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Biological implications of chemical and radiological warfare

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Thesis
BIOLOGICAL IMPLICATIONS OF CHEMICAL
AND RADIOLOGICAL WARFARE
by

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(A.B. University of Connecticut, 1956)
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ABSTRACT

This thesis is a major review of the acute biological effects of chemical and radiological weapons. These agents of modern warfare have a broader spectrum of biological effects than the weapons of past wars and also present more profound biological sequelae. In order to cope with the threat that these weapons pose, it is necessary to be familiar with the types of agents which might be used, the symptomatology, the modes of physiological effect, and the basic mechanisms of cellular action.

The acute radiation syndrome is covered in detail along with hypotheses of the cellular action of ionizing radiation and a review of methods for protection against radiation.

Chemical warfare agents reviewed here include both casualty and incapacitating agents. Typical of the modern chemical warfare casualty agents are the nerve gases which are fast acting, toxic, and effective regardless of the mode of entry into the body. Significant among the incapacitating agents are the psychotropic agents such as the lysergic acid derivatives which induce hallucinations and profound behavioral changes.

As potential agents in any armed conflicts of the future, atomic weapons have the ability to cause complete and decisive destruction of the target area. By contrast, chemical agents can cause selective damage restricted to personnel. The biological effects of both types of weapons must be better understood if effective means of defense are to be developed.

It is intended that this review will serve to describe the range of acute biological effects of CW and RW weapons and thereby identify areas of research to interested investigators.

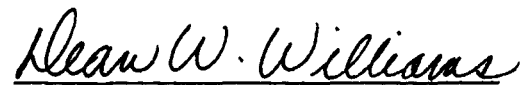
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INTRODUCTION

The biological effects of modern weapons have become more profound, present a greater spectrum of sequelae, and consequently will require proportionally more research before the scientific community can cope with this threat at a sophisticated and comprehensive level of understanding.

The first of the modern warfare threats to be reviewed is chemical warfare. Chemical agents were used in World War I by all of the major combatants, but were not considered to be decisive weapons (4). Fortunately, chemical warfare was not used extensively in World War II or Korea even though it had been developed to a high degree of destructive efficiency.

The second of the aspects of modern war to be discussed is the biological damage resulting from acute exposure to ionizing radiation. Already radiation effects - human, animal, and plant - have become a substantial part of scientific reporting. Radiation biology, for example, is becoming a very prominent and active part of biological research and as a part of this research, numerous studies have been made of the effects of fallout and Strontium-90. Extensive studies have been initiated and maintained on the radiation victims from Hiroshima, Nagasaki, and Rongelap to determine the effect of radiation on mutation, foetal development, malignancy, and aging. In fact, the Biological Abstracts and Index Medicus both have specific sections dealing with the subject of warfare effects.

Radiological and chemical agents not only differ from the more conventional lethal agents by being largely undetectable by human

senses, but they can exert their effect at the cytological and histological level to produce functional physiological impairment without inflicting gross structural damage. Also, these modern weapons exert effects ranging from lethality or incapacitation within minutes to anomalies which only become evident during succeeding generations.

When making a study of weapons effects, in this case a biological study, it is meaningful to discuss briefly the military value of such weapons. This tends to place the subject in better perspective by giving insight into the rationale for the selection of particular destructive agents, their probable mode of deployment, and to anticipate their probable effects. Weapons have always been selected for their ability to impair or terminate the life process, yet this selection criterion is not necessarily consistent with long-range or strategic goals. The ability to effect selective and controlled damage to a target area is a more sophisticated notion. For example, early in World War II, the Japanese and German military planners had considered using wooden projectiles in their small caliber firearms because these projectiles would be more likely to cause casualties than fatalities. The assumption was that a fatality removed only one man from action whereas a casualty removed at least three - the victim, a helper, and a medical aide. In addition, the victim usually required extensive medical attention. However, this tactical insight was soon given over to a more immediate objective - that of reducing the number of enemy soldiers on a permanent basis. The two classes of weapons reviewed here, nuclear and chemical, offer a range of effects from total destruction to temporary mental impairment.

If total target destruction is a strategic objective, then nuclear weapons are ideally suited to the task. They not only destroy personnel, materiel, natural resources, and contaminate terrain, but exert a lasting effect which may persist for years. Therefore, nuclear weapons are instruments of complete, immediate, long-term, and decisive action.

On the other hand, if long range objectives are considered (2) and the target area is to retain some value as a useful resource, then it is necessary to restrict damage to only the most critical objects. With chemical agents it is possible to restrict damage. Plants, animals, or personnel can be singled out and selectively incapacitated or killed. Not only would it be possible to make full use of military or industrial materiel after a lethal chemical attack, but under special circumstances it would even be possible to retain the human resource as well by using incapacitating agents. It can be argued, in fact, that some forms of chemical warfare are more humane than war by nuclear weapons. Thus, it has become possible to tailor war damage to suit very specific military objectives.

The following review is divided into two parts: the first discussing the effects of chemical warfare (CW) and the second part, nuclear warfare. In view of the breadth of nuclear weapons effects, only the acute radiation syndrome will be considered. Similarly, in the review of chemical warfare, the emphasis will be on the more toxic agents such as the potent nerve gases and the new class of psychotomimetic compounds.

CHEMICAL WARFARE

History of Chemical Warfare

Perhaps one of the earliest documented accounts of chemical warfare occurred about 600 years B.C. Solon of Athens is supposed to have defeated the army of Kirrha by putting hellebore roots in the Kirrha water supply. The Kirrhans, weakened and incapacitated by diarrhea, were then killed by the Athenians.

Later, around 200 B.C., the Carthaginians doped a quantity of their wine with mandrake root and then feigned a retreat leaving the drugged wine behind. The pursuing enemy stopped to partake of the wine, fell into a deep sleep, and were killed by the returned Carthaginians. One of the earliest recorded gas attacks occurred somewhere around 430 B.C. when the Spartans used burning sulfur and pitch to form sulfur dioxide in the siege of Plataea and Velium.

The large scale use of CW in modern times took place in the First World War. The French used tear gas grenades in trench warfare against the Germans as early as 1914, but the first use of lethal gas occurred in April, 1915, when the Germans used chlorine against Allied trenches and dugouts. Very quickly, gas-filled artillery projectiles replaced the grenade and the incapacitating gases gave way to casualty gases such as phosgene, diphosgene, chlorine, and mustard (2). In summary, a total of 124,000 tons of chemical agents were expended by all major combatants during World War I. These toxic agents caused about 5 per cent of the battle casualties. It is noteworthy that gas casualties had a better chance for recovery than gun-shot victims; ninety-five per cent of the

gas casualties recovered whereas only eighty-three per cent of the gun shot casualties recovered. As CW tactics improved, chemical agents became very effective in taking men out of action. For example, in 1918 it is estimated that one-half of the hospitalized British and French troops were gas casualties despite the fact that only about 5 per cent of the artillery rounds contained chemical fill (4). Despite the apparent effectiveness of CW agents, chemical warfare was not regarded as being a decisive form of combat. Instead, commanders considered the gases to be of value only for disrupting front-line activity, harassment, and keeping the enemy troops in a state of turmoil while masked troops advanced (4). This failure to appreciate the biological effectiveness of these weapons was perhaps due to the fact that the results were unpredictable and no clear tactics for the use of CW had been evolved at that time.

In World War II and Korea, chemical warfare was restricted to the use of smoke producers and incendiaries even though there was active development and stockpiling of lethal agents and the participants were prepared to use these toxic agents (2). It was during the Second World War that the German scientists developed the exceedingly toxic nerve gases.

Modern chemical warfare makes a departure from that of the First and Second World War by the advent of even more toxic agents, better means of delivery, and the possible use of chemical agents which disrupt mental behavior. The highly refined agents to be discussed here offer two prime advantages; first, most of them have little to no detectable odor and second, they are very fast acting even in small concentrations.

From a biological point of view, the following criteria are used for the selection of a suitable chemical warfare agent. First, the agent should be able to persist in aerosol form or remain intact on the surface of clothing and vegetation for an extended period of time before its chemical activity is altered. Second, the agent should exert its action - either lethal or incapacitating before the victim is aware of its presence. Third, the agent should be one which is physiologically active regardless of its mode of entry into the body. Inhalation and skin contact are the usual modes of entry for agents because field agents are usually dispersed as aerosols or gases.

At the end of the review of the biological effects of chemical warfare is a glossary of terms pertinent to CW.

Modern chemical warfare can be used tactically or strategically for the following purposes:

- (1) the production of widespread casualties and/or fatalities,
- (2) the control and subjugation of personnel by the disruption of somatic, sensory, or mental processes,
- (3) the destruction of critical resources such as crops, livestock, stored food, and water,
- (4) rendering geographical areas unsafe for ground travel because of persistent contamination (interdiction and harassment),
- (5) the demoralization of the target population by creating panic and disrupting civilian and military co-ordinated activities,
- (6) the disruption of medical services because of widespread casualties,

- (7) gathering intelligence information from captured troops (truth serums and narcosynthesis),
- (8) tagging by dyes or short half-life isotopes of concealed guerilla operatives for subsequent identification in remote villages.

Chemical Agents and Their Effects upon Mammals

It is possible to divide chemical warfare agents into two broad classes based upon the nature of the biological effect. The first are the casualty gases which produce either debilitation and protracted illness or death. The second class of agents are intended only to incapacitate by causing temporary sensory, physical, or mental impairment. The division between casualty-producing and incapacitating agents is not always clear cut. For example, mustard gas is primarily classified as a casualty gas, yet light exposure can cause prolonged incapacitation. Conversely, repeated exposures to some of the incapacitating compounds can produce either a cumulative toxicity or induce a precipitous sensitivity reaction. To help reconcile this difficulty in effect - variability, a convention has been adopted to differentiate incapacitating from lethal agents; generally, the lethal level of an incapacitating agent should be from a hundred to a thousand times greater than that

required to produce temporary incapacitation (2)¹.

The following table is compiled to give quick reference to a variety of the incapacitating and casualty gases. The summary will give name, chemical formula, odor, median lethal and median incapacitating dosage, rate of action, detoxification rate, skin and eye toxicity, and prime site of action. The casualty gases are also subdivided into categories according to their effect on particular organ systems; eg., the choking gases (respiratory), blood gases (hematopoietic, hepatic, and renal), nerve gases (neural enzymes) and vesicants or blister gases (the integument and mucosal membranes). Subdivisions within the incapacitating agents include the emetic gases, lacrimators, and psychogenic compounds.

