiveness of extract of calabar against atropine poisoning. Berl klin Wschr. 1:369-377, 1864.
19. Dunn MA, Sidell FR: Progress in medical defense against nerve agents. JAMA 1989:262:649-652
20. Ketchum, JS, Aghajanian GK, Bing, O: The human assessment of EA 1729 and EA 3528 by the inhalation route. CRDL Report No. 3226. US Army Report, 1964.
21. Ketchum JS, Tharp B, Crowell E, Sawhill D, Vancil M: The human assessment of BZ disseminated under field conditions. Edgewood Arsenal, MD, Edgewood Arsenal Technical Report 4140, 1967.
22. Klotz L, Furmanski M, Wheelis M: Beware the Siren's Song: Why "Non-Lethal Chemical Agents" are Lethal. Federation of American Scientists: Chemical and Biological Arms Control Program, March 2003
23. Sidell FR, Aghajanian GK, Groff WA: The reversal of anticholinergic intoxication in man with the cholinesterase inhibitor VX. Proc. Soc. Exp. Biol. Med.144-:725-730, 1973.
24. Ketchum JS, Kitzes D, Mershon M et al.: The human assessment of EA 3443. Edgewood Arsenal, MD. Edgewood Arsenal Technical Report 4066, 1967.
25. Allen RP, Safer DJ: Exercise and incapacitating effects of EA 3580A in man. Edgewood Arsenal Technical Memorandum 114-15, 1968.
26. Ketchum JS, Kysor KP: A model for predicting the effect of anticholinergic compounds on cognitive performance. In Berdjis, C (ed.): Proceedings of a Contractors Conference on Behavioral Sciences. Edgewood Arsenal Special Publication No. 100-11. 1965;90-102.
27. Ketchum JS, Kitzes D, Copelan H: EA 3167: effects in man. Edgewood Arsenal Technical Report 4713, 1973
28. Ketchum JS: Effects of EA 3167 in man. Edgewood Arsenal Technical Report. 1974; US Army report.

29. Hart JJ, Balter L: A study of possible residual effects of EA 3443 and EA 3580 on cognitive ability. Edgewood Arsenal Technical Report 4044t.1966.

30. Duvoison RC, Katz R: Reversal of central anticholinergic syndrome. JAMA 1963:206, 1968.

31. Sidell FR, Aghajanian GK, Groff WA: Op. cit.

32. Ketchum JS, Sidell FR, Crowell EB Jr, Aghajanian GK, Hayes AH Jr: Atropine, scopolamine and ditran: comparative pharmacology and antagonists in man. Psychopharmacology (Berlin) 2:140-165, 1973.

33. Ketchum JS, Sidell FR, Crowell EB Jr., et al. Op. cit.

34. Ketchum JS: Summary of comparative characteristics of ten belladonnoid chemical agents in man, tested in 600 volunteers at Edgewood Arsenal, Maryland from 1961-73. Report prepared for the Special Committee on Anticholinergic Agents (40 pages). Toxicology Committee, National Science Council, National Academy of Sciences, Washington, DC, 1981

35. Ketchum JS: Incapacitating Compounds. Item II on the agenda of the first meeting of the quadripartite standing working group on chemical warfare. Proceedings of the 1965 Quadripartite CBR Conference. US Army Report, 1965.

36. Abood, LG: Structure-Activity Relations of the Centrally Active Anticholinergic Agents, pp 275-284s. Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Volume 1 Panel on Anticholinesterase Chemicals, Panel on Anticholinergic Chemicals, Committee on Toxicology, Board on Toxicology and Environmental Health Hazards. (1982 Commission on Life Sciences, National Academy of Sciences).

37. Alexander E, Morris DP, Eslick RL, op.cit.

38. Locket S: Clinical Toxicology. London, England: Henry Kemptar; 1957. p4.

39. Taylor AS: On poisons in Relation to Medical Jurisprudence and Medicine. 3rd American edition. Philadelphia, PA: Henry C. Tea; 1875. p740.

40. Banerjee NR: The symptoms of datura – poisoning, with notes of thirty-two cases. Indian Med. Gas. 20:209-211, 1885.

41. Balazs J: Vergiftungs-Statistikaces Vingarn. Sammlung von Vergiftungsfallen.4:263-270, 1933

42. Peterson F, Haines WS, Webster RW: Legal Medicine and Toxicology. 2nd Edition. Philadelphia, PA: W. B. Saunders; 1923. p629.

