THE BLACK VAULT

THIS DOCUMENT CONTAINS
25 PAGES, COPY NO. 1
OF 3 COPIES.

AS A VEHICLE
FOR INCAPACITATING AGENTS

Prepared by:

24 December 1971

247

This report has been prepared by
as a part of a Government Contract. The views expressed
are those of personnel and not necessarily those
of the United States Government.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

AS A VEHICLE

FOR INCAPACITATING AGENTS

PROBLEM

To evaluate, especially from the physiologic point of view, as a vehicle for personnel incapacitating agents.

DISCUSSION

I. Potential Applications For Incapacitation

is a chemical with the rather extraordinary property of penetrating skin rapidly. The skin, long thought of as a virtually impenetrable barrier or as an only slightly, slowly permeable one, is easily, quickly, and reversibly breached Furthermore, many chemicals, when dissolved can cross the barrier along with

Such a property lends to consideration as a possible means of delivering an incapacitating chemical agent via the skin. Those drugs which interfere with a person's state of consciousness -- inducing loss of consciousness, panic, disorientation or hallucination -- could conceivably be administered, as well as drugs which incapacitate by causing motor dysfunction or muscular paralysis, or those which incapacitate by producing somatic preoccupation such as itching or burning. Since many incapacitating drugs require fairly critical dosage, the usefulness of a incapacitating agent mixture would

probably be limited to individuals, where the dosage could be more carefully controlled as to quantity and site of application. In a crowd situation, uniform dosage would be quite hard to obtain.

II.

* The lowest temperature at which vapors will ignite in air.

III. Physiological Considerations

A. Introduction -- Nature of the Skin.

A primary function of the skin is protection of the body. One way in which it does this is by serving as a barrier to penetration of chemicals -- harmful or otherwise -- into the body through its surface. It is a formidable barrier to such penetration. For example, the epidermis retards the diffusion of low molecular weight, water soluble nonelectrolytes (among the most diffusible of substances) by a factor of over one thousand times. [7]

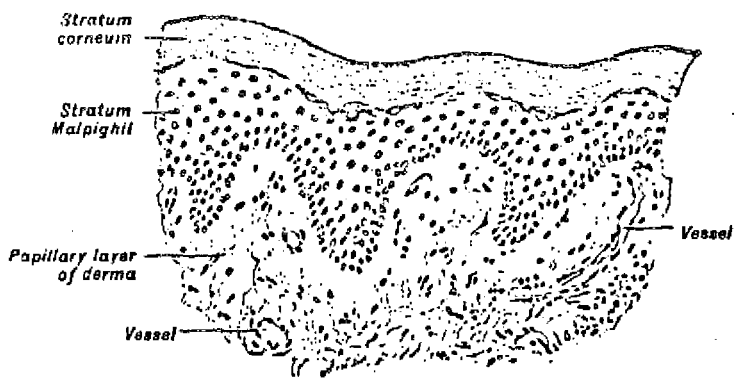

Figure 1. Section through the skin of the human shoulder

To get from the surface of the skin to the circulatory system, a substance must first penetrate the stratum corneum, or horny layer of the epidermis. This is a thin layer of dead, keratinized epithelial cells approximately 10 μ thick. Once this is passed, the stratum Malpighii, or living part of the epidermis (100 μ or so thick), then the papillary part of the dermis (100 - 200 μ thick in most places) must be traversed before the capillaries in the dermal papillae are reached. The stratum corneum constitutes by far the major part of the skin barrier insofar as resistance to diffusion is concerned. [7] If it can be breached, drugs can gain entrance to the body via

the skin -- eliminating the need to administer them orally, by injection, or by other routes.

B. Theories of Penetration.

The actual mechanism of penetration of the human skin is largely unknown, although several theories have been advanced. There is little or no evidence in support of any of the theories, however. According to the most widely held hypothesis, the molecules replace molecules of bound water in the stratum corneum. bonds are less tight than HOH - HOH bonds and, therefore, temporary dissociation, allowing chemicals to pass through, would be easier.[7] In order to allow other substances to penetrate the stratum corneum, saturation of the intermolecular spaces may be necessary. As says, "It is almost as if the penetrant is conducted through the horny-layer barrier by remaining dissolved in a continuous channel which occupies intermolecular spaces." This "opening up" of a pathway through the stratum corneum occurs for a limited time only; leaves the stratum corneum open to penetration by other chemicals for 1-1/2 to 3 hours only. It is suggested that by the end of this time the saturating quantity of has either diffused away from the stratum corneum or been absorbed into the circulation.