Casualty Gases

1. The Choking Gas - Phosgene. Phosgene is a "corrosive" gas. It reacts with water in the lungs to form hydrochloric acid (1). The hydrochloric acid in turn has its primary effect on the permeability of the capillary bed, thus permitting massive seepage of fluid into the alveolii thereby impairing normal exchange of respiratory gases. The

¹ There is a second very important reason for making such a distinction based on dose-level-effect. The incapacitating agents are being actively investigated because they offer the opportunity to effect military objectives without the loss of human life. This consideration is critical for example, when enemy operatives are mixed with innocent bystanders as in jungle and guerilla warfare. For humane and political reasons, it is undesirable to take action against an innocent or hostage population. Therefore, there must be assurance that the selected agent can be used safely for incapacitation with a minimal risk of death. Thus, the necessity of a large safety factor of 100 or 1000.

<u>CASUALTY GASES</u>	Symbol	Chemical Formula	Odor	Median-Lethal Dosage	Median-Incap- itating Dosage
<u>Choking Gases</u>					
1. Phosgene	(CG)	COCl_2	New-Mown Hay, green corn	3200	1600
2. Diphosgene	(DP)	ClCOOCCl_3	Same as CG	3200	1600
<u>Nerve Gases</u>					
1. Tabun	(GA)		Faintly fruity, none when pure	400 (for resting men)	300 (for resting men)
2. Sarin	(GB)		Almost none when pure	100 (for resting men)	75 (for resting men)
3. Soman	(GD)		Fruity, camphor, or none when pure	Same Range and effects as GA and GB.	
<u>Blood Gases</u>					
1. Hydrogen Cyanide	(AC)	HCN	Peach kernels	About 2,600; varies inversely with concentration	About 2,000 - 2,600
2. Cyanogen chloride	(CK)	CNCl	Peach kernels, also lacrimatory and irritating	11,000	7,000
3. Arsine	(SA)	AsH_3	Mild garlic	5,000	2,500
<u>Blisters Gases</u>					
1. Distilled mustard	(HD)	$(\text{ClCH}_2\text{CH}_2)_2\text{S}$	Garlic	600-1000 by in- halation; 10,000 by skin exposure	200 by eye effect 2000 by skin effect

Rate of Detoxification	Eye and Skin Toxicity	Rate of Action	Prime Site of Action
None	None	Immediate to several hours	Lungs
None	Slight lacrimatory effect	Delayed	Lungs
Slight	Very high	Very rapid	Anticholinesterase Agent
Cumulative	Very high	Very rapid	Similar to GA
Rapid; 0.017 mg. per kg body weight per minute	Moderate	Very rapid fatal in minutes	Celular respiratory enzymes
Rapid; 0.2 to 0.1 mg. per kg body weight per minute	Low; irritating to eyes and mucous membranes	Rapid, but less than AC	Similar to AC
None of importance	None	Delayed (hours to days)	Hematopoietic, renal, and hepatic systems
Very low	Eyes very susceptible skin less so	Delayed (hours to days)	Tissue damage

2. Nitrogen mustards	(HN-1)	$(ClCH_2CH_3)_2$	Fishy or musty	1,500 by inhalation	200 by eye effect
		NC_2H_2	.	20,000 by skin exposure	9,000 by skin effect
	(HN-2)	$(ClCH_2CH_2)_2$	Soapy to fruity	3,000 by inhalation	Similar to HN-1
	(HN-3)	NCH_3	None if pure	1,500 by inhalation	"
3. Lewisite	(LI)	$ClCH:CHAsCl_2$	Geraniums	1,200-1,500 by inhalation, 100,000 by skin contact	300 eye effect 1,500 skin effect
4. Phenylchloroarsine	(PD)	$C_6H_5AsCl_2$	None	2,600 by inhalation	16 as a vomiting gas, 1,800 by skin effect

ENCAPACITATING AGENTS

Vomiting Gases

1. Adamsite	(DM)	$(C_6H_4)_2NHAsCl$	None	30,000	22 (1 minute exposure) 8 (60 minutes exposure)
2. Diphenylchloroarsine	(DA)	$(C_6H_5)_2AsCl$	None		
				Same general properties as DM	
3. Diphenylcyanoarsine	(DC)	$(C_6H_5)_2AsCN$	Garlic and Almonds		

Tear Gases

1. Chloracetophenone	(CN)	$C_6H_5COCH_2Cl$	Fragrant	About 11,000	80
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Hallucinogenic Compounds

See text.

Cumulative	Similar to HD	Similar to HD	Similar to HD
Cumulative	Rapid eye effect	"	"
"	"	"	"
None	Similar to HD	Immediate irritation delayed blistering	Similar to HD plus systemic poisoning action
Rapid	Less toxic than HD	Immediate to eyes delayed skin	Resembles action of HD and vomiting gases
Rapid in small amounts	Irritating	Very rapid	Eyes, nose, throat
Rapid	Temporary severe eye irritation	Instantaneous	Lacrimary, respiratory tract irritation

development of the edematous condition reaches a maximum within 24 hours after exposure. Hemoconcentration is a secondary consequence of fluid loss into the lungs and the cause of death is anoxemia. If the victim does not succumb to anoxemia, the fluid accumulation in the lungs begins to be resorbed in about two days and recovery can be rapid provided that secondary infections do not develop in the traumatized pulmonary tissues. Chronic emphysema, bronchitis, bronchiectosis, and pulmonary fibrosis may be persistent sequelae in a small percentage of victims with severe exposures or complications (27, 40).

Toxicity - The median lethal dosage by inhalation is calculated to be 3200 mg. min/m³. The median incapacitating dosage is one-half the LCt₅₀. (See the appendix for definition of such designations as LCt₅₀). Repeated exposures to sub-lethal concentrations can be expected to carry the same threat as a single exposure to a lethal dose because the effects of phosgene are cumulative (27, 40).

Diagnosis, Treatment and Prognosis - The diagnosis of phosgene poisoning is difficult because the symptoms resemble those of nerve gas poisoning, upper respiratory infections, acute asthmatic attack, and other gases which produce pulmonary edema. Rest is probably the single most important form of treatment during the acute phases of the attack. The anoxia can be treated with oxygen administration. Antibacterial therapy may be administered to prevent pulmonary infections. The prognosis for a phosgene victim depends largely upon the course of events in the first 48 hours as

most fatalities will occur during this period. If the patient does not develop infections within the first week, the prognosis is good for recovery without sequelae.

Phosgene and its close relative diphosgene were very effective agents in World War I. However, the toxicity of these agents is less than that of such modern agents as the nerve gases and do not effect immediate casualties except when used in high concentrations. Thus, an individual exposed to phosgenes could conceivably perform vital tasks before becoming a casualty. It is doubtful whether phosgene and diphosgene would be used in modern warfare (27, 40).

2. The Nerve Gases - Tabun, Sarin, and Soman. As implied in the name, these three agents are neurotoxins, disrupting the microchemical mechanisms that transmit the nerve impulse. Acetylcholine is one of the most important synaptic transmitters. It is known to be released at the synaptic endings of cholinergic nerve fibers. In some yet undetermined manner, the acetylcholine is thought to activate the membrane of the adjacent neural or effector unit and a new impulse is generated. Cholinesterase which is present at these terminations rapidly splits the acetylcholine molecule into choline and acetic acid and the membrane returns to its normal polarity and the unit is ready to receive the next impulse (32). The normal functioning of many neural, neural-muscular, and neural-secretory tissues depend upon rapid polarizations and depolarizations as effected by the alternate actions of acetylcholine and cholinesterase. At the molecular level it is thought that the nerve gases act by attaching themselves at

critical sites on the cholinesterase molecule, thus inactivating it. Under the influence of these anti-cholinesterases, acetylcholine accumulates at the nerve endings and hyperstimulates nerves, glands, and muscles causing a myriad of effects which include convulsions, choking, cardiac irregularities, and other disfunctions. If enough cholinesterase has been inactivated, the increasing level of acetylcholine brings on flaccid paralysis and death.

Symptomatology - The symptoms resulting from autonomic disturbances are called muscarine-like and following local exposure are as follows:

pupils--miosis, usually to the smallest aperture, sometimes unequal,
ciliary body--frontal headache, pain on focusing, nausea, and vomiting,
conjunctiva--hyperemia and rhinorrhea,
bronchial tree--tightening of chest, wheezing on expiration.

Following systemic absorption of the gas, the symptoms are similar but more generalized:

pupils--miosis, unequal, smallest aperture,
ciliary body--blurring of vision,
bronchial tree--chest tightness, pronounced wheezing on expiration, dyspnea, increased bronchial secretion, chest pain, coughing, pulmonary edema, cyanosis,
gastrointestinal--anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness, "heartburn", tenesmus, diarrhea, and involuntary defecation,
sweat glands--increased sweating,

lacrimal glands--increased lacrimation,

heart--slight bradycardia

bladder--frequency, involuntary micturation.

The accumulation of ACh at the endings of motor nerves of voluntary muscle and in the autonomic ganglia cause "nicotine-like" results.

striated muscle--fatigue, weakness, twitching, fasciculation, and cramps,

sympathetic ganglia--pallor, rise in blood pressure.

Central nervous system effects include a host of disruptive symptoms such as giddiness, tension, nervousness, emotional lability, excessive dreaming, nightmares, headaches, withdrawal, bursts of slow, high voltage EEG waves, slowness of recall, ataxia, coma, diminution of reflexes, Cheyne-Stokes respiration, convulsions, depression of respiratory and circulatory centers, dyspnea cyanosis, and a fall in blood pressure.