43. Webster RW, ed: Legal Medicine and Toxicology. Philadelphia, PA: W.B. Saunders; 1930 p629.

44. Wangeman CP, Hawk MH: The effects of morphine, atropine and scopolamine in human subjects. Anesthesiology 3:24-36, 1942

45. Ketchum JS: Incapacitating Compounds. Item II on the agenda of the first meeting of the quadripartite standing working group on chemical warfare. Proceedings of the 1965 Quadripartite CBR Conference. US Army Report, 1965.

46. Kitzes DL, Vancil ME. Estimate of Minimal Effective Doses of BZ by the Intramuscular Route in Man. Edgewood Arsenal Technical Memorandum 2-30, 1965.

47. Ketchum JS, Tharp B, Crowell E, et al. (1967) op. cit.

48. Ketchum JS (1963) op. cit.

49. Sidell FR: A summary of the investigations in man with BZ conducted by the US Army, 1960-1969. CSL 000-137, 1970.

50. Kitzes DL, Ketchum JS. (1965) op. cit

51. Ketchum JS, Kitzes D, Mershon M, et al. (1967) op.cit.

52. Ketchum JS, Shiner P, Kysor et al. (1972) op. cit.

53. Kitzes DL, Ketchum JS, Weimer JT, Farrand RL. (1967) op.cit.

54. Aghajanian GK, Kitzes DL, et al. (1965) op.cit.

55. Hayes AH, Copelan H, Ketchum JS: The effect of high intramuscular doses of atropine sulfate on the human electrocardiogram. Clin Pharmacol Ther 12: 482-486, 1971.

56. Ketchum JS, Sidell FR, Crowell EB Jr., et al. (1973) op. cit.

57. Elkin EH, Freedle RO, Cott HP Van, Fleishman EA: Effects of drugs on human performance. The effects of scopolamine on representative human performance tests. Technical Report 1, Contract No. DA-18-035-AMC-282[A], 1965.

58. Ketchum JS, Goodman EP: Human responses to four anticholinergic deliriants. Proceedings of the 1962 Army Science Conference at West Point, NY. US Army Report, 1962

59. Ketchum JS, Sidell FR, Crowell EB Jr., et al. (1973) op. cit.

60. Abood LG, Ostfeld A, Biel JH: Structure-activity relationships of 3-piperidyl benzilates with psychotogenic properties. Arch. Internat. Pharmacodyn. Therap. 120:186-200, 1959.

61. Tharp BR, Mershon M, Bottiglieri N: Estimate of intravenous MED_{50} of CS 27349 (219758). Edgewood Arsenal Task Plan 7010, Sep 1964

62. Sidell FR, Ketchum JS, Markis JE, Kysor KP. Compound 302,196: intramuscular administration to man. Edgewood Arsenal Technical Report No. 4634, 1972.

63. Ketchum JS, Kitzes D, Copelan H (1973) op. cit.

64. Ketchum JS (1974) op.cit.

65. Copeland HW: MED_{50} of agent 3834. (1968) op. cit.

66. Cucinell SA, Cummings EG, Holgate SH: Sweat inhibition and performance decrements in man following percutaneous exposure to EA 3834. Edgewood Arsenal Technical Report EB-TR-76004, 1975.

67. McCarroll E, Markis J, Ketchum JS et al. (1971) op. cit.,

68. Hayes, AH, Jr: CAR 301060: Estimate of minimal effective dose in man. Edgewood Arsenal Technical Memorandum, 1967

69. Copelan HW: MED_{50} of agent 302282. Report No. IV. Contract No. DA-18-035-AMC-126 (A), 1967

70. Copelan HW: MED_{50} of agent 302282. Final Report. Contract No. DA-18-035—AMC-126 (A), 1967.

71. Copelan HW: MED of agent 302668. Final Report, Contract No. DA-18-035—AMC-126 (A), 1967

72. Karger S: Incapacitating dose of CAR 302668 in man and efficacy of physostigmine as an antidote. Edgewood Arsenal Technical Memorandum 114-20, 1968

73. Sidell FR, Karger S, Simons CJ, Weimer JT: Compound 302668: aerosol administration to man. Edgewood Arsenal Technical Report 4395, 1970.

74. Sim VM: Compound 302,668: summary report. Edgewood Arsenal Special Publication 100-95, 1971.

75. Arthur D. Little Inc. and Sterling Winthrop Res. Inst: Preclinical pharmacology and toxicology of candidate agent 226086. Quarterly Report.1 Mar. 1966 – 1 Sept 1966. Contract No. EA 18-108-AMC-103(A), 1966.

