DEPARTMENT OF THE ARMY
UNITED STATES ARMY INTELLIGENCE AND SECURITY COMMAND
FREEDOM OF INFORMATION/PRIVACY OFFICE
FORT GEORGE G. MEADE, MARYLAND 20755-5995

REPLY TO
ATTENTION OF:

August 30, 2005

Freedom of Information/
Privacy Office

Mr. Russ Kick

Dear Mr. Kick:

References:

a. Your electronic Freedom of Information Act (FOIA) request of December 16, 2004, to the Department of the Army, Freedom of Information and Privacy Acts office for the documents BZ Psychochemical War Agents (377F-05) and Clinical and Military Medical Aspects of Psychopoisons (378F-05). Your request was forwarded through Army channels and received in this office on January 19, 2005.

b. Our letter of January 20, 2005, advising you that the information you requested must be searched for at another element of this command, and we were unable to comply with the statutory 20-day time limit in processing your request

As noted in reference b above, our search has been completed and we have been provided with the documents responsive to your request. We have completed a review of the information and determined it is partially releasable to you. The documents BZ Psychochemical War Agents (377F-05, enclosure 1) and Clinical and Military Medical Aspects of Psychopoisons (378F-05, enclosure 2) are provided for your use. All fees associated with this request are waived.

Information has been sanitized that is predominantly internal in nature the disclosure of which would significantly risk circumvention of agency regulations or statutes. This information is exempt from the public disclosure provisions of the FOIA pursuant to Title 5 U.S. Code 552 (b)(2).

The withholding of this information constitutes a partial denial of your request. You have the right to appeal this decision to the Secretary of the Army. Your appeal should be forwarded to this office within 60 days from the date of this letter. After the 60-day period, the case may be considered closed; however, such closure does not preclude you from filing litigation in the courts.

If you have any questions concerning this action, feel free to contact this office at (301) 677-2127. Please refer to the case numbers cited above.

Sincerely,

Susan J. Butterfield
Director
Freedom of Information/Privacy Office
Investigative Records Repository

Enclosures

A & P BRANCH

DEPARTMENT OF THE ARMY
U.S. ARMY FOREIGN SCIENCE AND TECHNOLOGY CENTER
220 SEVENTH STREET NE.
CHARLOTTESVILLE, VIRGINIA 22901

TRANSLATION

In Reply Refer to:
FSTC-HT-23-1911-72
DIA Task No. T70-23-01

Date: 20 March 1973

ENGLISH TITLE: CLINICAL AND MILITARY MEDICAL ASPECTS OF PSYCHOPOISONS

SOURCE: Zeitschrift Fur Militarmedizin, 6/1971, pp 315-332

AUTHOR: W. Bousseljot

LANGUAGE: German

COUNTRY: Germany

REQUESTOR: AMXST-TD, Mr. Klugerman

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SI-3-52 542

NOTICE

The contents of this publication have been translated as presented in the original text. No attempt has been made to verify the accuracy of any statement contained herein. This translation is published with a minimum of copy editing and graphics preparation in order to expedite the dissemination of information.

[redacted]. Other requests for this document must be referred to the US Army Foreign Science and Technology Center.

Enclosure 2

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This paper gives an overall view of the division of psychopoisons into psychotomimetica and disturbers. We shall not go into a detailed discussion of substances already widely known, but we shall try to order the psychotomimetica from a clinical standpoint into 2 psychopathologically different groups. In addition to a detailed description of the general intoxication symptoms, synthetic substances of both groups are described. Finally, the military application of psychopoisons and possible medical treatments are discussed.

In military medical literature, psycho poisons (psychological warfare agents) are understood to be chemical warfare agents, which produce psychotic states or other disturbances of the central nervous system, and thus lead to the temporary disability of the affected party. In the last 15-20 years, these substances have resulted in a new development towards chemical warfare on the part of the NATO forces, and they play an increasingly large role in Western military literature.

At the same time, the Western powers attempt to make these substances appear harmless to the general public by means of appropriate publications in the mass media, where mention is made of temporarily incapacitating weapons which are not harmful and therefore 'humane'. The real aim of this development of chemical warfare agents is made quite clear in the following statements by the director of the Medical Research Department of the Warfare Agent Laboratories of the U.S. Army, of 1960(15):

"Atomic bombs destroy people and materials. Perhaps we can outlaw them or refrain from using them. Highly toxic substances kill people but leave untouched substances which can later be usefully employed. Psycho warfare agents, applied in the correct dosage, render people temporarily incapable of action or combat, but do no damage to either people or materials. They allow a surprised enemy to be taken prisoner without effective resistance or productive action. They also permit simultaneous usage

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against friend and enemy, for instance, in enclosed areas or strong points where there are still civilians who are for the most part unprotected."

Lohs (17) points out that this tendency to trivialize psycho poisons as non-fatal or even non-harmful, is scientifically and politically misleading. Apart from the incalcuable later effects (manifestation of a psychotic state), the use of these substances can lead to acute dangers to the life of the recipient and those around him, in the form of psychotic actions (aggression, suicide,13). Moreover, it is impossible to control the dose accurately (18); thus harmful effects cannot be ruled out. It is certainly possible to determine the average, but not the actual, concentration, because this is dependent on many factors which cannot be calculated in advance. Also, the reactions of the victims will be completely different depending on age, body weight, sex and state of health.