Toxicity - The nerve gases are absorbed rapidly through any moist, vascular tissue. Most rapid absorption occurs through the eye or oral and pulmonary mucosa. For example, if the gas concentration is high, the compound can be carried from the lungs into systemic circulation such that systemic effects appear in one minute. Following a minimal symptomatic exposure (MSE), pupillary constriction is the first symptom to appear. Next, respiratory symptoms appear - chest tightness, wheezing, and nasal discharge. At four times the MSE, the symptoms are more pronounced and of longer duration. At six to eight times the MSE, systemic effects appear in addition to the ocular and respiratory symptoms. All

individuals exposed to fifteen to twenty times the MSE become gas casualties. The lethal exposure is estimated to be thirty to fifty times the MSE, which for Sarin the most toxic agent, is about 100 mg-min/m³. The median incapacitating dosage is 75 mg-min/m³. The skin effect of Sarin is dramatic, for a drop of liquid (1.7 grams) absorbed through the skin or eye is a median lethal dose. Daily exposures to non-symptomatic dosages of nerve gases can result in the sudden appearance of symptoms.

Treatment and Prognosis - If death is to be averted for victims who have absorbed amounts of gas in the lethal range, treatment must be initiated immediately after exposure. Essentially, treatment consists of atropine administration, maintaining the airways clear, and oxygen therapy. Atropine is thought to inhibit ACh by competitive inhibition at the ACh receptor sites and thus can be used to counteract the effects of these war gases. Unfortunately atropine has little to no effect upon alleviating respiratory paralysis induced by nerve gases, and artificial respiration must be used in conjunction with atropine in severe cases of poisoning. The normal initial dosage for atropine is 2 milligrams. Intravenously, its maximal effect occurs within 6 minutes. Atropine given by itself without the effects of AChE depressor causes atropine symptoms which include oral and pharyngeal dryness, warmth, flushing, slight tachycardia, and possibly, pupillary dilatation. The individual may also experience feelings of drowsiness and slowness of motor activity. Although these symptoms will be evident to the individual, they are not

disruptive. In fact, if they occur after an individual has received emergency treatment for nerve gas poisoning, it is a good indication of successful treatment. In cases of severe poisoning, as much as 24 milligrams of atropine can be given over a 24-hour period. When treatment is more leisurely, barbituates and anticonvulsants may be administered to victims who display untoward behavior and convulsions, respectively (40).

Cholinesterase can be depressed as much as 40 per cent of normal by heavy poisoning. By periodic examination of the plasma and red blood cells, both of which contain AChE, it is possible to plot the recovery of this enzyme over time. In some instances, recovery to normal levels may not occur for fifty to eighty days (7).

Some recent experimental work on nerve gas poisoning has shown that a series of compounds called oximes can reverse the neuromuscular block and reactivate AChE. However, the oximes appear to be slow acting and should be used in conjunction with atropine (29).

Prognosis for the victim can be rendered with a fair degree of certainty two or three days after exposure. Those who survive this period will probably recover with little effect unless permanent damage has occurred to the central nervous system as a result of anoxia.

The following references were used for the preparation of the section on nerve gases: (1, 7, 8, 9, 13, 15, 27, 28, 29, 32, 40).

3. The Blood Gas - Hydrogen Cyanide. One of the prominent blood gases is hydrogen cyanide. Contacted by inhalation, this agent quickly enters the bloodstream. Here, the cyanide ion is believed to

combine with iron-containing cytochrome oxidase thereby blocking this hydrogen transfer mechanism and disrupting cellular respiration (1, 32). The disruption of cellular respiration is particularly critical in the respiratory center and death can occur rapidly due to pulmonary failure. Death from hydrogen cyanide poisoning leaves the blood well oxygenated, so the skin has a pink color characteristic of carbon monoxide poisoning (27, 40).

Symptomatology - The symptoms for AC poisoning depend largely upon the duration and concentration of the exposure. In high concentrations, a few breaths of the gas will cause an increased depth of respiration in seconds, violent convulsions in half a minute, and cessation of heart action in a few minutes. Following a moderate exposure, headache, vertigo, nausea, and possibly convulsions and coma may ensue. Prolonged exposure to low concentrations can produce extended tissue anoxia and damage to the central nervous system. Usually recovery is complete from mild exposures.

Toxicity - Because the body detoxifies hydrogen cyanide at a rapid rate - 0.017 mg per kilogram body weight per minute - the toxicity varies with dosage. At a concentration of 200 mg-min/m^3 , the lethal dosage is about 2000 mg-min/m^3 . However, at 150 mg-min/m^3 , the lethal dosage is near 4500 mg-min/m^3 .

Diagnosis, Treatment, and Prognosis - The initial symptoms from hydrogen cyanide poisoning resemble those of nerve gas poisoning. However, the absence of miosis and the presence of respiratory stimulation serve to distinguish between the two. The first recommended emergency therapeutic measure is inhalation of amyl nitrite. The nitrite combines

to oxidize the hemoglobin iron to the ferric state to form methemoglobin. The methemoglobin then has an affinity for the cyanide ion and cyanomethemoglobin is formed. Following the nitrite treatment, sodium thiosulfate is administered to combine with the cyanide to form thiocyanate which is not highly toxic and is excreted readily. It has been suggested that a mammalian tissue enzyme, rhodanese, catalyzes the transfer of the sulfur to cyanide. Thus, rhodanese may be combined with the thiosulfate as an antidote or treatment for this type of poisoning (1, 40). The prognosis for an AC victim can be rendered quite rapidly. If the victim does not die within several hours, recovery will probably be complete. However, a companion blood gas, cyanogen chloride, may cause permanent damage to central nervous system (40).

4. The Blister Gases. The fourth category of casualty producing agents are the blister gases. These toxic compounds were the most effective casualty-producing gases used in World War I. The blister gases could be classed as incapacitating agents since they usually produced only non-fatal casualties. There are three general classes of blister gases or vesicants. The first is mustard (H) which has sulfur as the central atom. The second class are the nitrogen mustards (HN-1,-2, and -3) which have ammonia as the central atom with various organic radicals replacing the ammonia hydrogens. The third class are the arsenical vesicants with arsenic (AsH_3) as the central atom and organic radicals replacing the hydrogens (27, 40). The specific formulae for the three classes of vesicants can be seen in Table 1.

There is less known about the fundamental biochemical effects of the vesicants than about other lethal CW compounds. Although the physiological-pathological effects of the vesicants have been well described, far less is known about the initial effects at chemical-cellular levels. For example, arsenic - the central atom of the arsenical vesicants, is known to inactivate enzymes by attaching itself to the sulphhydryl (SH^-) groups (1). However, it is still uncertain as to which of the enzymes are the critical ones and the most fundamental action of the vesicants is obscure.

Because the blister gases or vesicants are generalized tissue irritants and cellular poisons, the symptoms vary according to the area and extent of exposure. The eye, of course, is vulnerable to exposure and conjunctivitis can follow exposure to a dosage barely perceptible by odor. Ocular involvement results in photophobia, pain, lacrymation, rhinitis, and blepharospasm. These symptoms alone are sufficient to produce a casualty. When the dosage is more concentrated, the cornea may become permanently damaged. Secondary infections may also develop and complicate the trauma and prolong convalescence. When the vesicants contact the skin, intraepidermal vesicles develop which are painful and can become infected. Inhalation of these vapors causes damage to the laryngeal and tracheobronchial mucosa. Involvement may range from progressive pulmonary fibrosis to the development of a necrotic cast in the bronchial tree. Again, these tissues are susceptible to infections and most blister gas deaths are the result of secondary respiratory infections.

Ingestion of the liquid or concentrated vapor causes damage to the epithelial lining cells of the upper gastrointestinal tract with necrosis, desquamation, and hemorrhage. Nausea, vomiting, pain, diarrhea, and prostration follow the systemic absorption of the vesicants. In addition, the mustard gases have a predilection for hematopoietic and lymphoid tissues. This effect is quite rapid, with severe aplasia developing in 12 hours. The leucocyte count can be used for prognosis of recovery. Very heavy exposures induce central nervous system symptoms such as cerebral depression, cardiac irregularities, and bradycardia (27, 40).

Toxicity - The median lethal dosage for inhalation of the mustard vapor is 1500 mg-min/m^3 . By skin absorption for masked personnel, the LCt_{50} is $10,000 \text{ mg-min/m}^3$. The median incapacitating dosage by eye injury from vapor is 200 mg-min/m^3 , and is between 2,000 and 1,000 mg-min/m^3 for skin absorption (for masked personnel). Mustard is detoxified very slowly so that repeated exposures to low concentrations may be cumulative (27).

Treatment and Prognosis - Decontamination is the first step in the treatment of any of the toxic agents but is especially important with the mustards because they are insidious and can be on the skin long before symptoms appear. Eye injuries call for the use of BAL (British Anti-Lewisite) eye ointment to irrigate the eye surface. The skin is decontaminated by M-5 protective ointment which is rubbed over the contaminated skin. Both compounds act by neutralizing active portions of the mustard molecule. However, they are effective only for topical application. Once the victim can receive more thorough treatment after

decontamination by BAL and M-5, eye injuries are treated with sodium sulfacetamide solution to prevent infections. Very painful ocular symptoms can be alleviated with atropine sulfate solution. Other antibacterial agents can be substituted for sulfacetamide. Treatment of mustard erythema consists of relieving itching as by the use of calamine solution. The blisters are covered with petrolatum gauze which is left in place as long as possible. Denuded areas are treated in the normal fashion with petrolatum dressings, mild antiseptic solutions, and saline washing to remove dead tissue and exudates. Treatment of the respiratory tract injuries is aimed at reducing the discomfort and coughing by use of codeine and alkaline gargle. Antipneumococic drugs are given if the damage is more extensive. Mustard gastrointestinal and systemic symptoms may be alleviated by subcutaneous injection of atropine. This treatment, however, is effective only for reducing the severity of symptoms. When the damage has occurred in the vascular and hematopoietic system, nutritional status should be maintained as well as fluid and electrolyte balance.

The prognosis for mustard burns varies according to the area affected and the extent of injury. Ocular burns must be regarded very seriously and attempts must be made to avoid corneal scarring. When secondary infections develop, the chances for uneventful recovery are lessened considerably. The same is true for respiratory involvement. When shock and pronounced leucopenia are seen in severely burned victims, the prognosis is poor (40).

The mustard gases caused the majority of the casualties in World War I, (4) but it is doubtful if they would be the most effective agents for modern warfare since they have a distinctive odor which could serve to alert well-trained troops to take protective steps. However, they might find some application in a limited war situation such as a jungle theater of operations where the vesicants would persist for some time on moist, foliated terrain.