76. Ketchum JS: Summary of comparative characteristics of ten belladonnoid chemical agents in man (1981) op.cit.

77. Sim VM, Bertino JR, Collier D, Geiger LE, Klee G, Clovis ER, Kimura KK, Goodman AI, Clark BJ: Clinical Investigation of EA 1729. Edgewood Arsenal, MD: Chemical Research and Development Laboratory; CRDL Technical Report 3074. US Army Report, June, 1961.

78. Cohen S: LSD: the varieties of psychotic experience. J. Psychoactive Drugs Oct-Dec;17(4):291-96, 1985.

79. Abramson HA, Jarvik ME, Kaufman MR, Kornetsky C, Levine A, Wagner M: Lysergic acid diethylamide (LSD-25): I. Physiological and perceptual responses. J. Psychol. 39:3-60, 1955

80. Klee G, Bertino JR, Sim VM: Clinical psychiatric studies of subjects receiving EA 1729. Chemical Warfare Laboratory Report 2159. August 1957.

81. Klee GD: Summary of psychological, physiological and biochemical studies performed under University of Maryland Contracts DA-18-108-CML-5519 and DA-18-108-CML-6337 in cooperation with Army Chemical Center personnel. May 1959.

82. Wickstrom C, Ketchum JS: Competitive "lightning chess" performance in volunteers after double blind-administration of small doses of LSD vs. scopolamine. Edgewood Arsenal, Maryland, Unpublished manuscript, 1964.

83. Aghajanian GK, Bing OH: Persistence of lysergic acid diethylamide in the plasma of human subjects. Clin. Pharmacol. Ther. 1964;5:611-614.

84. Ketchum JS. Chemical Warfare Secrets Almost Forgotten. Santa Rosa, CA: ChemBook Inc; 2006-2007

85. Ketchum JS, Aghajanian GK, Bing O: The Human Assessment of EA 1729 and EA 3528 by the Inhalation Route. Edgewood Arsenal, MD: Chemical Research and Development Laboratory; 1964. CRDL Technical Report 3226.

86. Ketchum JS. Incapacitating compounds. (1965) op. cit.

87. Hardman HF, Domino EF, Seevers MH: The chemistry and pharmacology of EA 1476 and the chemistry and pharmacology of certain compounds affecting the central nervous system of animals and man. Reports issued under Contract No. DA-18-108-CML 5663 between 1956 and 1959. U.S. Department of the Army, Chemical Warfare Laboratories, Army Chemical Center, MD.

88. Ketchum JS. The marijuana story and EA 2233. Medical Research Laboratory, Edgewood Arsenal, MD, Unpublished manuscript, 1963

89. Sidell FR, Pless JE, Neitlich H et al.: Dimethylheptyl-delta-6α10α-tetrahydrocannabinol: effects after parenteral administration to man. Proc. Soc. Exp. Biol. Med. 1973;142:867-873.

90. Hollister LE: Tetrahydrocannabinol isomers and homologues: controlled effects of smoking. Nature 1970;227:968-969.

91. Ketchum JS: Marijuana, Alcohol and Driving Performance: a Protocol for assessment of driving performance in volunteers after administration of alcohol and marijuana, alone or in combination, compared to placebo. Department of Justice, Sacramento California, 1979.

92. Ketchum JS, Reeve V, Hollister L: Effects in volunteers of alcohol and marijuana on driving performance. Department of Justice, State of California, Sacramento, CA Unpublished data, 1982.

93. Biasotti, AA, Boland, P, Mallory, C, Peck R, Reeve VC: Marijuana and alcohol: a driver performance study, final report. California Office of Traffic Safety Project # 087902. California Department of Justice Report, Office of the Attorney General, Sacramento, California, September 1986.

94. Moscowitz H: General hallucinogens, pp 77-90. In Willette RE (Ed.): Drugs and Driving. NIDA Research Monograph, March 1977.

95. Klonoff H: Marijuana and driving in real-life situations. Science 176:317-324, 1974.

96. Sidell FR, Pless JE: Ethyl alcohol: blood levels and performance decrements after oral administration to man. Psychopharmacologia. 1971;19(3):246-61.

97. Ketchum JS, Reeve V, Hollister L: (1982) op. cit.

98. Glassman EB, McLaughlin GA, Forman DT, Felder MR, Thurman RG: Role of alcohol dehydrogenase in the swift increase in alcohol metabolism (SIAM). Studies with deer mice deficient in alcohol dehydrogenase. Biochem Pharmacol. 1985 Oct 1;34(19):3523-6.