It can be assumed that in the next few years certain synthetically produceable psycho poisons will be taken over by the imperialistic armies to a great extent, amongst which the piperidylglycolates have recently become the focal point of interest (3). It is scarcely possible to predict exactly which substances are going to be used, as the number of newly discovered or synthesized substances is constantly increasing, and the accessible information is, according to Lohs(17), vague and not free from obvious deceptions.

Therefore we intend to give here only an overall view of subdivisions, general symptoms and principles of usage of psycho poisons, without dealing with all relevant substances in detail.

1. Subdivision of Psycho Poisons

Within the armies of the Warsaw Pact, psycho poisons are regarded as "chemical warfare agents producing temporary disability", and are further subdivided into

- psychotomimetica and
- disturbers.

(13) In the NATO area, however, they speak of psycho warfare agents which are regarded as "substances producing disability", and subdivided into psychotoxic (psychotomimetica) and psychotropic substances (14).

1.1. The psychotomimetica cause psychopathological images such as those generally observed in cases of exogenous psychosis, where the prominent symptom is one of an acute exogenous reaction (Bonhöffer). As a result of the psychotic injury, physical disability results.

The psychotomimetica can be further subdivided according to their chemical composition (table 1). For practical purposes, however, it seems better to proceed from the intoxicated psychopathological image in order to subdivide further. The relevant substances may be divided into 2 groups according to this criterion.

Table 1

Subdivision of psychotomimetica according to their chemical composition (Franke, 9).

1. Indole derivatives

1.1. Lysergic acid derivatives
- lysergic acid diethylamide
- lysergic acid ethylamide
- lysergic acid hydrazide
- lysergic acid morpholide

1.2. Tryptamine derivatives
- N.N.-dimethyltryptamine (DMT)
- bufotenine
- psilocybin, psilocin

2. Phenylaminoalkane

- mescalin
- trimethoxyphenyl-aminopropane (TMA)

3. Piperidine derivatives

- sernyl
- piperidylbenzilate and -glycolate

1.1.1. Substances of the LSD type

In the case of all these substances, the psychopathological symptoms are very similar after an average dose, and basically correspond to an LSD intoxication. Optical hallucinations predominate, based on a psychotoxic basic syndrome. Under experimental conditions, these substances preserve the subject's insight into the artificiality of the situation, and there are no outstanding disturbances of consciousness. To this group belong amongst others:

- LSD
- psilocybin
- mescalin
- tryptamine derivatives

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1.1.2. Substances of the Ditrane type

Here the dosage which produces an optical hallucination is very small. Even light doses lead to heavy disturbances of consciousness with delirious symptoms and strong mnesic disturbances; contact with the reality of the environment and insight into the artificiality of the situation are lost. In addition to optical hallucinations, there are strong hallucinations of an acustic, tactile and olfactory nature.

To this group belong amongst others:
- ditrane and other piperidine derivatives
- lysergic acid monoethylamide
- butoxamine.

1.2. In the disturber group, we include those substances which produce either objectively identifiable disturbances of the psyche or central nervous system, or subjectively experienced changes, thus leading to a definite physical disability (12).

There is no sharp distinction between the 2 psychopathologically effective groups of psychotomimetica, or between psychotomimetica and disturbers; rather, there are transitional stages which largely depend on the dose taken (19). For example, a small dose of ditrane is similar to an LSD type hallucination, whereas a slight increase of the dose causes disturbances of consciousness, and a further increase - independent of the psychic development - results in inadequate physical actions.

2. Symptoms of psychopoisonous effects

2.1. General effectiveness of psychotomimetica

The psycho-physical disturbances caused by psychotomimetica reveal a variety of common symptoms, which are all more or less identifiable in all these intoxicants. The following symptom complexes can be individually distinguished in experimentally released psychoses (13,16):

Vegetative symptoms

Vegetative symptoms generally precede psychic effects. As a rule, there is a predominantly restraining sympathetic tone, but at the same time parasympathomimetic traits can be identified. The following are found in individual cases: general lack of well-being, outbreaks of perspiration, sensations of hot and cold, retching or vomiting, weakness and exhaustion, mydriasis, bradypnea, bradycardia or tachycardia, hyper- or hypotonia, flow of tears, pilo erection, headaches. Slight temperature increases, blood sugar increase and leukocytosis are also often identifiable.

Motor disturbances

Here the most important factors are atactic disturbances such as difficulty in walking, reaching to one side, disturbance of finer movements and of speech. Sometimes very definite choreic- athetotic images are produced (for example with TMA), whilst with bufotenine an obvious nystagmus is identifiable.