Simulation of a Gas Attack

The probable effects of gas attacks have been calculated for a number of situations. One such simulation involves a hypothetical attack on San Francisco (6, 20). The conclusions were based on existing knowledge of meteorological data and the known biological effects of Sarin. It was established that by utilizing several available delivery methods, one square mile of the city could be covered with a cloud of gas 30 feet high at an average concentration of 50 mg/m^3 . This average concentration would persist for about 30 minutes. The casualty effects were predicted as follows:

- a) The first 20 per cent of the population in those portions of the city covered by the gas (11.5 square miles coverage in total) escape unscathed on the basis of chance alone. These people were taking showers, trapped in closets, working in sewers, and so on.
- b) The second 20 per cent of the population were fringe victims. That is, they received a just-symptomatic dosage of less than 7 mg-min/m^3 . At worst, these individuals would have had a slight headache.

- c) The third group, consisting of 15 per cent of the population, were classified as mild cases of gas poisoning. Having absorbed between 7 and 15 mg-min/m³ dosages, they experienced nausea, headache, dizziness, and some breathing difficulty.
- d) The fourth group, also 15 per cent, were moderate cases. They received between 15 and 40 mg-min/m³ and less hardy members of this group, such as infirmed older people and infants, require atropine treatment to survive.
- e) The 13 per cent group were seriously injured. They received between 40 and 100 mg-min/m³. In order to survive, these victims would require prompt medical care, atropine, and artificial respiration.
- f) The last 16 per cent group are doomed. They will have absorbed between 100 and 200 mg-min/m³ dosages of Sarin and even those few fortunate enough to receive immediate medical care would have little chance of surviving this dosage.

The majority of the deaths were calculated to have occurred within the first day, the marginal cases within two days, and by three days, most of the deaths would have occurred. At best, only 65 per cent of the San Francisco population would have survived this single attack by the nerve gas Sarin.

Incapacitating Agents

Incapacitating agents are selected for their ability to cause a transient disruption in the normal activities and behavior of an individual.

These agents may cause incapacitation in the following ways:

- a) Impairment of his sensory faculties so that the individual is unable to see or hear (or feel). It is also effective if this temporary impairment is accompanied by pain. Tear gas is a standard incapacitating agent. It causes excess tearing and severe ocular pain which becomes overwhelming even to the most desperate of individuals.
- b) Induction of disruptive somatic feelings and symptoms. Here, the vomiting gases serve as an example of agents which cause physical incapacitation. When such symptoms as nausea, malaise, vomiting, and diarrhea occur, the individual is little disposed to performing routine tasks. In addition to the obvious physical distress, the so-called sick-gases have a tendency to affect the attitude of the individual as well as his somatic integrity.
- c) By eliciting aberrant mental behavior, lassitude, or unconsciousness. Some of the new psychotomimetic agents induce bizarre mental behaviour and these effects are persistent for as much as twelve hours post-exposure.

The biological and chemical mode of action of these agents is not well understood and although they doubtless cause some impairment of the normal CNS synaptic activity, no exact mechanisms have been elaborated.

1. The Vomiting Gases (Sternutators). The sternutators produce a strong irritation in the upper respiratory tract causing lacrimation, coughing, sneezing, nausea, vomiting, and malaise. They are dispersed as

aerosols and affect the eyes and oro-nasal membranes. They are usually used for riot-control in outdoor areas because in confined areas they can cause serious illness and death.

Diphenylchloroarsine (DA) is typical of the three listed sternutators. All three have arsenic as the central atom. Arsenic itself, as described previously, has a propensity for the sulphhydryl groups on enzymes. Undoubtedly, the major radicals attached to the arsenic atom also contribute to the toxic effects. While many of the toxic irritants can induce nausea and vomiting, the specific molecular configurations responsible for the cytological, histological, and physiological responses remain obscure.

Symptomatology - DA produces a feeling of pain and a sense of fullness in the nose and throat. This is accompanied by headache and burning in the throat and tightness in the chest. The eyes become irritated and lacrymation is induced. Coughing is uncontrollable. Ropy saliva is produced. Nausea and vomiting are prominent. Mental depression occurs during the progress of symptoms. Symptoms appear within minutes after exposure and persist for at least one-half hour.

Toxicity - The median temporarily-incapacitating dosage is as low as 12 mg-min/m^3 if received over ten-minute periods. The median lethal dosage is $15,000 \text{ mg-min/m}^3$. An incapacitating dosage is detoxified within one or two hours.

Treatment - Frequent inhalations of chloroform give symptomatic relief. Aspirin may relieve the headache and general discomfort. Symptoms resulting from field exposures usually disappear within two hours. However, severe pulmonary injury and death can result from exposure to high

concentration in confined spaced (40).

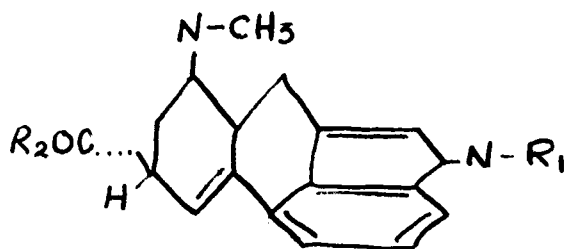
2. Tear Gases (Lacrimators). Lacrimators are local cellular irritants which are very effective in producing symptoms in low concentrations. They are used as riot control and training agents. For example, Bromobenzylcyanide produces a burning sensation of the mucous membranes plus severe irritation of the eyes. This produces sharp pain in the eyes, blepharospasm, and copious lacrimation. The rate of action is practically instantaneous. Liquid or extensive contamination of the skin can cause vomiting.

Toxicity - The median incapacitating dosage by ocular effect is very low, about 30 mg-min/m³. The median lethal dosage is around 4,000 mg-min/m³, but this dosage could not be absorbed under field conditions as BBC is rapidly detoxified.

Treatment and Prognosis - The damage to the ocular tissue (from the vapor) is self-limiting and requires little treatment except eyedrops. If liquid BBD contacts the eye, it should be neutralized by a solution of sodium sulfite. If burns occur, they may require several weeks to heal (40).

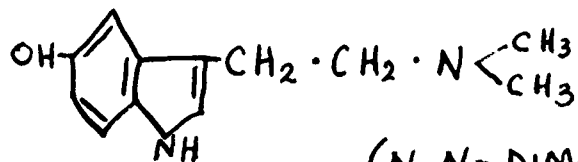
3. The Psychotropic Agents. The following compounds have been shown to cause hallucinations, disorientation, and changes in thought, perception, and mood:

1. d-lysergic acid diethylamide (LSD) and its derivatives

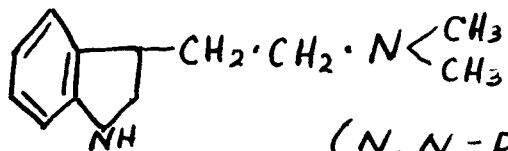


	R ₁	R ₂
d. LSD ₂₅	H	N < $\begin{matrix} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{matrix}$
ALD ₅₂	COCH ₃	N < $\begin{matrix} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{matrix}$
LAE ₃₂	H	N < $\begin{matrix} \text{H} \\ \text{C}_2\text{H}_5 \end{matrix}$

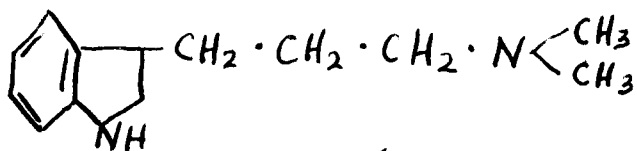
2. bufotenine and related indole alkylamines



(N,N-DIMETHYL-5-HYDROXYL TRYPTAMINE)

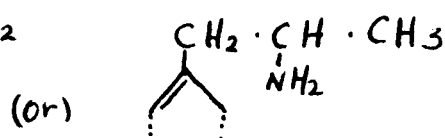
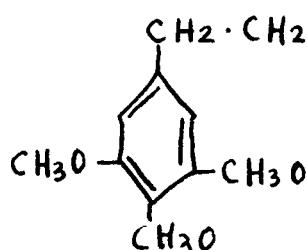


(N,N-DIMETHYL TRYPTAMINE)



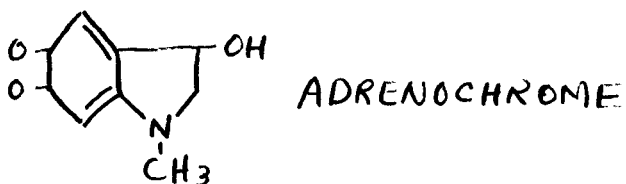
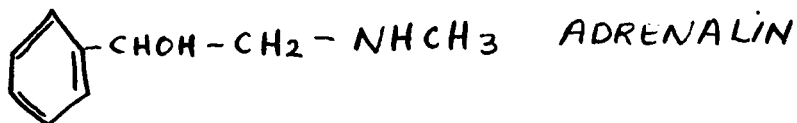
3-(3-DIMETHYLAMINOPROPYL)-INDOLE

3. mescaline

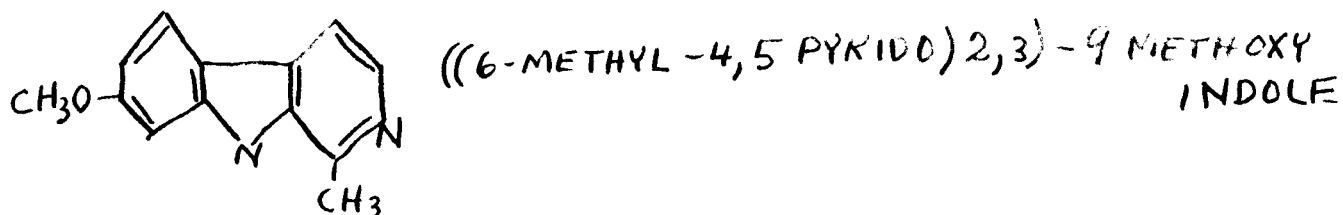


3, 4, 5 - TRIMETHYLOXYPHENYLETHYLAMINE

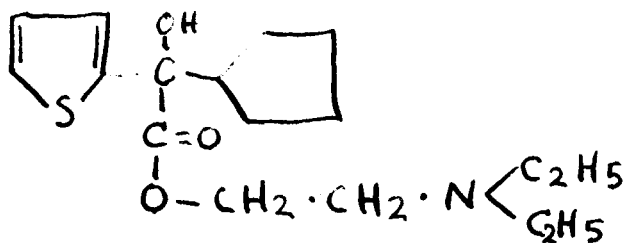
4. oxidation products of epinephrine and adrenochrome