99. Biasotti, AA et al. (1986) op. cit.

100. Tharp B, Ketchum JS. Performance effects of fluphenazine, haloperidol. Clinical Research Division, Medical research Laboratories, Edgewood Arsenal, MD, Unpublished manuscript, 1965.

101. Government Report: Inspector General of the Army Report. "Use of Volunteers in Chemical Agent Research," 3/10/76

102. Abood, LG: Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents (1982) op. cit,

103. Ketchum JS: Summary of comparative characteristics of ten belladonnoid chemical agents in man, tested in 600 volunteers at Edgewood Arsenal, Maryland from 1961-73. Report prepared for the Special Committee on Anticholinergic Agents (40 pages). Toxicology Committee, National Science Council, National Academy of Sciences, Washington, DC, 1981.

104. Permissible Medical Experiments." Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Nuremberg October 1946 - April 1949, Washington. U.S. Government Printing Office (n.d.), vol. 2, pp. 181-182.

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(Note: Drugs studied are in bold font)

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An anti-chemical warfare activist, Dr. Martin Furmanski, was highly sympathetic to my efforts to bring forth an accurate and honest reconstruction of Army research with incapacitating (and other) agents. He even visited me and composed an enlightening summary of many relevant laws and treaties for my use in a related publication. An unnamed consultant in England provided, at the request of film producer Sebastian Seville, a detailed review and commentary of an earlier draft of this book. He noted that it was "not a bad book, but could have been so much better" were it not for my political naiveté. I thought this to be a fair and even favorable comment and wish I could meet his expectations. However, I did not intend to do more than summarize what I know to be true and did not feel qualified to advance any specific political viewpoint. I would prefer to think of my book as historical (as well as unashamedly autobiographical). I hope it will stimulate some discussion and a review of the relevant issues, but not be viewed as advocacy of any particular national policy.

Many of the personnel at what is now considered the medical research component of Aberdeen Proving Grounds (instead of the separate installation previously known as Edgewood Arsenal) also proved to be highly supportive. I had early misgivings that my work might raise some red flags in their Security Office, but was pleasantly surprised when none appeared. Mr. Lloyd Roberts, who deals with the release of information to those who request it, was especially helpful. He provided me with copies of old reports and films that I had not seen since the 1960s, when they were highly classified. Dr. Margaret Filbert, a physiologist and

pharmacologist who began work at Edgewood Arsenal in 1950 as a research assistant and now, after 57 years of uninterrupted employment, handles special projects in the office of the Commander, provided major support and interesting new information as we corresponded throughout the past year.

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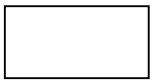
Writing a book, as many have said but few realize until they try it, can at times seem like an endless process. But with the continuing support of all the people mentioned – especially my steadfast wife Judy (amanuensis and general factotum) – this book at last seems ready to print. What a relief!

J.S.K.



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: To Jason:

Please print one blank 2-sided sheet after the above acknowledgements pages, to end the book. This is the conventional practice.

ABOUT THE BOOK

Chemical warfare watchers, from scientists to policy advocates, often wonder what went on at the Army Chemical Center during the 1960s. It was a decade in which thousands of Army enlisted men served as volunteers for the secret testing of chemical agents. The actual historical record, however, has until now remained disturbingly incomplete.

What chemicals was the Army studying? Why was the program never fully documented in books available to the public? Who planned and carried out the tests, and what was their purpose? How, and by whom, were the volunteers recruited? How adequately were they instructed before giving their informed consent? What long range effects, if any, have been found in follow-up studies?

Written by the physician who played a pivotal role in psychoactive drug testing of hundreds of volunteers, the story breaks an official silence that has lasted almost fifty years. Dr. James Ketchum may be the only scientist still equal to the task. His book goes a long way toward revealing the contents of once classified documents that still reside in restricted archives.

The author spent most of a decade testing over a dozen potential incapacitating agents including LSD, BZ and marijuana derivatives. His 380-page narrative, loaded with both old and recent photographs, derives from technical reports, memoranda, films, notes and memories. Written primarily for the general reader, but supplemented by a voluminous appendix of graphs and tables for the technically inclined, Dr. Ketchum's book combines a subjective diary with an objective report of the external events that shaped and eventually terminated the program. Informal and autobiographical in style, it includes numerous amusing anecdotes and personality portraits that make it simultaneously intriguing and informative.