Disturbances of optical perception

Beginning with simple elementary hallucinations (extended after images, grid images, flickering, glowing, spraying, glittering, colorful smoke or stripes, etc.), the effect proceeds to more complex images with a scenically arranged course of events. Characteristic here are constant change and multiplicity of images, with simultaneous appearance of micropsia and macropsia, and illusionary recognition of the environment. These are generally so-called pseudo-hallucinations with retained reality judgement (i.e. the person concerned is aware of the unreality of his perceptions) which, depending on the dose taken, can turn into genuine hallucinations.

Disturbances of acustic perception

are of minor significance, and generally take the form of elementary hallucinations (acousmae): rumbling, roaring, clinking, ringing, voices or simply hyperacousmae.

Smell and taste hallucinations

are very rare.

Abnormal body sensations

take the form of a "variety of partly extraordinarily enjoyable, partly strangely anxious sensations"(13), with disturbances of body image, body changes, reduced sensations of pain or comfort, and of hot and cold.

Disturbances of time and space perception

The sensation of time is slowed down, speeded up or completely removed, and spacial dimensions, such as the form of objects, appear changed.

Synesthesia

is characteristic of most psychotomimetica, (for example, transfer of acustic phenomena into the optical and physical spheres).

Changes in consciousness

The type and extent of disturbance of consciousness is essentially dependent on the dose taken and the type of psychopoison. Most substances produce a dream-like change of consciousness, passivity, dream-like engrossment, turning away from the real world and strong leaning toward the psychotic inner life. According to Leuner (16), as the effect of the poison increases, an "increasing loss of self-control" takes place, which makes the realization of choices more difficult by decreasing the functioning of the will; this can lead to the disappearance of the intention to make decisions at all. Presence of mind and the sense of orientation are often retained to a large extent.

Changes in thought processes

Predominant here are formal thought disturbances with loss of line of thought; therefore leaping, incoherent thought processes result, up to the point of rapid succession of ideas. On the other hand, a decided stagnation of the flow of thought can sometimes take place. There is frequently a reduction in abstract and conceptual thinking. Less frequent are disturbances of thought content, such as abnormally significant experience, related ideas and paranoid symptoms.

Changes of affectivity

Specific changes are not identifiable here. Considerable emotional instability is the most frequent feature, with oppositional changes of mood where a euphoric state often dominates.

By narrowing consciousness down to the psychotic level of experience, an 'affective anesthesia' can come about with respect to the real environment.

Psychotoxic basic syndrome

Leuner (16) groups together the changes of consciousness, thought and affectivity as a psychotoxic basic syndrome, because these changes can be found relatively unspecifically in all cases of toxic psychosis and are distinguished by their unusual stability.

2.2. Synthetic substance LSD: lysergic acid diethylamide (17,19)

LSD is a crystalline substance which melts and decomposes at 83°C, is soluble in water as a tartrate, and in this form does not reach melting point until about 200°C.

The psychic effects of this substance were discovered in

1943 by Hofmann, in the laboratory of Sandoz AG. Since 1954, total synthesis has been possible, but at present it is more economical to partially synthesize from lysergic acid in the form of ergot alkaloids.

LSD is effective under experimental conditions in a dosage of 0.5 - 1 microgram per kg, i.e., an average of 30 - 60 micrograms per person, taken orally or inhaled. For military use, the so-called threshhold dose of 10-20 micrograms, or the psychosis dose of 60 micrograms per person (based on an average weight of 70kg) is given. The lethal dose, in the case of intravenous administration, with an LD_{50} of 0.3 micrograms per kg (rabbits) and 46 micrograms per kg (mice), is extremely high. In the case of oral administration, vegetative symptoms appear after 20 mins, whilst the psychic symptoms take 40-60 mins to appear. The maximum psychic effect is reached after 2-3 hours, and after 8-12 hours the effect generally dies down.

On the subject of the course of an LSD psychosis, the impressive description by Cerletti and his fellow workers (17) is repeated here at length:

"With an oral dose of 30-60 micrograms of LSD, vegetative-nervous physical symptoms appear after about 15-30 mins, preceding the psychosis, such as enlarged pupils, slight increase in heart rate and blood pressure, which indicate a central emotional disturbance. Less frequently, signs of parasympathetic stimulation occur, such as increased saliva flow, nausea and vomiting. These slightly troublesome effects disappear in the further course of the reaction. Psychic changes begin to predominate, such as disturbances of perception, of the emotional state, of thought and of the ego-consciousness (depersonalization). Perception distortion manifests itself predominantly in the visual area; initially there are elementary hallucinations such as spots, lights, foggy patches, snow flakes, geometric forms, etc., which are generally small and colorful and cross the field of vision in groups. In addition to these optical phenomena, which are first perceived with closed eyes or in the dark but may later be seen with open eyes in bright sunlight, an illusionary attitude to the environment soon develops: objects seem to undergo a color change, to be unusually sharply outlined or strangely unfamiliar and distorted. Stationary objects appear to be in motion; for example, spots on a laboratory work bench appear as hoards of rapidly fleeing salamanders. Surfaces move rhythmically back and forth, or in wave formation like a water surface. Distances are lengthened or shortened, and perspective may sometimes change rapidly. Faces appear altered or distorted in expression; here the momentarily affective attitude of the subject is very important. The strongest form of perception disturbance are figure hallucinations (visions), in which people,

animals, buildings, even whole cities and landscapes, appear, often of great beauty and only occasionally ugly or frightening. These figure hallucinations occur only rarely, and the reaction does not generally extend beyond the elementary images and illusions (geometric figures etc.). Acustic phenomena usually take the form of increased hearing sensitivity. Abnormal taste or smell perception does not play a very significant role, but anomalies of the tactile sense are not unusual. At the high point of the reaction, disturbances of the body image develop. In extreme cases, the body may be felt to be too long or too short or as not belonging to the subject, or the entire body or a part of it may be felt to be unusually heavy or light.