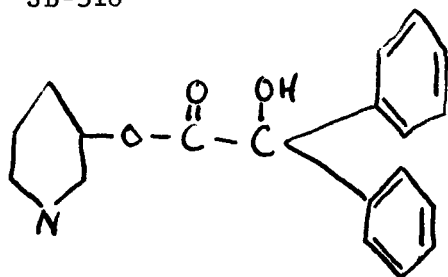
5. harmine (and substituted pyrindoles)



6. WIN-2299

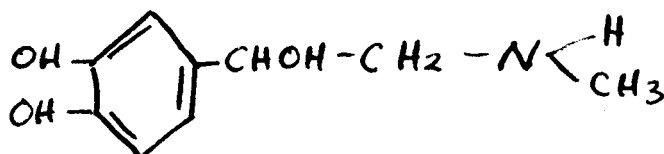
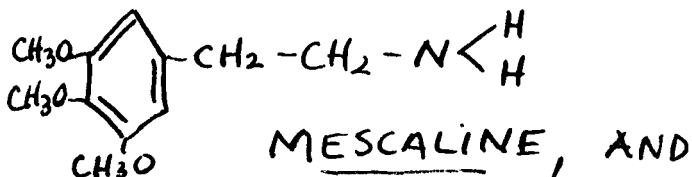
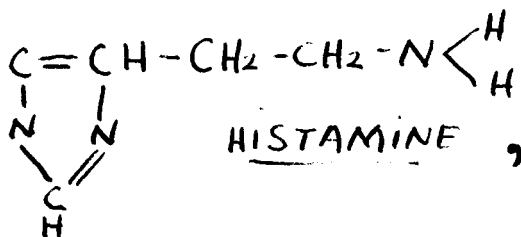
2-DIETHYLAMINOETHYL CYCLOPENTYL (2-THENYL)
GLYCOLATE

7. JB-318

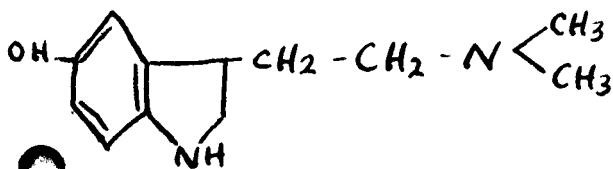
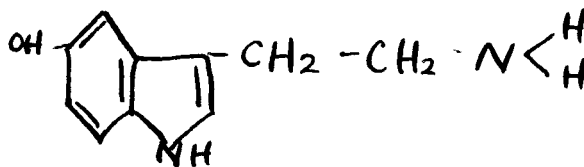


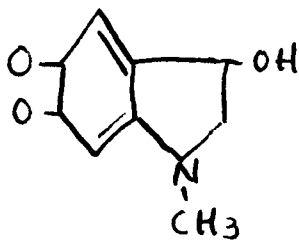
N,ETHYL-3-PIPERIDYL BENZILATE

Although there seems to be no specific chemical configuration for hallucinogenic effect, it is interesting to note the similarity in basic structure of several of the biogenic amines such as:

ADRENALIN

OF:

BUFOTENINE,SEROTONIN, AND



ADRENOCROME. (39)

It is beyond the scope of this thesis to present a detailed review of the basic neurochemistry of the CNS and its possible relationship to psychogenic compounds. The experimental data in this area of research remains in the formative stages and any conclusions regarding exact modes of action would be at best theoretical. The recent studies in this area have been reviewed (18, 30, 35) and suggest that the remarkable structural similarity between the biogenic amines and the psychogenic agents are in some way causally related.

A) Recently the well-known hallucinogen, LSD, has been tested as aerosol CW agent. LSD is easily absorbed orally, passes from the blood to all tissues, and is excreted quickly in the bile (35). Although LSD passes slowly into cerebrospinal fluid, only small concentrations (1 microgm/Kgm) are required to induce prolonged behavioral changes. It is suggested that LSD produces behavioral abnormalities by interfering with the physiologic actions of serotonin in the brain (18). Although its mechanism of action is unclear, LSD has been shown to alter the electrical activity in the brain. Some of the behavioral effects of LSD can be blocked by glutamic and succinic acid suggesting that LSD

may cause psychological effects by disturbing the brain's carbohydrate metabolism. In addition to its central effects, LSD has been shown to cause peripheral vasoconstriction in isolated organs, pilo-erection, mydriasis, salivation, and lacrimation (39).

B) Bufotenine effects include cyanotic flushing, nystagmus, mydriasis, and a transient increase in blood pressure. Bufotenine also is a powerful smooth muscle constrictor and may cause central nervous system effects by producing anoxia via selective vascular constriction in some brain regions. Intravenous injection of 8-16 mg in human subjects has produced such effects of primary visual disturbances, time and space alterations, and parenthesis (39).

C) Harmine was brought to attention through its use by South American natives to produce hallucination and intoxication. Injection of 150 to 200 mg dosages of harmine hydrochloride in schizophrenic patients produced visual, auditory, and somatic hallucinations, and numbness. Harmine may also induce convulsions in mice and monkeys (39).

D) Mescaline (or peyote), an alkaloid extracted from the cactus Lophophora williamsi, has long been used by American Indians for its hallucinogenic properties. Oral ingestion of about 300 mg produces in the normal subject symptoms of anxiety, hyperreflexia of the arms and legs, tremors, and vivid color perceptions and optical illusions of brightly illuminated colored patterns.

Animal experiments with mescaline have produced a variety of effects varying with dosage and species. Injected intravenously in cats, the effects include pilo-erection, involuntary defecation and urination, cardiac

and respiratory irregularities, and alterations in EEG patterns. Enzyme studies show that mescaline has a slight stimulating effect on cytochrome oxidase activity and inhibition of succinic dehydrogenase. In addition, mescaline inhibits the transmission of the nerve impulse from neuron to neuron (39).

E) The biochemical investigations of mental disorders lead to the suggestion that adrenalin metabolites might be associated with schizophrenia. Specifically, adrenochrome and adrenolutin may give rise to the hallucinations and be a part of the neurohormonal imbalance which exists in altered mental states. Despite the difficulty in studying these oxidized derivatives, it is known that adrenochrome interferes with oxygen consumption by brain tissue (in vitro) by uncoupling oxidative phosphorylation. It also inhibits decarboxylation of glutamic acid and blocks cholinesterase. In that acetylcholine is active in the function of several cerebral areas including the mesodiencephalic activating system, it is postulated that the equilibrium between acetylcholine and serotonin may be a major factor in two types of abnormal behavior, psychoses, and neuroses. It is possible that the adrenalin oxidation products may play a role in disturbing this equilibrium (18, 39) and any compound altering this metabolism may be a potential CW agent.

F) The piperidyl benzilate esters (JB-318) were originally intended as possible antispasmodics in the treatment of duodenal ulcer. Therapeutic trials showed that the tertiary amine hydrochlorides produced hallucinations. 5-15 mg oral dosages in human subjects produced megalomaniac and paranoid delusions, and visual and auditory hallucinations (39).

General Comments (The Psychotropic Agents) It has been difficult to find a chemical common denominator to account for the behavioral effects produced by these various compounds. Similarly, it is not yet possible to describe a single (or unique) anatomic locus or mode of action. The consensus of opinion is that alterations in central synaptic activity are involved.

Symptomological and Psychological Effects of the Hallucinogenic Agents From the military application standpoint, the primary interest in these compounds are the general effects, the most consistent patterns of behavior, and those symptoms which most reliably indicate that these drugs are in effect. LSD has been actively investigated and there are at least 750 papers describing the effects of LSD upon man and animals. Therefore, the following description of LSD-induced psychological effects will be used to represent the effect of all the psychotropic CW agents.

It is generally agreed that the optimum dosage of LSD for man is one microgram per kilogram body weight. The peak effect is reached between 1-1/2 and 2-1/2 hours after ingestion and the effects last up to 12 hours. The body apparently reaches a tolerance for LSD very quickly for a maximum-effect dosage of 100 mg will produce little to no effect after three daily administrations. However, the tolerance is also short-lived and will not last more than 3 to 5 days if daily administration is discontinued.

The first observable effects of LSD appear about one-half hour after ingestion and are mostly autonomic and motor in nature. They include dilatation of the pupils, palpitations, tachycardia, blood pressure fluctuations,

and, less frequently, sweating, coldness of the hands, headache, dizziness, and nausea. There may be subjective feelings which accompany these early physiological symptoms, but they are variable. The subsequent psychological effects include hallucinations of both personal and non-personal nature. Non-personal hallucinations appear in the form of geometric designs with vivid color, while personal hallucinations involve vivid recollections and distortions of past experiences. Active feelings include euphoria and omnipotence sometimes coupled with anxiety and suspicion. There is a flight of ideas and difficulty in concentrating. Sensory sensitivity is markedly increased such that ordinary lights become blinding and normal noises can seem unbearably loud. Summarized, the psychological effects include illusory phenomena and distortion of external objects.

Experimenters have attempted to quantify the behavioral disturbances by having experimental subjects perform various intellectual and motor tests, but the results have been quite variable. About all that can be said is that effects are pronounced but individual in character. Some few individuals become quite paranoid while others may suffer greatest impairment only in complex reasoning tasks (39).

It still is early in the study of these drugs to state whether or not they could be used as effective CW agents. They are by far the most imaginative of the CW agents because they offer the possibility of not only disrupting the mental processes of the enemy, but doing so without his even being aware of the disruption.

Defense Against the CW Threat

Defense against the chemical warfare threat is an extremely complex and demanding task. Discussion of adequate counter measures and control of the biological effects of CW agents is beyond the scope of the present review and has been summarized in a number of recent studies.³ However, it should be emphasized that the research in CW defense is quite active and should be seriously considered by responsible research organizations.

³The following references were useful for a review of CW defense:

2, 3, 6, 11, 12, 14, 20, 25, 29, 35, 37, 41.