ABOUT THE AUTHOR

James S. Ketchum, M.D. is a Board Certified psychiatrist and Assistant Clinical Professor at UCLA, who received his education at Dartmouth and Columbia colleges, Cornell Medical School, Letterman and Walter Reed Hospitals, and Stanford University.

In addition to his research at Edgewood Arsenal, he has broad experience in the area of alcohol and drug abuse and has published numerous scientific articles and book chapters. His teaching activities include many invited lectures, seminars and the direct supervision of medical students. As a clinician he spent 30 years in hospital and office settings, as well as a variety of community clinics and residential treatment centers. Currently he resides and writes at home in Santa Rosa, California.

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[1] Bliss CI. The Statistics of Bioassay. New York, NY: Academic Press; 1952

[2] Alexander E, Morris DP, Eslick RL: Atropine poisoning: report of a case with recovery after ingestion of one gram. New Engl. J. Med. 1946;234:258-259.

[3] Forrer GR: Atropine toxicity in the treatment of schizophrenia. Journal of the Michigan State Medical Society. 1950;49:184-185.

[4] Kimura KK: Current information from Hoffman-LaRoche, Inc., on RO2-3308 as of February 1960. Chem Warfare Laboratories Special Publication 2-29, 1960.

[5] Moran LJ, Kimble JO, Mefferd RB: Repetitive psychometric measures: equating alternate forms. Psychol Rept. 14:335, 1964.

[6] Aghajanian GK, Kitzes DL, Harper DG, Bottiglieri NG: EA 3580A: Estimate of minimal effective dose in man. Edgewood Arsenal, Md. CRDL Technical Memorandum 2-12. 1965

[7] Ketchum JS, Kysor KP: Effects of secobarbital on time estimation performance. Edgewood Arsenal, Md. Unpublished manuscript, 1962.

[8] Simmonds JS "VITA" time estimation apparatus: control data on 10 normal volunteers. Edgewood Arsenal Technical Memorandum 114-119, 1967.

[9] Ketchum JS, Kysor KP: A model for predicting the effect of anticholinergic compounds on cognitive performance. In Berdjis, C (ed.): Proceedings of a Contractors Conference on Behavioral Sciences. Edgewood Arsenal Special Publication No. 100-11, 90-102, 1965.

[10] Ketchum JS: The human assessment of BZ. CRDL Technical Memorandum No. 20-29. US Army Report, 1963.

[11] Zvirblis P, Kondritzer AA: Adsorption of H^3BZ and C^{14}atropine to the mitochondrial fraction of the rat brain. Edgewood Arsenal Technical Report 4042, 1966.

[12] Bell C, Gershon S, Carroll B, Holan G: Behavioural antagonism to a new psychotomimetic JB-329. Arch Intern Pharmacodyn Ther. 147:9-25, 1964.

[13] Miller JJ, Schwarz H, Forrer GR: Atropine coma therapy. Oral presentation to Michigan State Medical Society, 1957.

[14] Ketchum JS: Soldier's Predicament. Sound-color film. Graphics Arts Department, Chemical Research and Development Laboratories, Edgewood Arsenal, MD:1963.

[15] Ketchum JS:: The Longest Weekend. Sound-color 16mm film. Graphics Arts Department, Chemical Research and Development Laboratories, Edgewood Arsenal, MD. 1962.

[16] Forrer GR, Miller JJ: Atropine coma: a somatic therapy in psychiatry. Am J Psychiat; 115:455-458, 1958.

[17] Abood LG, Ostfeld AM, Biel J: A new group of psychotomimetic agents. Proc. Soc. Exp. Biol. Med. 97:483-486,1958.

[18] Kleinwachter I. Observations concerning the effectiveness of extract of calabar against atropine poisoning. Berl klin Wschr. 1:369-377, 1864.

[19] Dunn MA, Sidell FR: Progress in medical defense against nerve agents. JAMA 1989:262:649-652

[20] Ketchum, JS, Aghajanian GK, Bing, O: The human assessment of EA 1729 and EA 3528 by the inhalation route. CRDL Report No. 3226. US Army Report, 1964.

[21] Ketchum JS, Tharp B, Crowell E, Sawhill D, Vancil M. The human assessment of BZ disseminated under field conditions. Edgewood Arsenal, MD, Edgewood Arsenal Technical Report 4140, 1967.

[22] Klotz L, Furmanski M, Wheelis M: Beware the Siren's Song: Why "Non-Lethal Chemical Agents are Lethal, Federation of American Scientists: Chemical and Biological Arms Control Program, March 2003

[23] Sidell FR, Aghajanian GK, Groff WA: The reversal of anticholinergic intoxication in man with the cholinesterase inhibitor VX. Proc Soc Exp Biol Med.144-:725-730, 1973.