The emotional state is predominantly euphoric; sometimes compulsive laughter develops. Depression and anxiety may be observed occasionally; different moods can succeed each other rapidly. Thought disturbances are expressed by reduced attentiveness, difficulty in concentrating, and rapid succession of ideas. In a negative, mistrustful atmosphere, inimical, paranoid thoughts may arise against those present, and they are often expressed without inhibition. It is important to note that the subject of the experiment almost always knows that all these abnormal reactions and experiences are caused by the chemical substance. Consciousness is retained but can be altered as in a dream, especially in the case of lively hallucinatory activity. The sense of time is often disturbed, generally in the form of an overestimation of time. Very intensive reactions on LSD can have the result that the normal feeling of identity with oneself is weakened (depersonalization). In connection with depersonalization, predisposed people can come to the point of experiencing a dissolution into the universe ('cosmic consciousness'), which is later remembered as a joyful, enriching experience. In addition to depersonalization, the high point of an LSD reaction can produce a sensation of the unreality of the environment, which is naturally defined by its illusionary nature to a great extent."

2.3. Synthetic substance ditrane

Ditrane is the most effective compound of the group of piperidylglycolates. Chemically, it is a mixture of 30% N-ethyl-3-piperidylcylopentylphenylglycolate and 70% N-ethyl-2-pyrrolidylmethylcyclopentylphenylglycolate. The effective dose is 70-200 micrograms per kg of body weight in the case of oral administration; this corresponds to an average of 5-15mg per person.

The psychotic symptoms appear after about one hour and last for 12-24 (or 48) hours.

The intoxication symptoms are distinguished by the initial appearance of vegetative symptoms (mydriasis, dryness of the mouth, hyperemia of the skin, hypertonia, tachycardia).

At the same time, walking and speech become disturbed; ataxia develops. A heavy disturbance of consciousness predominates in the psychic area, with amientiel-delirious symptoms. Contact with the reality of the environment, and insight into the artificiality of the situation are lost, and definite mnetic disturbances result. Thought processes and concentration become difficult, and the logical sequence of thoughts is lost. In addition to optical illusions, acustic and tactile hallucinations are also experienced strongly; delusions and paranoia are common.

The emotional state is distinguished by emotional changes from euphoria to dysphoria and sometimes agression.

2.4. Disturbers

The use of this type of substance as a warfare agent is based on the fact that it is not necessary to produce a psychotic state to guarantee disability, especially as behaviour in a state of toxic psychosis can never be predicted exactly. For example, it is sufficient to disturb the perceptive functions, the time/space sensations or the motor functions, in order to minimize the combat ability of a soldier. It is conceivable that with such substances as these, quite definite military personnel can be reached (such as aircraft pilots, truck drivers, radar and control personnel), where the introduction of disability would become easier depending on the degree of differentiation of the victim's activity.

The number of chemical compounds which could be used in this way is so large that we cannot go into different substances individually. Substances which produce the following symptoms would be suitable:

- physical disability (sedatives, tranquillizers, stimulants, neuroleptics)
- disturbance of hearing and balance
- disturbance of vision
- lowering of blood pressure
- vomiting
- inhibition of the motor functions (tremors, paresis).

The following substances of this group are mentioned as examples in the available literature (15,20).

Tremorine

This substance produces strong tremors, connected with muscle weaknesses, excessive saliva flow and miosis.

IDPN

The application of this compound to experimental animals leads to an irreversible situation where the animals run around in circles, describing a circle with their heads, without endangering their lives.

Substance "beta"

In the U.S. Army, this designation is used for a chemical warfare agent whose chemical structure is not known and which causes "confusion, psychic weakness, temporary blindness and deafness" (15).

3. Possibilities of military application

3.1. The military application of psychically effective substances as psycho poisons is limited to compounds which fulfil the following conditions (2,12):

- the effective dose must be appropriately small (in the region of a microgram to a few milligrams)
- relatively simple industrial production (at present piperidine derivatives are the least complicated)
- must be capable of aerosol form for use in open country; according to Häsig (3), almost all substances can be transformed into aerosols by the use of propellant gases, in so far as the substance is soluble in the liquified gas. A concentration suitable for combat use is then achieved by dropping a few aerosol generators by parachute.
- low freezing point (for use in cold temperatures)
- absorbability
- the substances must be colorless, odorless and tasteless, and may not have any other immediately observable psychological effects, so that the effective dose is taken before any protective measures can be begun.