GLOSSARY OF TERMS PERTINENT TO CHEMICAL WARFARE

The following terminology and definitions are basic to a technical discussion of chemical warfare effects:

- (1) Aerosol--a solid or liquid divided into uniformly fine particles (or droplets) which are suspended in the air for an extended period of time.
- (2) Concentration--the amount of gas or substance present in a volume of air. Concentration is usually expressed as milligrams of contaminant per cubic meter of air. As will be seen by the next term, concentration is an incomplete description to depict the degree danger from a toxic agent because of the time element of exposure.
- (3) Dosage--this unit is capable of quantifying the danger from a particular toxic agent because it is calculated as the concentration (C) of the agent multiplied by the time (t) of exposure. Ct can be expressed as mg-min/m³.
- (4) Ct product--this term is useful in describing the severity of repeated exposures to agents which exhibit cumulative toxicity. Thus, an agent with₃ cumulative toxicity such as phosgene, a Ct product of 200 mg/m₃ for five minutes would be equal to a Ct product of 100 mg/m₃ for ten minutes. The Ct product is not as useful for describing repeated exposures to agents that are rapidly detoxified by the body.
- (5) Contamination density--this term states the weight of con-₂ taminant per area of substrate; for example, mg/m² or oz/yd². This term is useful for describing cutaneous exposures. With knowledge of contamination density, it is possible to predict the effect of an exposure if the particular agent in question is effective by contact.
- (6) Persistency--this reflects the duration of toxic effectiveness of a chemical agent once it is exposed to environmental conditions. The persistency of a disseminated agent depends upon its physical and chemical properties and the environmental conditions such as heat, light, moisture content, precipitation, and terrain. Agents can be selected for their relative persistence or non-persistence. For example, it would be advantageous to use a non-persistent chemical if there was the intention of immediate post-attack occupation.
- (7) Toxicity--toxicity denotes the propensity of an agent to cause its detrimental effects at low concentrations. Toxicity is also

used in a relative sense; an agent can have acute or chronic toxicity, or can be described with reference to the rapidity of onset of effects.

- (8) Median lethal dose (LCt₅₀)--this term describes the time of exposure and dosage required to kill 50 per cent of a sample population. The use of LCt₅₀ is convenient for scaling or computational purposes in a war game, but is apt to be a misleading concept in field use for one reason: the surviving 50 per cent of the exposed population is not to be assumed unaffected by this exposure; it is simply that they do not become affected within a specified time period. Other scaling concepts are useful such as median-incapacitating dosage, median-lethal dose by skin absorption, and so on.
- (9) Mode of entry--some of the war chemicals, such as tear gas, are only toxic if absorbed via a specific route as opposed to the nerve gases which are toxic whether they be absorbed through the skin, eyes, lungs, or alimentary canal. It is more advantageous to have an agent which is effective regardless of its mode of entry into the body.
- (10) Rate of action--this characteristic of an agent is significant for two reasons. If an attack is to effect immediate casualty so that no alarm or retaliation can take place, the agent logically must have a rapid rate of action. Toxicity is usually equated with rate of action although they are different in the strictest sense. Toxicity has concentration as the principle variable whereas rate of action reflects upon the speed of physiological activity. The nerve gases, for example, have a rapid rate of action--seconds, as opposed to the mustards which may take hours to cause blisters (27).
- (11) Stability--this property of chemical agents is one of concern for ordnance and logistics in that the manufactured agent should be chemically stable during periods of transport, storage, and dissemination.
- (12) Effect variability--there are many conditions of exposure that may vary the intended effect of the particular agent. Some of the more prominent conditions are:
 - (a) how long the victim was exposed to the toxic agent,
 - (b) the speed with which evasive or protective action can be taken,
 - (c) the leakage rate or permeability of protective garb and mask,
 - (d) the exposed surface area of the vulnerable route of entry,

- (e) physical condition of the individual, and
- (f) rate of detoxification, especially if the period of exposure is prolonged. The rate of detoxification is the rate at which the body will eliminate or detoxify a particular toxin. In some instances, if the rate of action of a chemical warfare agent is slow (in a relative sense), the agent can be distributed throughout the body and the stress absorbed in a large volume of tissue. On the other hand, rapidly acting agents begin action immediately upon contact with the body and cause acute local effects which can be lethal. Sarin, the nerve gas, demonstrates this phenomenon: the lethal dosage for Sarin is about 100 mg per m³ when the exposure period is from 30 seconds to several hours. However, a concentration as low as 15 mg/m³ can be fatal if it is received in one breath because this amount of compound would not have time for distribution throughout the body before it exerted its lethal effects exclusively on tissues in the pulmonary system (27, 40).

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BIOLOGICAL EFFECTS OF RADIOLOGICAL WEAPONS

The Acute Effects of Ionizing Radiation

The acute effects of ionizing radiation on living systems have been recognized since the early research in radiation biology. However, it remained for Quastler (71) to establish that a continuity of physiological phenomena appear following exposure to penetrating radiation. Over the course of time following exposure, classes of phenomena appear which are characterized by specific dose-temporal symptomatology. Using man as the mammal subjected to a range of exposures, the acute response according to dosage would appear to be as follows:

Table 1

<u>Total Dose from a Single Exposure</u>	<u>Mode of Death</u>	<u>Time After Exposure</u>	<u>Critical Sensitive System</u>	<u>Final Cause of Death</u>
5000-20000r	CNS	Hours to two days	unknown	unknown
1200-5000r	GI	4-8 days	epithelial lining of GI tract	ulceration septicemia fluid-electrolyte disruption
350-1000r	Marrow	12-30 days	hematopoetic system stem cells + replacement cells	septicemia + hemorrhage

Ionizing Radiation and Its Interaction with Matter

In order to better understand the theories of radiation damage, it is useful to be familiar with the events that occur as radiation dissipates its energy in living matter. There are two classes of ionizing radiation. The first is particulate radiation which is a stream of atomic or subatomic particles capable of transferring their kinetic energy to target atoms and molecules. Particulate radiation can consist of charged particles, such as electrons, or neutral particles, such as neutrons. The second form of ionizing radiation is electromagnetic radiation which consists of self-propagating electrical-magnetic cyclic disturbances capable of affecting the internal structure of matter. When electromagnetic radiations such as X or gamma rays dissipate their energy in matter, they release this energy in discrete units or quanta (38).

Both particulate and electromagnetic radiation can be present in a range of energy levels. . . If a very high energy particle were to interact with matter until all the excess energy had been dissipated, a number of distinct physical phenomena would be observed. However, for the purposes of this review, only the phenomenon of excitation and ionization will be considered. Ionization is a form of chemical activation whereby an electron is ejected from an atom (or molecule) resulting in the creation and spatial separation of two oppositely charged particles or ions. The parent atom assumes a positive charge as a result of

the loss of the negatively charged electron while the electron may attach itself to a neutral atom (or molecule) giving the latter a negative charge.(38).

Excitation is the process whereby the incident energy only alters the motion of the planetary electrons. With the "excitation" of these electrons, reorganizations occur and the bond forces between constituent atoms tend to weaken. One or more of the weakened bonds may rupture, loosing stable and unstable fragments into the environment. In both cases, ionization and excitation, the target atoms and molecules acquire a high degree of chemical (electronic) energy and quickly participate in chemical reactions which are frequently different from the sequential reactions normally scheduled by the cell (68).

When ionizing radiation interacts with living matter, it dissipates its energy in four discrete stages starting with the physical stage and ending with the biological stage. In the first, or physical stage, radiation leaves the target atoms or molecules in an excited and/or ionized state. This is the period during which primary products are created. The second, or physical-chemical stage is the period during which the high energy primary products of stage one undergo further

collisions creating secondary products. The third stage of this energy transfer process is the chemical stage. Here the primary and secondary products of stages one and two have reached thermal equilibrium and all of the excess energy has been dissipated. The chemical products of this third stage are: (a) stable molecules which may or may not be the same as the original molecule, and (b) chemically reactive radicals. Because at least 80% of the living cell is water, the incident radiation has the highest probability of reacting with water. Therefore, a majority of these radicals will be hydrogen-oxygen combinations, namely HO_2^\bullet , OH^\bullet , and H^\bullet or the various ionized forms of water, H^+ , OH^- , H_2O^+ , H_3O^+ , HO_2^+ , and H_2O^- (92, 94).

It is important to note that the first three stages are complete in less than a millionth of a second. In addition to these effects it has been shown that there is a measurable increase in H_2O_2 probably by combination of either $\text{OH} + \text{OH}$ or $\text{H} + \text{HO}_2$. Longer lived organic free radicals are also produced but the biological effect of both H_2O_2 and the organic free radicals is unknown (94).

Stage four is called the biological stage because this is the period when the chemical products of the chemical stage enter into biological reactions. Up to this point, there had been no biological response to the radiation's action because of the distinct brevity of

the first three stages. However, when the free radicals and ions enter into chemical, biochemical, and physiological reactions, the biological stage is initiated and may be manifest for years involving all orders of organization in the body including heredity (38).

Thus, stage three ends the physical period of radiation's action upon matter and stage four begins the biological period. The following section introduces two theories to explain cellular damage by ionizing radiation.

Theories of Radiation Action upon Cells

There are two theories that attempt to describe the mechanism of radiation action upon the cell. These theories may contradict or complement one another, depending upon the experimental conditions or the interpretation of the results. Nevertheless, both theories appear to be accepted at least in part and both may be operative in an environment as varied and complex as the living cell.

The first theory asserts that the absorption of radiation is not a continuous process but a predictable series of quantized hits, the number of hits depending upon the energy of the radiation and the volume of the target. The biological sequelae of radiation absorption are thought to be the direct result of the chemical disruption of

critical biological molecules. Consequently, this has been called the direct action theory. By contrast, the indirect action theory holds that the primary biological effect of radiation is not the result of direct hits on critical targets but the indirect result of the creation of chemically reactive ions and radicals from inter- and intra-cellular water. These ions and radicals then react with biological molecules to disrupt normal processes. While the direct action theory may better explain some of the effects of radiation on nucleoproteins, the indirect action theory appears to be more flexible for explaining the range of effects in complex subcellular systems (83, 94).