[24] Ketchum JS, Kitzes D, Mershon M et al. The human assessment of EA 3443, Edgewood Arsenal, MD. Edgewood Arsenal Technical Report 4066, 1967.

[25] Allen RP, Safer DJ: Exercise and incapacitating effects of EA 3580A in man. Edgewood Arsenal Technical Memorandum 114-15, 1968.

[26] Ketchum JS, Kysor KP: A model for predicting the effect of anticholinergic compounds on cognitive performance. In Berdjis, C (ed.): Proceedings of a Contractors Conference on Behavioral Sciences. Edgewood Arsenal Special Publication No. 100-11. 1965;90-102.

[27] Ketchum JS, Kitzes D, Copelan H. EA 3167: effects in man. Edgewood Arsenal Technical Report 4713, 1973

[28] Ketchum JS: Effects of EA 3167 in man. Edgewood Arsenal Technical Report. 1974;US Army report.

[29] Hart JJ, Balter L: A study of possible residual effects of EA 3443 and EA 3580 on cognitive ability. Edgewood Arsenal Technical Report 4044t.1966.

[30] Duvoison RC, Katz R. Reversal of central anticholinergic syndrome. JAMA. 1968;206:1963.

[31] Sidell FR, Aghajanian GK, Groff WA: Op. cit.

[32] Ketchum JS, Sidell FR, Crowell EB Jr, Aghajanian GK, Hayes AH Jr: Atropine, scopolamine and ditran: comparative pharmacology and antagonists in man. Psychopharmacology (Berlin) 2:140-165, 1973.

[33] Ketchum JS, Sidell FR, Crowell EB Jr., et al. Op. cit.

[34] Ketchum JS: Summary of comparative characteristics of ten belladonnoid chemical agents in man, tested in 600 volunteers at Edgewood Arsenal, Maryland from 1961-73. Report prepared for the Special Committee on Anticholinergic Agents (40 pages). Toxicology Committee, National Science Council, National Academy of Sciences, Washington, DC, 1981

[35] Ketchum JS: Incapacitating Compounds. Item II on the agenda of the first meeting of the quadripartite standing working group on chemical warfare. Proceedings of the 1965 Quadripartite CBR Conference. US Army Report, 1965.

[36] Abood, LG. Structure-Activity Relations of the Centrally Active Anticholinergic Agents, pp 275-284s. Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Volume 1 Panel on Anticholinesterase Chemicals, Panel on Anticholinergic Chemicals, Committee on Toxicology, Board on Toxicology and Environmental Health Hazards. (1982 Commission on Life Sciences, National Academy of Sciences).

[37] Alexander E, Morris DP, Eslick RL, op.cit.

[38] Locket S. Clinical Toxicology. London, England: Henry Kemptar; 1957. p4.

[39] Taylor AS. On poisons in Relation to Medical Jurisprudence and Medicine. 3rd American edition. Philadelphia, PA: Henry C. Tea; 1875. p740.

[40] Banerjee NR: The symptoms of datura – poisoning, with notes of thirty-two cases. Indian Med Gas.1885;20:209-211.

[41] Balazs J: Vergiftungs-Statistikaces Vingarn. Sammlung von Vergiftungsfallen.1933;4:263-270.

[42] Peterson F, Haines WS, Webster RW: Legal Medicine and Toxicology. 2nd Edition. Philadelphia, PA: W. B. Saunders; 1923. p629.

[43] Webster RW, ed: Legal Medicine and Toxicology. Philadelphia, PA: W.B. Saunders, 1930 p629.

[44] Wangeman CP, Hawk MH. The effects of morphine, atropine and scopolamine in human subjects. Anesthesiology. 1942;3:24-36.

[45] Ketchum JS: Incapacitating Compounds. Item II on the agenda of the first meeting of the quadripartite standing working group on chemical warfare. Proceedings of the 1965 Quadripartite CBR Conference. US Army Report, 1965.

[46] Kitzes DL, Vancil ME. Estimate of Minimal Effective Doses of BZ by the Intramuscular Route in Man. Edgewood Arsenal Technical Memorandum 2-30, 1965.

[47] Ketchum JS, Tharp B, Crowell E, et al. (1967) op. cit.

[48] Ketchum JS (1963) op. cit..

[49] Sidell FR: A summary of the investigations in man with BZ conducted by the US Army, 1960-1969. CSL 000-137, 1970.