3.2. The use of psycho poisons and their penetration into the organism can take place in the following ways:

- 'injection' by impregnated splinters
- inhalation (gas or aerosol)
- absorbtion through the skin (skin-affecting gases or contamination of objects with e.g. LSD)
- orally, for instance by contamination of drinking water, or use as a sabotage instrument in large kitchens (6,12).

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3.3. The use of psycho poisons can

- be applied to sabotage (by contamination of central water supply and stores) or
- be applied during the course of combat.

According to statements by Western military sources (Bäsig, 2), psychochemical warfare agents are especially intended:

- for use against unprotected civilians or military units which are acting independently and have only inadequate supplies and protection
- to eliminate special command headquarters, information centers, security forces
- against targets which are to be suppressed temporarily (security forces, operating personnel in industrial and traffic installations)
- in a case where it is necessary to take the enemy alive
- against units which have been subject to strong physical and psychic burdens in recent combat, or against fresh units who have little combat experience (high probability of panic)
- in engagements on one's own territory when the use of other means seems unsuitable, for instance, in consideration of one's own population
- against one's own population in case of unrest.

3.4. According to Klose (15), the U.S.Army already has 4 different psycho poisons whose chemical structure has not yet been published, and which are known under the following names:

- substance "alpha"

  Here we are dealing with a warfare agent with an uncomfortably irritating effect, which begins 30 mins after administration. According to the given parameters, this substance is 3 times as effective as sarin, but the necessary contamination density is said to be only a tenth of the value of sarin.

- substance "beta"

  (Already described in paragraph 2.4)

- substance "sigma"

  The only information we have on this substance is that its effect is said to last 8 hours.

- substance "BZ"

  This is a piperidine derivative, which causes strong

optical and acustic hallucinations, connected with unpleasant sensations up to the strongest anxiety states. Klose (15) also gives concrete details of 2 American bomber types which are fitted with "BZ", and of some sprayer types already in use.

An eye-witness report on the use of "BZ" by the U.S. Army in Vietnam was published by Gestewitz (10).

4. Possible medical treatments

4.1. The normal methods of medical assistance are probably of little importance for the majority of those affected by psycho poisons, as all psychopathological images will disappear within 24 hours even without therapy. Some people may, however, retain psychotic disturbances or definite psychoreactive symptoms or combined injuries. They must be treated in the appropriate way.

4.2. A real prophlyaxis is practically impossible in the case of psycho poisons. Statements have certainly been made on the topic (12), such as the suggestion that a week-long treatment with 200-600mg chlorpromazine a day, or 5-12.5mg reserpine, can prevent toxic psychosis. Such a practice would, however, also inhibit the combat ability of the person treated, and is therefore scarcely to be recommended.

In addition, the possibility of chemical identification of these substances under field conditions is at present uncertain, so that identification of psychochemical warfare agents can only take place on the basis of the symptoms. Because of the relatively long interval before the symptoms appear, by this time all those subject to the effect of the substance will have taken the appropriate dose. As these substances are almost always used in aerosol form, a protective mask is adequate protection, and therefore should be worn at the least suspicion.

4.3. First aid measures can therefore only consist of making the victim wear a gas mask in order to prevent further poisoning. Comforting and calming of the victims must be organized, to counteract anxiety tendencies and illusionary perception of the situation - as far as one can still make the abnormality of the situation understandable to the victim. Moreover, all those affected must be immediaely disarmed.

Complete disorganization of the unit can only be avoided by a rapid and decisive operation. It must also be taken into account that soldiers who wre not expecting any such intoxication, will react abnormally or with signs of a pseudo-sickness, and panic can spread very easily.

4.4. Administration of medical help requires that:

- after removal of weapons, the victims are separated from those who are unharmed
- care is taken of extreme cases
- observation of the injured for the next 8-10 hours is organized.

The actual treatment could then be an unspecific sedative (e.g., sinophenine), readily available as an antidote. As the psychopathological images generally die down without treatment in a few hours, if necessary one can restrict oneself to treatment of the worst cases or of those who have very important tasks to fulfil (15).

The following antidotes are mentioned in the literature on the subject:

For LSD:
- propaphenine (50-100mg)
- frenquel (20-100mg per os, immediate effect with 200mg)
- 5% phosphate buffered succinic acid (5ml/min) (11)

For ditrane:
- tetrahydroaminoacridine (30-60mg; almost complete interruption of situation by change of peripheral autonomous effect)

4.5. As a decontamination measure, it is sufficient to wash the surfaces of weapons and equipment with water and washing powder (2). Contaminated food and drinking water must be destroyed, as it is not possible to decontaminate them at present.

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TRANSLATION

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[redacted] Other requests for this document must be referred to the US Army Foreign Science and Technology Center.