High concentrations are needed for effective penetration.[7] This may be a result of the 1:2 or 1:3 associational complex formed with water. A 75% or greater has space remaining available for association with tissue water molecules -- they can be removed from the stratum corneum and replaced

C. Substances "Carried"

Various investigators have conducted experiments in conjunction

with a wide variety of chemicals in hopes of getting them through the skin barrier. As a general rule, low molecular weight, nonionized chemicals pass through the most quickly, those which are ionized and/or of higher molecular weight pass through more slowly, if at all, and substances of high molecular weight such as insulin and ragweed allergen do not pass through at all.

Some substances which have been tried and which do penetrate the stratum corneum

It should be stressed that nearly all of these studies measured penetration only through the stratum corneum or into the skin. They do not imply penetration into the bloodstream. Indeed, many of these substances, including have been found to penetrate only through the stratum corneum into the epidermis and dermis, where they may form a reservoir. Some, such as may remain in the stratum corneum for the most part.

D. Penetration Studies.

1. Stratum Corneum.

There are two main factors to consider in the penetration through the skin barrier -- the speed of penetration and the quantitative amount of penetration. Neither has been established with any degree of precision, but some figures are available.

found that 1.5% penetrated (as established by serial stripping of the skin's horny layer with cellophane tape) to the base of the horny layer in one minute. The liquid was applied as a "pool" by means of glass cylinders taped to the back of male Negroes. He also found that in a glass cup produced whealing as early as two minutes after application. For whealing to occur (most probably due to histamine liberation from the mast cells) penetration below the stratum corneum must have occurred. These results were obtained with present in depth above the area treated, however -- not with it spread over the skin or applied in small quantities.

on the back and spread it with a glass rod. They noted signs of reaction (whealing, especially around the hair follicles) in 5 to 15 minutes. The differences in whealing times between work may indicate that the absorption time is a function of the amount enabling quicker penetration than thin layer.

obtained anesthesia of the eardrum (which has a stratum corneum just like any other skin area) sufficient to allow painless myringotomy (cutting of the eardrum) within one minute after wiping the eardrum with

In another study, penetrated to the base of the horny layer in 20 minutes. In the time was 55 minutes, and in 120 minutes was the time for penetration. These results emphasize the need to use high concentrations for rapid, maximum penetration.

Published studies on the quantitative penetration have been almost nil. in gel form on the elbow and let it stand for 30 minutes. By then wiping off and weighing what remained at the

end of that time, they calculated that 25-40% of had been absorbed. This was obviously a rough determination only.

eight hours after dermal application, that 20% of the applied dose was still in the epidermis. He did not mention where or how the remaining 80% was distributed.

These two studies demostrate that dermal application is no assurance that all of the compound will penetrate the skin. Furthermore, of that portion which does penetrate, some may remain in the epidermis for a considerable length of time. These studies were alone; chemicals "carried" may or may not behave in like manner. At present, it would be almost impossible to predict what the behavior of a given chemical agent would be with regard to percent absorption or penetration rate without actually running tests on that particular chemical.

One variable which has been little investigated is the location of the skin to be penetrated. It is known that, with regard to such things as water diffusibility, certain areas of the body are considerably more permeable than others. For example, scrotal skin is considerably more permeable than abdominal skin.[7] There are several variables which may be at work. The skin itself (epidermis and dermis) varies in thickness, and the stratum corneum itself may vary in either thickness or structure. Other than on the soles of the feet and the palms of the hands, where the stratum corneum is considerably thicker, but has a higher diffusivity, the stratum corneum varies little in thickness. It may vary in nature, however, as in the forehead, where there is a less orderly, more open arrangement of the cells.[7] There may also be some difference in the thickness and composition of the stratum corneum among various peoples -- for example, Negroes vis-a-vis Caucasians.