Cell Damage by Radiation

The types of damage to cells by radiation may be better understood by first considering the operation of the normal cell. If the cell is viewed as a biological entity capable of maintaining precise metabolic activities and also capable of reproducing itself in precise fashion, it can be divided into a few simple parts according to basic function. First is the nucleus which contains the mechanism for specifying the character of the cell as it matures, the nature of the tasks it will perform at maturity, and the identity of the daughter cells which result from cell divisions. The second major functional constituent of a cell is cytoplasm. The cytoplasm is intracellular material exclusive of the nucleus and

contains subcellular components necessary for cellular metabolism, repair, and maintenance. Extremely complex biochemical sequential reactions are constantly occurring both in the nucleus and cytoplasm, but it is within the cytoplasm that most of the somatic functions occur. The cytoplasmic activity is normally high except during cell division when it becomes quiescent and apparently supplies energy for the dividing nucleus. The third major component of cells are the membranes. Not only do these membranes hold the various subcellular components together, they also provide the substrate for a great number of the chemical reactions within the cell. There is evidence to the effect that these membranes actively participate in the transport of vital chemicals into and out of the respective cellular compartments.

From this brief review of the cell, it is possible to distinguish three basic types of damage that could occur within the cell as a result of radiation absorption. First, damage to the genetic mechanism within the nucleus would exert a detrimental or lethal effect when the cell initiated its division process. As early as 1903, Bohn speculated that radiation of chromatin, a substance necessary for cellular growth and reproduction, was the vehicle through which radiation exerted its lethal effects (38). As evidence for cell damage through genetic mechanisms, it can be demonstrated microscopically that chromosomes

are actually broken by radiation (39). The second form of evidence for nuclear damage is the deferred death phenomenon. Here, the cell grows to abnormal size after irradiation but cannot divide. Similarly, cells irradiated in the resting or nondividing phase may not show the lethal effect until the process of division occurs. The implication here is that the nonreproductive activity of the cell can proceed normally, but that irreversible damage has occurred in the genetic structure. Chromosomal studies have shown that an exposure of only 50 roentgens is required to break one chromosome (39). However, additional evidence indicates that the genetic mechanisms are not always involved in the lethal effect. That is, nuclear disruptions other than genetic can cause cell death. For example, biochemical studies of bone marrow cells have shown that irradiation inhibits the synthesis of DNA (35).

A second possible mode of radiation damage to the cell is through disruption of the intracellular phospholipid membranes. Following radiation exposure, the enzymatic activity of the cell is higher than normal and some of the important enzymes can be collected outside of the cell. It is thought that radiation changes the permeability of the membranes, permitting critical enzymes to leak out of their respective compartments. The release of hydrolytic enzymes,

for example, can cause hydrolysis of proteins or DNA while the release of calcium ions can cause coagulation of nuclear proteins. Both of these reactions are detrimental (53).

A third possible mode of radiation damage to the cell is on the enzymes within the cytoplasm. Normally, the cytoplasm is relatively resistant to detrimental effects of radiation because many of its metabolic functions are duplicated. However, absorption of a moderately high dosage of radiation within the cytoplasm can disrupt enough of the cell's functions to cause permanent and lethal injury (78). The sulfhydryl groupings on the enzymes are vulnerable sites for ionization. Despite the fact that many of the damage sites on the cytoplasm are trivial with respect to the over-all capability of the cell, on the basis of chance alone, some of these chemical alterations could occur at a time when the cell is especially vulnerable (78).

The Effect of Ionizing Radiations on Mammalian Tissues and Organs

Although the damaging effects of radiation originate at the cellular level, different tissues and organs show considerable variation in their response to ionizing radiation. For one, rapidly growing cells appear to be more radiosensitive than stable mature cells (69). As another factor, the maintenance and posture of some resistant tissues and organs are intimately related to the condition of the radiosensitive

vascular system. Therefore, major tissues and organs may be discussed in order of their relative radiosensitivity (2).

1. The blood forming, or hematopoietic, system which resides in bone marrow, is the most radiosensitive organ system in the body. Since both direct and indirect destructive effects may be mediated through the vascular system, subacute radiation exposures, which may cause no subjective effects whatsoever, often can be detected by examination of the white blood cells (47). Following a median-lethal, whole body dose (about 500 r) of gamma rays, the lymphocyte count begins dropping immediately and reaches its ebb between 3 and 6 days. The granulocytes begin falling off in about 3 days, the platelets in about 9 days, and the red blood cells in about 12 days. There is a hemorrhagic tendency when the platelet count decreases and a reduced capability to resist bacterial invasion when the total white blood cell count drops precipitously. Therefore, symptoms directly related to changes in the blood constituents will be slow in onset, appearing perhaps in several weeks (34). The reason for this is that while body cells, blood or otherwise, may have their capabilities impaired by radiation, the lethal cellular effect may not be encountered until the cell begins its mitotic division (38). Also, it takes some time for

bacterial pathogens to penetrate ulcerated tissue and begin proliferating in the blood stream.

2. The gastrointestinal tract is also relatively radiosensitive and as an organ system is second only in sensitivity to the blood forming system. There are a range of direct effects on the gastrointestinal tract depending upon the severity of the dosage. At low levels of direct insult or involvement, the general physiological function is disrupted. In time, ulcers may appear in the tract which eventually cause direct hemorrhage. As the radiation level is increased, the secretion of gastric juices is halted and at exposures greater than 1,000 r, the permeability of the gut is severely altered so that body fluids are lost into the gastrointestinal tract. Somatic homeostasis is highly responsive to alterations of the gut. When the gut has been irritated by ulceration and sloughing of the lining tissues, this induces a feeling of malaise and nausea which may in turn induce both vomiting and/or diarrhea. If these symptoms are acute and large amounts of fluid and electrolyte are lost, the blood's acid-base balance may be disturbed and the blood chlorides reduced. Drastic reductions in blood chlorides can result in neurological changes as severe as tetany (8).

3. The endocrine system is relatively radioresistant. Supra-lethal radiation dosages must be absorbed before the endocrines are directly involved (47). The adrenals, while not sensitive to radiation, do show evidence of increased activity which increases cellular metabolism, which in turn increases the individual's over-all sensitivity to radiation. Whether the adrenals respond to toxins released into the systemic circulation or to the systemic stress reaction is not clearly understood (28, 50).

4. The central and peripheral nervous system is perhaps the most radioresistant organ system in the body. However, recent evidence suggests that there are complex effects resulting from exposure to even low levels of radiation (32). Extra-lethal doses (5,000 r) are required to elicit gross neurological changes (67), but some functional changes, such as decreased excitability and imbalances between excitation and inhibition, have been observed at near-lethal doses (around 700 r) (47). The nervous tissue of the eye enjoys a similar high degree of radioresistance. Destruction of the rods requires 1,700 to 2,000 r and destruction of the cones requires 10,000 to 30,000 r (29). The lens, cornea, and conjunctiva are all more sensitive than the retina. The approximate radiation threshold

for lens-opacity effect (cataracts), for example, is about 500 r (8), which is about median-lethal for humans. $\frac{1}{2}$

5. Skin and muscle are also radioresistant. Again, supralethal dosages must be encountered before the radiation causes direct effects (47).

Variables Associated with Radiation Exposure

An instantaneous, whole-body exposure may be as small as that from normal background radiation or as large as that which is lethal for 100 per cent of the exposed personnel. Within this range, from background to 100 per cent lethality, there are not enough data to specify the exact effects for each increment of radiation. However, one finding is clear, the variability of effects decreases as the dose increases. The following table gives a general expression of the expected effects of acute whole-body irradiation. Recognize, however, that in such tabular form the descriptions of symptoms at the higher dose levels will be better than those of the lower end.

1. Experimental ocular lesions in animals can be produced with exposures around 2,000 r. These lesions are characterized by conjunctival congestion, the swelling and narrowing of pupils, and retinal edema. This damage, however, is due primarily to vascular irritation and breakdown (12).

Expected Effects of Acute Whole-Body Radiation Doses (31)

<u>Acute dose (in roentgens)</u>	<u>Probable Effect</u>
0 to 50	No obvious effect, except possibly minor blood changes.
80 to 120	Vomiting and nausea for about 1 day in 5 to 10 per cent of exposed personnel. Fatigue but no serious disability.
130 to 170	Vomiting and nausea for about 1 day, followed by other symptoms of radiation sickness in about 25 per cent of personnel. No deaths anticipated.
180 to 220	Vomiting and nausea for about 1 day, followed by other symptoms of radiation sickness in about 50 per cent of personnel. No deaths anticipated.
270 to 330	Vomiting and nausea in nearly all personnel in first day, followed by other symptoms of radiation sickness. About 20 per cent deaths within 2 to 6 weeks after exposure; survivors convalescent for about 3 months.
400 to 500	Vomiting and nausea in all personnel on first day, followed by other symptoms of radiation sickness. About 50 per cent deaths within 1 month; survivors convalescent for about 6 months.
550 to 750	Vomiting and nausea in all personnel within 4 hours from exposure, followed by other symptoms of radiation sickness. Up to 100 per cent deaths; few survivors convalescent for about 6 months.
1000	Vomiting and nausea in all personnel within 1 to 2 hours. Probably no survivors from radiation sickness.
5000	Incapacitation almost immediately. All personnel will be fatalities within a week.

In the above table, a range for the median-lethal dose is specified as being between 350 and 600 r. The concept of median-lethal, or LD_{50} (lethal dose for 50 per cent of an exposed population) has been used in some scientific and military literature as a scaling concept. It gives no individual information, but is a convenient reference defining a midway point in the total range of gross effects. However, in regard to radiation exposure, the 50 per cent population which does survive should not be presumed to be unaffected.

The designation $LD_{50/60}$ is used to specify 50 per cent mortality in 60 days. It has been suggested that this is a more convenient designation for group exposure effect than simply LD_{50} (9).

There is disagreement as to a specific LD_{50} for man and the range is from 350 to 700 r (16, 31). It should be noted that the LD_{50} is not the same for the initial radiation pulse at the fireball stage as it is for short-range fallout. An LD_{50} as low as 375 r has been estimated for fallout exposure because the radiation source will be entering the body from many directions, whereas LD_{50} of 650 r might be more accurate for exposure to the initial pulse because it is unidirectional (57).

The second variable associated with radiation-exposure effects is the rate of exposure. While 500 r instantaneous exposure is about a median-lethal dose, this amount if received over a period of 10 years would only serve to shorten the life span. It is estimated that for adults receiving more than 100 r, the life span is reduced by about 10 days for each additional roentgen (8). Recognize however, that the lifespan-shortening effect of radiation is still to be completely described.