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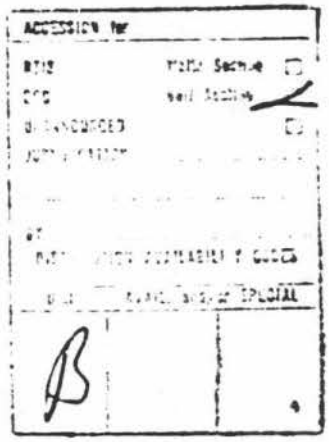
Enclosure 1



War agents, with a BZ code designation in the literature belong to a group of toxic agents with temporary disabling effects; their toxic effect is on the human vegetative and normative functions, thus their designation as psychochemical war agents. There are, though, other designations, such as hallucinogens, depersonilizers, fantasticums, psycholites, and so on, but the designation psychochemical war agents is the generally accepted terminology in the military literature. The BZ agents, as chemical weapons, are standardized in the USA army since 1963 (10, 23) and there is information on their use in the Vietnam war (21).

The complete chemical structure of this agent (or group of agents) was not known for a long time. According to data from the literature, however, it was justifiably suspected that these are compounds from the group of anticholinergic substances which with their chemical structure represent esthers of higher heterocyclic alcohols (piperdinol, pyrolidinol, hinuchlidinol, and so on) with diphenilglycol (benzyl) acid.

The general chemical formula of these esthers is shown in Figure 1

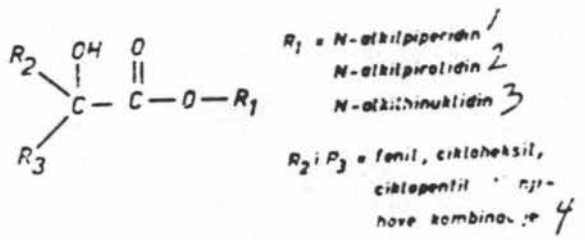


Figure 1

Key: 1 -- Alkylpiperidine

2 -- Alkylpyrolidine

3 -- Alkylhinuchlidine

4 -- pheryl, cyclohexyl, cyclopentite, or their combinations

These compounds were probably discovered during research for effective spasmolitic drugs, or new antidotes for treating poisoning from anticholinesterase compounds. (13)

According to a fairly large number of data (22, 23, 27) BZ agents are hinuchlidine esthers of the diphenilglucolic acid and have the following formula:

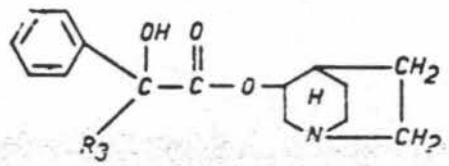


Figure 2

As shown in the above formula it is obvious that the general chemical

structure of the esther, given in Figure 1, is not destroyed: the residue of hinuchlidinole alcohol is in position R, while R_2 and R_3 represent the residues of the diphenylglucolic acid.

In addition to hinuchlidine esthers (BZ), as a model of the substance, a series of compounds were synthetized and examined among which the best known are peperidilbenzylate (JB - 336), then ditran (JB - 329), and other compounds from this group. With respect to physical-chemical properties, these compounds are white crystals, of a slightly bitter taste, insoluble in water when used in the form of a base. However, when transformed into hydrochloric acid salts they become easily soluble in water.

As for the role of the chemical structure on the occurrence of psychopharmacological effects, systematic research has shown that for the psychomimetic action of these compounds the molecule must contain the OH group on the alpha-C atom and the tertiary nitrogen atom in heterocyclic alcohol (2).

Toxicologic and Pharmacologic Properties

BZ agents, same as other modular compounds of this group, belong to relatively slightly toxic compounds. The average lethal dosage for rodents amounts to 100 to 200 mg/kg of body weight at the time of intraperitoneal administration. In case of the agent intravenous injection the toxicity is greater and the average lethal dose amounts to 25 to 30 mg/hg of body weight. However, even these quantities are very large compared to the dosages that have psychopharmacologic effects on humans. The disabling concentration for humans of BZ agents in the atmosphere should amount to about 4,000 mg/min/m^3, or only 0.07 mg/kg of body weight (22). Under experimental conditions the psychopharmacologic effect of BZ agents on humans occurs after intramuscular injection of 0.006 mg/kg of body weight (27), or 0.05 to 1 mg/kg, for ditran injections (4, 12).

Such small quantities of BZ agents and modular compounds that have strong psychopharmacologic effects indicate the high selectivity and specificity of psychomimetic influence of BZ agents on the human organism.

As for the pharmacologic aspects, the diphenylglycolic acid esthers are antiholinergic compounds with a characteristic psychomimetic effect on humans (1, 2, 18) and strong effect on the central nervous system and higher level nervous activity in animals (2, 6, 16, 17, 18). BZ agents act similarly to atropine and under experimental conditions it was demonstrated that they stop spasms caused by acetycholine, reduce the increased arterial blood pressure in animals caused by irritation of the vagus, remove bronchial spasm and spasms in other smooth musculature, cause mydriasis and accomodation paralysis, block the excretion of salivary and exocrene glands and so on. In brief, they have the antiacetylcholine effect of the antimuscarine type. In comparison with atropine, however, the anticholinergic effect of BZ agents is much stronger, even 10 to 100 times stronger than that of atropine (3, 2, 19).