2. To the Bloodstream.

Most of the previously discussed studies of time and rate of penetration considered the stratum corneum and epidermis only. If the site of

action of the "carried" drug is the epidermis -- fine, all of the major factors have been considered. But drugs which have the brain or body organs other than the skin as sites of action must go not only through the stratum corneum, but also through the remainder of the epidermis and then a portion of the dermis before they reach the bloodstream which can transport them. This is where may fall down.

studied the influence on dermal clearance (the time required for the circulation to remove injected substances from the dermis). Fluorescein, a fluorescent dye, was injected intradermally -- 0.1 ml in saline, and in 25%, 50% and 75% solutions. The clearance time for the control (in saline) was 1.8 hours and the times for the solutions were 3, 5.5 and 18 hours, respectively.

The effects on dermal permeability were studied by measuring the penetration rate of 1% aqueous fluorescein through abdominal skin which had been stripped of its epidermis. The results are summarized in the table below.

TABLE I

DERMAL PENETRATION RATES OF VARIOUS

	Saline Control			
Penetration rate, in $\mu g/cm^2/hr.$	79.6	17.5	1.3	0.6

In the case of seems to inhibit or retard passage through the dermis. offers no theory or hypothesis to account for this, stating simply that "the diffusivity of connective tissue was probably being depressed One qualification, however, is applied to the intact skin would probably not attain such high concentrations in the dermis as were used in these experiments, so that dermal clearance

and permeability probably would not be retarded as much in normal use as was observed under the experimental conditions.

For incapacitating agents which act on the brain, the most important consideration is not how fast penetrates the horny layer, but how quickly it, or a drug administered reaches the bloodstream. using tagged given dermally, found traces of radioactivity in blood drawn as early as five minutes was applied, but the level did not reach a maximum until 4-6 hours later, reaching a plateau where it remained for some time.

One other published experiment, which gives times and blood concentrations for humans, showed one hour after administration, but the peak level (approximately twice the one hour level) was not attained until four to eight hours after administration.

These two experiments It can be seen that a measurable may penetrate to the bloodstream in as little as five minutes. Whether or not chemicals "carried" by can enter as rapidly would have to be determined experimentally. Other substances may or may not reach the bloodstream this quickly, depending on several factors such as molecular weight, configuration, solubility in tissue water and lipids, and reactivity to tissue components. The in blood keeps building up to a peak which is only reached after several hours; such behavior would not be acceptable for most brain-active incapacitating agents, for a dose powerful enough to incapacitate in five minutes would continue to increase for several hours, with serious and quite possibly fatal results. Unless the therapeutic ratio * of the drug is quite high, safety could not be insured. This, however,

* Ratio between the lethal dose and an effective dose.

assumes that the chemical agent would behave the same way [redacted] which may not be the case. There is a possibility, but only a slight one, that a peak concentration of an incapacitating agent could be reached quickly. In this case, maximum effect of the drug would appear soon after administration and a lower, safer dose could be used; the initial incapacitating dose would be the maximum dose received.

One report, [redacted] showed apparent worthwhile results in feeding through the skin [redacted] Such things as glucose, carotene (vitamin A), vitamin B_{12}, and some amino acids were absorbed in fairly significant amounts, as signified by blood levels and weight gain. The blood glucose level was 165% of the initial value within 30 minutes [redacted] application. The net elevation at that time, which does not account for any glucose which may have already entered the bloodstream and then been metabolized, accounted for about 3% of the dose administered to the skin.

E. Fate and Metabolism [redacted]

The metabolic pathways [redacted] takes in the body are still relatively unknown. Gas chromatographic and radioactive tagging techniques [redacted] show that it is excreted as unchanged [redacted] and as two metabolic byproducts -- dimethyl [redacted] are excreted in the urine; [redacted] leaves the body via the lungs. Fecal elimination is negligible. [redacted] Urinary excretion accounts for most of the [redacted] removal as the lungs eliminate only 1-3%.

Most subjects [redacted] by the dermal or any other route have a characteristic "bad breath" said to resemble [redacted] This is caused by the presence of the [redacted] which appears in the

---

* A rather special case, [redacted]

breath soon after administration and continues for 24 hours or so.