[50] Kitzes DL, Ketchum JS. (1965) op. cit

[51] Ketchum JS, Kitzes D, Mershon M, et al. (1967) op.cit.

[52] Ketchum JS, Shiner P, Kysor et al. (1972) op. cit.

[53] Kitzes DL, Ketchum JS, Weimer JT, Farrand RL. (1967) op.cit.

[54] Aghajanian GK, Kitzes DL, et al. (1965) op.cit.

[55] Hayes AH, Copelan H, Ketchum JS. (1971) op. cit.

[56] Ketchum JS, Sidell FR, Crowell EB Jr., et al. (1973) op. cit.

[57] Elkin EH, Freedle RO, Cott HP Van, Fleishman EA: Effects of drugs on human performance. The effects of scopolamine on representative human performance tests. Technical Report 1, Contract No. DA-18-035-AMC-282[A], 1965.

[58] Ketchum JS, Goodman EP: Human responses to four anticholinergic deliriants. Proceedings of the 1962 Army Science Conference at West Point, NY. US Army Report, 1962

[59] Ketchum JS, Sidell FR, Crowell EB Jr., et al. (1973) op. cit.

[60] Abood LG, Ostfeld A, Biel JH: Structure-activity relationships of 3-piperidyl benzilates with psychotogenic properties Arch. Internat. Pharmacodyn. Therap. 120:186-200, 1959.

[61] Tharp BR, Mershon M, Bottiglieri N: Estimate of intravenous MED_{50} of CS 27349 (219,758). Edgewood Arsenal Task Plan 7010, Sep 1964

[62] Sidell FR, Ketchum JS, Markis JE, Kysor KP. Compound 302,196: intramuscular administration to man. Edgewood Arsenal Technical Report No. 4634, 1972.

[63] Ketchum JS, Kitzes D, Copelan H (1973) op. cit.

[64] Ketchum JS (1974) op.cit.

[65] Copeland HW. MED_{50} of agent 3834. (1968) op. cit.

[66] Cucinell SA, Cummings EG, Holgate SH: Sweat inhibition and performance decrements in man following percutaneous exposure to EA 3834. Edgewood Arsenal Technical Report EB-TR-76004, 1975.

[67] McCarroll E, Markis J, Ketchum JS et al. (1971) op. cit.,

[68] Hayes, AH, Jr:: CAR 301060: Estimate of minimal effective dose in man. Edgewood Arsenal Technical Memorandum, 1967

[69] Copelan HW: MED_{50} of agent 302282. Report No. IV, Contract No. DA-18-035—AMC-126 (A), 1967

[70] Copelan HW: MED_{50} of agent 302282. Final Report, Contract No. DA-18-035—AMC-126 (A), 1967.

[71] Copelan HW. MED of agent 302668. Final Report, Contract No. DA-18-035—AMC-126 (A), 1967

[72] Karger S. Incapacitating dose of CAR 302668 in man and efficacy of physostigmine as an antidote. Edgewood Arsenal Technical Memorandum 114-20, 1968

[73] Sidell FR, Karger S, Simons CJ, Weimer JT. Compound 302668: aerosol administration to man. Edgewood Arsenal Technical Report 4395, 1970.

[74] Sim VM: Compound 302,668: summary report. Edgewood Arsenal Special Publication 100-95, 1971.

[75] Arthur D. Little Inc. and Sterling Winthrop Res. Inst:. Preclinical pharmacology and toxicology of candidate agent 226086. Quart. Rept., 1 Mar. 1966 – 1 Sept 1966, Contract No. EA 18-108-AMC-103(A), 1966.

[76] Ketchum JS: Summary of comparative characteristics of ten belladonnoid chemical agents in man (1981) op.cit.

[77] Sim VM, Bertino JR, Collier D, Geiger LE, Klee G, Clovis ER, Kimura KK, Goodman AI, Clark BJ: Clinical Investigation of EA 1729. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; CRDL Technical Report 3074. US Army Report, June, 1961.

[78] Cohen S: LSD: the varieties of psychotic experience. J. Psychoactive Drugs Oct-Dec;17(4):291-96, 1985.

[79] Abramson HA, Jarvik ME, Kaufman MR, Kornetsky C, Levine A, Wagner M: Lysergic acid diethylamide (LSD-25):I. Physiological and perceptual responses. J. Psychol. 39:3-60, 1955

[80] Klee G, Bertino JR, Sim VM: Clinical psychiatric studies of subjects receiving EA 1729. Chemical Warfare Laboratory Report 2159. August 1957.