BZ agents and other compounds from this group cause various disturbances of higher level nervous activities, known as the "central anticholinergic syndrome" (18). In experimental animals this syndrome is manifested through psychomotor excitation, ataxia, adynamy, certain changes in EEG and various disturbances in animal behavior (effect on learning, performance and extinguishing of conditioned behavior.) The central anticholinergic syndrom is particularly strong in dogs who for several reasons are the most suitable experimental subjects for the study of BZ agents. The appearance and intoxication dynamics of BZ agents toxic effect on dogs approximates most closely the clinical findings in humans (3, 4, 20). Namely, BZ agents cause in dogs the identical neurovegetative changes as in men, while the disturbances in

behavior and motor activities (ataxia, loss of contact with the outside world) are very similar to changes observed in humans after taking the substances mentioned above.

Clinical Picture of Intoxication with BZ Agents

The clinical picture of the intoxication of humans with BZ agents and modular compounds of this group is essentially not different from the one found after taking larger amounts of atropine and related natural alkaloids. The clinical manifestation of intoxication with this group of agents consists of disturbances in the neurovegetative system and psychological functions.

1. Disturbances of the Vegetative System

The first signs of BZ agents toxic action are peripheral vegetative disturbances which occur regularly, in varying degrees of severity, after taking the agent. In the majority of cases observed were tachycardia, complete or considerable drying of the mouth and upper respiratory ducts, skin reddening, urine retention, tremor of the fingers, mydriasis with changes in pupils reaction to light and accomodation paralysis. Among the problems of a subjective nature we should mention a burning sensation in the throat and mouth, sensation of heat in the body and retrosternal pain. Vegetative disturbances of central origin, unrest, ataxia, more difficult coordination of movements, dizziness, headache, sleepiness, increased reflex activities, hyperthermy and hyperthony occur simultaneously, or somewhat later, with these symptoms of vegetative disturbances. Depending on the progress of vegetative intoxication symptoms, we differentiate the intoxication initial period which includes the above mentioned peripheral vegetative disturbances and the second, stupor stage, which includes the described central vegetative disturbances (15).

The vegetative disturbances appear very soon, up to 30 minutes after taking BZ agents and usually last several hours, except mydriasis, which disappears only after several days.

2. Disturbances of Psychological Functions

The first symptoms of damage in psychological functions appear even during the vegetative disturbances. The disturbances of psychological activities are complex, varied and have a dramatic character. This stage of intoxication is characterized by a gradual progress of a series of different psychological disturbances, from dizziness to severe delirious conditions of the intoxicated persons.

a) Delirious Condition

The delirious conditions following intoxication with BZ agents is manifested by the clouding of consciousness and the thinking process, temporary and full loss of contact with the surroundings, hallucinations, illusions, asynergy, strong psychomotor unrest and breaks in attention continuity.

The basic psychopathological syndrome is certainly the delirious condition. It initially appears as dizziness, then gains in intensity until the intoxicated person almost completely loses contact with the outside world. Such a condition is accompanied by different hallucinations (visual, audio, smell, tactile, and so on), which represent the basic disturbances of perception. Among the affected disturbances the strongest are discomfort and fear. Of special interest for the military important are disturbances in speach and understanding in addition to disorientation and loss of contact on the part of the intoxicated person. Speach becomes incoherent, fragmented, and is accompanied by inadequate and incomprehensible mumbling. Profane and declaratory phrases, metaphors and literary enunciation of simple phrases dominate the speach. In such cases it is sometimes difficult and impossible to grasp what the patient understands and thinks when replying to questions.

The reason is that the intoxicated one seldom understands the question, cannot remember what he was thinking himself when formulating the reply, nor is in condition to define it adequately. Only in rapid and semi-automatic answers it is possible to establish contact with the patient.

The delirious - hallucinatory intoxication phase usually starts to develop 1 to 1.5 hours after the onset of intoxication, and begins to subside after 6 to 8 hours.

The form, severity and progress of acute psychotic episodes do not depend only on the dosage of BZ agents or the chemical structure of modular compounds, but also on the individual psychodynamic characteristics of the person. This is the so-called "non-specific" component in the action of all psychomimetic substances which depends on the person himself, particularly his emotional condition prior to intoxication.

b) Lethargic Condition

Upon completion of the delirious phase of intoxication there is a lethargic condition which usually develops 12 to 24 hours after the intoxication. Sleepiness or deep sleep, sluggishness, adinamy, tiredness, and so on, predominate in this phase. Certain authors call the described disturbances as "delayed effects" of these substances (12). Comatose can occur in cases of intoxication with large doses of BZ agents.

On the basis of the described intoxication clinical picture, it is obvious that there is definite regularity and dynamics in the appearance, progress and disappearance of certain symptoms of BZ agents intoxication. In addition to clearly defined neurovegetative disturbances, the psychological difficulties of the intoxicated person develop gradually from dizziness through advanced hallucinatory-delirious phase, the latter to

be replaced by the lethargic phase. This is why it is possible to differentiate diagnostically between BZ agents intoxication and acute psychological conditions caused by psychomimetic substances (LSD, mescaline, and similar). In table 1 we present a comparative clinical picture of the action of BZ agents, LSD, anticholinesterase and anticholinergic compounds, which can serve as a basis for differential diagnosis.