F. Local Reactions and Toxicity.

applied dermally in the concentration typically is accompanied by transient burning, itching, and erythema (reddening). Its exothermic reaction with water causes an increase in skin temperature. In a significant number of cases, may cause wheeling. This is assumed to be a result of histamine liberation. A study of over 1000 German patients who were given dermally for a 15-minute period per application yielded the following data on skin reactions:

6 - 8% showed no local reaction;

33% had a slight reaction (warmth, itching and erythema);

56% had the "typical" reaction (burning, itching, erythema for 3 - 4 hours, and occasional local urticaria);

2 - 5% had a more severe reaction (dermatitis, urticaria, and occasional vesiculation).

In only about 3.5% was it necessary to discontinue therapy. This was due to the local skin reactions which disappeared upon discontinuation of the treatment. There were sometimes complaints of transient nausea and headache among those but no serious complications. The "bad breath" was noticed in most subjects, and 50% or so reported they could "taste" the In all of the studies done on humans (including over 4000 individuals in one of the studies) no serious side effects have been noted. The temporary effects were those noted above, and no permanent changes or damage have been reported.

tested sensitivity of the conjunctiva * to drops of Two drops caused only temporary stinging and burning, and, in some cases,

* The membrane covering the anterior eye and the inner surface of the eyelids.

mild injection (congestion) of the conjunctival vessels. These effects soon disappeared.

if dropped onto the eardrum, may be painful, but will cause no long-lasting or permanent damage.

was withdrawn as a clinical drug in the United States in 1965 by the Food and Drug Administration because of reported lens changes in dogs which had been given up to 5 grams per kilogram The FDA has subsequently allowed resumption of clinical testing. There was fairly extensive in humans in this country before the FDA ban, has been available as a prescription drug No evidence of any human eye toxicity due to has been observed even in the highest experimental doses given (1 g/kg per day for 12 weeks in one study, 30 g per day for up to 21 months in another).[27] Rhesus monkeys have been given 1 - 3 ml of per kg orally or 1, 3, or 9 ml/kg dermally daily for periods of up to 18 months and no toxicologic or pathologic changes have been seen, other than skin reactions. Monkeys have been given intravenous dos as high as 4g/kg with no deaths.

No estimates of an LD_{50} * have been made for monkey or man, but in view of the high experimental doses that have been given already, the LD_{50} would be far higher than any dose which would be given for purposes of "carrying" an incapacitant.

Substances given in combination however, may result in an altered toxicity. reported an interaction between alcohol in 1967. He claims to have found increased rates of mortality in rats given

---

* The dose lethal to 50% of those to whom it is administered.

high doses after previously having been injected with alcohol. He also said he found more psychomotor impairment in humans given alcohol (orally) and (via the skin) than would be expected from alcohol alone. This interaction should be investigated further is to be considered for use in incapacitation since there could be complications if the were used on drunken subjects.

Interactions between various drugs other than alcohol should also be investigated further. One group of investigators found that increased the toxicity (as reflected by a change in the LD_{50}) administered orally to rats by a factor of up to six times.

Thus, there is a possibility could facilitate the body's absorption of drugs from such sites as the gastrointestinal tract. Such facilitated absorption could conceivably cause an otherwise safe dose of a drug to become a serious or possibly fatal dose when given

It can be seen, on the basis of the fairly extensive work which has been done, applied externally in small quantities can be expected to have temporary, local effects causing some annoyance and discomfort, but no long-term or permanent damage. Whether or not this would be true of mixed with a given chemical agent would depend upon the nature of the chemical and how it acts in conjunction Such knowledge would have to be established by experimentation, using the specific chemical agents to be considered. It would be quite desirable to have further data on the interaction of alcohol as well as any other drugs which potential subjects might take before or administration.

C. Physiological Conclusions.

For use as a "carrying" agent for incapacitants, would have to be used in fairly high concentrations, probably To assure useful speed of penetration and to ensure penetration it would have to be applied in volume, perhaps one ml or more, as shown by various investigators.

can fairly well be ruled out as a means of quick delivery for psychotropic agents, or any other agent with the internal organs as a target. The chances are very good that any agent delivered would not reach peak blood levels for several hours. For a drug to be effective quickly (say, reaching the blood in significant amounts in five minutes) it would have to be administered as quite a large dose. This is because, so far as is known, only a small percentage of the administered dose will reach the circulation in that initial five minute period.