[81] Klee GD: Summary of psychological, physiological and biochemical studies performed under University of Maryland Contracts DA-18-108-CML-5519 and DA-18-108-CML-6337 in cooperation with Army Chemical Center personnel. May 1959

[82] Wickstrom C, Ketchum JS: Competitive "lightning chess" performance in volunteers after double blind- administration of small doses of LSD vs. scopolamine. Edgewood Arsenal, Maryland, Unpublished manuscript, 1964

[83] Aghajanian GK, Bing OH: Persistence of lysergic acid diethylamide in the plasma of human subjects. Clin. Pharmacol. Ther. 1964;5:611-614.

[84] Ketchum JS. Chemical Warfare: Secrets Almost Forgotten, In press, 2006

[85] Ketchum JS, Aghajanian GK, Bing O. The Human Assessment of EA 1729 and EA 3528 by the Inhalation Route. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; 1964. CRDL Technical Report 3226.

[86] Ketchum JS. Incapacitating compounds.(1965) op. cit.

[87] Hardman HF, Domino EF, Seevers MH. The chemistry and pharmacology of EA 1476 and the chemistry and pharmacology of certain compounds affecting the central nervous system of animals and man. Reports issued under Contract No. DA-18-108-CML 5663 between 1956 and 1959. U.S. Department of the Army, Chemical Warfare Laboratories, Army Chemical Center, Md.

[88] Ketchum JS. The marijuana story and EA 2233. Medical Research Laboratory, Edgewood Arsenal, Maryland, 1963 unpublished manuscript.

[89] Sidell FR, Pless JE, Neitlich H et al. Dimethylheptyl-delta-6α10α-tetrahydrocannabinol: effects after parenteral administration to man. Proc. Soc. Exp. Biol. Med. 1973;142:867-873.

[90] Hollister LE: Tetrahydrocannabinol isomers and homologues: controlled effects of smoking. Nature 1970;227:968-969.

[91] Ketchum JS: Marijuana, Alcohol and Driving Performance: a Protocol for assessment of driving performance in volunteers after administration of alcohol and marijuana, alone or in combination, compared to placebo. Department of Justice, Sacramento California, 1979.

[92] Ketchum JS, Reeve V, Hollister L: Effects in volunteers of alcohol and marijuana on driving performance. Department of Justice, State of California, Sacramento, CA Unpublished data, 1982.

[93] Biasotti, AA, Boland, P, Mallory, C, Peck R, Reeve VC. Marijuana and alcohol: a driver performance study a final report. California Office of Traffic Safety Project # 087902. California Department of Justice Report, Office of the Attorney General, Sacramento, California, September 1986.

[94] Moscowitz H: General hallucinogens, pp 77-90. In Willette RE (Ed.): Drugs and Driving. NIDA Research Monograph, March 1977.

[95] Klonoff H: Marijuana and driving in real-life situations. Science 176:317-324, 1974.

[96] Sidell FR, Pless JE: Ethyl alcohol: blood levels and performance decrements after oral administration to man. Psychopharmacologia. 1971;19(3):246-61.

[97] Ketchum JS, Reeve V, Hollister L: (1982) op. cit.

[98] Glassman EB, McLaughlin GA, Forman DT, Felder MR, Thurman RG: Role of alcohol dehydrogenase in the swift increase in alcohol metabolism (SIAM). Studies with deer mice deficient in alcohol dehydrogenase. Biochem Pharmacol. 1985 Oct 1;34(19):3523-6.

[99] Biasotti, AA et al. (1986) op. cit.

[100] Tharp B, Ketchum JS. Performance effects of fluphenazine, haloperidol. Clinical Research Division, Medical research Laboratories, Edgewood Arsenal, MD, Unpublished manuscript, 1965.

[101] [Government Report] Inspector General of the Army Report. "Use of Volunteers in Chemical Agent Research," 3/10/76

[102] Abood, LG. Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents (1982) op. cit,

[103] Ketchum JS: Summary of comparative characteristics of ten belladonnoid chemical agents in man, tested in 600 volunteers at Edgewood Arsenal, Maryland from 1961-73. Report prepared for the Special Committee on Anticholinergic Agents (40 pages). Toxicology Committee, National Science Council, National Academy of Sciences, Washington, DC, 1981.

[104] Permissible Medical Experiments." Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Nuremberg October 1946 - April 1949, Washington. U.S. Government Printing Office (n.d.), vol. 2., pp. 181-182.