Table 4

Comparative Clinical Picture of the Effect of BZ Agents and Certain Other Hallucinogenes (As given by Joycen (13))

Compound	Hallucination	Paralysis	Hyperthermy	Bradi-Psychosis	Vertigo	Hypertension	Head-Ache	Lacrimation Salivation	Diarrhea
BZ	+	+	-	+	+	±	+	-	?
LSD	+	-	?	+	?	?	-	±	-
Anticholinesterase	+	+	+	+	+	+	+	+	+
Anticholinenergines	+	-	+	?	+	-	-	-	-

With respect to the effect of LSD, a typical representative of true hallucinogenic compounds (5) serving as a model of psychochemical war agents, it is important to realize the following differences between BZ agents and LSD intoxication. First of all, the mental confusion, that is delirious condition which is typical of BZ intoxication does not occur with LSD intoxication. Furthermore, the LSD caused hallucinations are moving "scene-type", less unreal and do not have the dramatic character as in the case of BZ agents intoxication. Smell and tactile hallucination rarely occur after taking LSD. Finally, paranoid and other ideas of relations can occur during

the action of BZ agents, which is not the case with LSD. Besides, it should be pointed out that LSD has a strong antiserotonic pharmacological effect, while BZ agents act as antiacetycholines. LSD has adrenolitic and antihistamine properties, but not the BZ agents. As for neuropharmacological aspects, the basic difference between LSD and BZ is in the effect on the reticular formation in the CNS (central nervous system), the activity of which is depressed by BZ, and potentiated by LSD.

Methods of Application and Intoxication with BZ Agents

BZ agents are intended primarily for use under conditions of limited or local warfare and are very suitable for carrying out special war actions, such as disturbing and paralizing command posts, communications centers, various diversions, and so on (25). The general thinking is that BZ agents are not intended for massive use under field conditions.

Like all potential psychochemical war agents, BZ agents will be used most likely in the form of aerosols. In case of diversions it is possible to contaminate food and liquids. Consequently the introduction of agents into the organism can be through inhalation or perorally.

BZ Agents Intoxication First Aid and Treatment

To our knowledge there is presently no specific antidote for the complete cure of intoxication caused by BZ agents. Many experiments, on both animals and humans, show that in cases of intoxication with BZ agents anticholineesterase drugs can be used in principle (2, 4, 7, 15, 27). Particularly suitable are compounds that can reversibly inactivate the action of cholinesterase, such as eserine, neostigmine, galantamine, and similar. According to certain authors (14) eserine is administered intramuscularly in 1 mg doses, while other authors (15, 27) state that 0.4 mg of eserine can remove the majority of

psychological disturbances and vegetative difficulties caused by BZ agents Galantanun can be also used -- 2 to 4 ml in a 25 percent solution (14).

The antidote effect of eserine is short-lived and after 1 to 2 hours symptoms of psychological disturbances develop again and it is necessary to repeat the administration of eserine.

In the therapy of intoxication with BZ agents, in addition to eserine it is possible to administer tetrahydroaminocrydine (known as tacrine) intravenously in 30 mg doses. This compound also inhibits reversibly the action of cholinesterase (9, 11, 24) and acts stimulatively on the CNS (26).

Past experiments on humans have shown that organic-phosphorous anticholinesterase compounds (VX, sarine, DFP) can alleviate certain psychological disturbances due to BZ agents (15, 27), but because of their high toxicity these compounds are not recommended for human use.

Consequently, eserine is the most suitable drug and has a definite advantage compared to other cholinesterase compounds as due to its short-lived effect the repeated administration of eserine does not cause symptoms of extended toxicity, nor grave damages to the organism. Nevertheless, eserine can be used only under strict control of professional medical personnel despite the fact that it can be administered in repeated injections. (3).

First aid for BZ agents intoxication consists of putting on the protective mask and evacuating the injured to the indicated institution where special medical assistance can be given (divisional medical station).

In addition to eserine, all other therapy of BZ agents intoxication is symptomatic and includes the use of sedatives (barbituates or magnesium sulphate), (14). As for the use of sedative drugs for BZ agents intoxication, we emphasize that the administration of tranquilizing drugs from the phenothiazine group (largactil and simular), which are otherwise used as

effective antidotes in the case of treatment of psychosis caused by LSD, is contraindicative. It is considered that the administration of largactil in the case of BZ agents intoxication potentiates the psychomimetic effects of BZ agents, particularly those which are evident in the lethargic phase of intoxication (3, 8, 27). The use of analeptic or cardiotonic drugs is recommended in the cases of more severe comatose conditions caused by BZ agents.

Finally, it should be emphasized that with respect to the specific therapy of BZ agents intoxication there is no final position, particularly in the stage treatment, and there is no defined antidote drug in the military medicine inventory of other armies. For these reasons the research in this sector is very intensive.

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