There are too many variables to be certain of the fraction of the delivered dose which is likely to reach the target organ. This is especially critical for dosages of the psychotropic drugs. Whether all the material lands on the skin, how much remains in contact with the skin, how calloused or "tender" the subject's skin may be -- all may affect dosage and absorption. Such possible factors as individual variation "penetrability" and possible insensitivity to the "carried" agent also enter in. All these factors would tend to eliminate most "brain-active" agents from consideration because of their relatively low therapeutic ratio.

Incapacitation by somatic preoccupation is a major remaining area. Intense itching or burning can be quite incapacitating. Applied in the conventional manner, skin irritants such as itching powder can be removed by washing.

could cause the skin irritant to penetrate into the skin, where a reservoir could be formed. Once within the skin, washing and rinsing could not remove them and might actually increase the irritation. Several hours of intense itching or other irritation could ensue. Quite possibly agents could be found which would penetrate the stratum corneum and go no further, eliminating the danger of overdosage which is such a distinct possiblity when psychotropic agents are used.

IV. Other System Factors

One factor to be considered is the relatively

For use at cool temperatures, this would either have to be changed to a lower value by some means or would have to be heated prior to use.

Delivery could be made fairly simple. Used against individuals at close range, the could be delivered by a simple water pistol type device. For longer ranges, the mixture could be loaded into capsules that would break on contact after being thrown or fired from a gun.

The person who receives would be aware of it. itself has a noticeable odor, which could be masked with perfumes, but probably not removed. Soon after administration local reactions would appear -- burning, itching, and the like. Finally, subjects would be aware of having been sprayed or squirted with a liquid. For these reasons, it is highly doubtful could be administered surreptitiously.

Ordinarily, when an individual is squirted or sprayed with a liquid, the usual reaction is to wipe it off his skin. Since the takes a finite time to penetrate -- several minutes at least -- much of the administered material would probably be removed well before it had any time to penetrate. This is a fairly strong argument against applying to exposed skin areas, although wiping may have some effect of "rubbing it in" and spreading it.

These objections can be overcome by applying the to the clothing. The person receiving this solution on his clothing would be aware of it, but clothing removal would normally be too drastic an evasive measure to take, unless the nature of the liquid and the consequences of non-removal were known to the subject. If the liquid were applied to the

pants (or skirt), clothing removal would be especially unlikely, for psychological reasons. wetting the clothing would be in contact with the skin, possibly for a long enough period of time to allow penetration or partial penetration before the reaction to the burning and itching would be strong enough to motivate clothing removal. By then, such evasive tactics could be too late.

were sprayed on the clothing, the genital area would be an ideal target, since the scrotal and genital skin is likely to be more "permeable" to than skin in most other areas of the body. Various psychological factors would enter in here also.

to the clothing would probably not work in situations where the clothing was already wet, as by rain, by firehoses, etc. This could be a potential countermeasure -- hosing oneself down. Use of rain gear could also serve to protect the subjects

The problems of storage and shelflife could be important; these factors would have to be investigated for the various incapacitating agents both individually and in conjunction

V. Recommendations

A. The [redacted] "carry" psychotropic or other incapacitants which depend on the bloodstream to carry them to their target organs can, in all probability, be ruled out if quick incapacitation is desired. There is a chance that an effective agent could be found which would penetrate the stratum corneum [redacted] and then go into the bloodstream faster than [redacted] but such a chance seems remote.

B. [redacted] should be considered as a possible vehicle for "implantation" of skin irritants. Studies should be made with various irritants, checking for absorption time, duration of action and effectiveness.

C. [redacted] comes into active consideration as a vehicle for skin irritants, several other operational characteristics should be determined by direct investigation.

1. Studies [redacted] absorption through different types of clothing should be undertaken. Various materials -- cotton, leather, synthetics -- should be checked, as well as the effects of several layers of clothing, loose vs. tightfitting garments, etc.

2. Investigation of the suspected interaction [redacted] alcohol should be carried out. Also to be considered are possible interactions [redacted] and other drugs which a subject may have taken prior to or subsequent [redacted] administration.

3. Storage and shelflife [redacted] and various agents should be investigated.