A third exposure variable is the area of the body which is irradiated. A 500 r whole-body instantaneous exposure could be fatal to 50 per cent of the involved personnel, but this same dose might be used as medical treatment for a local malignancy. In fact, doses in the thousands of roentgens have been delivered to small tumors with no general reaction, and 400 r doses may be delivered to body areas 20 by 20 centimeters and causes only transient radiation illness (87).

Another critical variable is the portion of the body which is irradiated. If certain portions of the body are shielded, the tolerance for lethal doses may be substantially increased. In animal studies, for example, when the skull, vertebral column, or pelvis were shielded, the experimenters could double the median-lethal dose.

In fact, shielding only three or four vertebrae extended the period of survival. Head shielding has also been shown to reduce severe loss of lining tissue of the alimentary canal. Preserving the integrity of the alimentary canal thus extended the survivability of the protected animals (2). Since the upper abdomen is among the more highly radiosensitive areas of the body (39), shielding the trunk as well as the head would offer even further protection for short-term exposures to radiation. The experimental work on marrow transplantation and shielding will be reviewed in greater detail later in this section.

The physical condition of the subject is still another factor which influences survivability (at least in the median-lethal range). A subject in poor physical condition is more apt to be sensitive to the indirect effects of radiation such as the induced anemia, the hemorrhagic tendency, and the reduced defense capability of the white blood cells. Similarly, a subject exhibiting the physiological stress reaction is also more radiosensitive than the resting subject (28, 30). By contrast, having alcohol in the system seems to extend one's tolerance to radiation (31).

Classification of Radiation Victims

Observations of radiation effects have come from four main sources:
(a) occupational accidents, (b) the use of isotopes and X rays for radio-

therapy, (c) nuclear detonations, and (d) animal experiments. The amount of reliable information of radiation effects on humans is limited in quantity. While there were large numbers of victims in Japan, the dosimetry could not be accurately determined so that symptoms and sequelae cannot be reliably correlated with dose (40). In the few clinical cases that are reviewed later, the dosimetry was accurately determined.

When the possibility of nuclear attack is considered, civilian and military defense planners and physicians have found it convenient to group anticipated radiation victims into categories based upon classes of exposure effects. As the intensity of dosage is increased, its damaging and/or lethal effects are inflicted on different body organ systems. Therefore, for clinical convenience in the treatment of large numbers of patients, the following four categories have been proposed (8).

1. "No Obvious Disease" - the portion of personnel exposed to as much as 200 r will have transient, intermittent nausea up to the third day post-irradiation. The degree of expected vomiting is dependent upon the dose, individual radiosensitivity, amount of stomach contents, and psychological disposition. These victims are presumed to require no specific therapeutic measures or hospitalization.

2. The "Hematopoietic Syndrome" - the second category of radiation illness is characterized by sufficient radiation, 200 to 1,000 r, to involve or insult the blood forming system. The clinical symptoms for this category may include any of the following: nausea and possible vomiting up to several hours post-irradiation, possible fever late in the illness probably due to secondary infection resulting from the decreased defense capability of the blood stream, and diarrhea at the same time as vomiting, although not as a certainty.

Increased bleeding tendencies appear later in the course of the illness, around 2 to 3 weeks. Prominent changes in the blood stream include: a decrease in total white blood cell count soon after exposure. This symptom, if it can be analyzed, may give one of the more accurate assessments of exposure and prognosis. Specifically, a drop from the normal lymphocyte count of 1,000 to 3,000/cc to 500/cc probably puts the patient in the fatal category. The platelet count decreases and is related to the bleeding tendency later in the illness. Secondary infections may appear later in the illness because of the decreased infection defenses of the blood stream and because of the loss of integrity of the gut lining tissues. Death will occur in approximately 50 per cent of the victims in the dosage range from 350 to 700 r and somewhere between 50 and 100 per cent of the victims in the 700 to 1,000 r range.

This is the largest and most difficult category of patient because diagnosis is difficult, the symptoms may be protracted, and the range of effects is from no-immediate-effect to death. Large quantities of therapeutic agents will be required and the patients will require care for long periods of time. There is no single set of therapeutic measures for patients in this category other than "good patient care" consisting of rest, antiemetics (to control vomiting), nutritional supplementation, water and salt balance maintenance, antibiotics, transfusions, and possibly bone marrow therapy.

3. The "Gastrointestinal Syndrome" - the third category of illness is for those receiving between 1,000 and 5,000 r, and involves both the blood forming system and the gastrointestinal tract. The symptoms will be rapid in onset, severe, and of a short duration ending almost always in death within two weeks. The principal symptoms are pronounced nausea, vomiting, fever, diarrhea and general debilitation. After several days of these initial symptoms, a short cessation of symptoms may be enjoyed, but the symptoms reappear prior to death.

As a class of patients or victims, these individuals will be easier to diagnose and the degree of incapacitation will preclude the possibility of their being able to participate in normal activities.

4. The "Central Nervous System Syndrome" - the fourth category of radiation by organ system insult is characterized by direct involvement of the central nervous system. The required whole body dosage is greater than 5,000 r. These patients can be expected to be completely incapacitated minutes after exposure and death will occur in hours (57).

Survivability as Related to Symptoms

As it is unlikely that the civilian defense or military physician will have instruments capable of performing body dosimetry, he will be forced to make decisions as to the care and disposition of patients on the basis of obvious symptoms. With this in mind, radiation victims might be sorted into three groups as follows:

A. Survival Improbable - if vomiting occurs promptly after exposure, continues over several hours, is followed by diarrhea, fever, and prostration, the prognosis is grave. Death can be expected within a week or two.

B. Survival Possible - nausea and vomiting may occur soon after exposure but will be of a short duration, not exceeding several hours. After a day or two of mild symptoms, the patient will enter a period of relative well-being although weakness may still prevail. The longer this latent period of well-being, the greater the probability of survival.

After the latent period of two to three weeks, new symptoms will appear, primarily due to changes in the blood stream. Therapy can attempt to bolster the lagging bacterial defense capability, prevent hemorrhaging from ulcerated tissue, maintain proper electrolyte balance, and supplement the diet to provide for nutritional losses in the ailing gut. The early course of the disease may be traced by taking a total white blood cell count a week after exposure. If the total w. b. c. count is below 800 per cubic centimeter, prognosis is grim, while if it is greater than 1,500 per cc., prognosis is encouraging. This group will be very responsive to medical care (59).

C. Survival Probable - victims experiencing only transient nausea and malaise and a leveling-off of depressed lymphocyte count within 24 to 48 hours may be expected to survive with a minimum of treatment (57).

Clinical Case Histories of Irradiated Personnel

One example of radiation exposure where reasonably accurate dosimetry was possible occurred in a fallout incident in 1954. Following a test detonation in the Pacific Proving Grounds, fallout settled on the Pacific island of Rongelap. Sixty-four native inhabitants were directly exposed to the fallout and were evacuated (along with

all the island inhabitants) for medical treatment and rehabilitation. It was estimated that the maximum absorption for some victims over a two day period was 175 r of penetrating gamma radiation and possibly as much as 5,000 rads of beta radiation confined to the skin. Two-thirds of these people were nauseous during the first two days and a smaller fraction experienced vomiting and diarrhea. Two days after direct exposure to the beta radiation, the victims experienced transitory itching and burning of the skin, and some lacrymation. Two weeks later, skin lesions (on the neck, junction of arm and torso, and between the toes) appeared along with partial epilation. The localized skin lesions were superficial (in depth) much like severe sunburn. The patients were not incapacitated by the skin lesions and examination of the burn scars showed no further breakdown four years after exposure. No spectacular or statistically significant after-effects of the radiation could be detected in a thorough five-year study (8).

In the Los Alamos incident previously noted, there were cases falling into each of the four disease categories. Here the radiations were fast neutrons, hard (penetrating) gamma rays, and soft (low penetrating ability) X rays. The whole body dosimetry was ascertained

with reasonable accuracy, but the dose to the hands of individuals touching the reactor can only be approximated. However, this approximation is noted only for academic purposes considering the severity of exposure.

In disease category one, "no obvious disease," there were 7 victims ranging from one who received as much as 186 r soft X rays and 10.7 r gamma, to another who received as little as 31 r soft X rays and 1 r gamma radiation. None of these victims experienced gastrointestinal symptoms nor did they report any subjective complaints. They resumed normal activity after a period of prescribed rest and a 4-year post-examination revealed no changes induced by the radiation.

In disease category two, "hematopoietic syndrome", with doses from 200 to 1,000 r, there was one victim irradiated by 390 r of 80KV soft X rays and 26.4 of gamma rays. The patient vomited once several hours after exposure, after which there were no G.I. disturbances. For several days he reported feeling weak and tired, and on the sixth day his temperature rose, but soon returned to normal. In fifteen days he was released from the hospital and in ten weeks regained

his complete physical endurance. For a period of four years he was beset with a transient low sperm count, but fifty-eight months later his wife had a normal child. He developed an incipient cataract in the lens of the right eye which substantially reduced visual acuity. At the time of the last examination this was the only apparent residual effect of the radiation.

The following two victims might be placed in either category, three or four, for while their whole body dosages were less than 1,000 r, their hands received several thousand r. In one case the patient was exposed to 480 r soft X rays, 100 r gamma rays whole-body, and as much as 40,000 r soft X rays on his hands. This patient was in distress and prostrated for 24 hours following exposure, after which time he was alert. On the fifth day he developed a fever and declined slowly until his death at 25 days. In the second case, the patient was exposed to whole-body radiation of 1,930 r soft X rays, 114 r gamma radiation, and up to 30,000 r soft X rays on his hands. He was ill within one hour after exposure, followed by a five-day period of good general condition. On the fifth day the white blood cell count dropped and on the sixth day his fever rose and pulse rate increased until his death at nine days (34).

Behavioral Effects of Ionizing Radiation

Beginning in 1951, an Air University research group conducted a study of 263 patients receiving radiation therapy for systemic neoplasms (8, 65). In addition to clinical observations to determine the course of the malignancy following radiation, the therapists administered psychomotor performance tests consisting of two-hand coordinator and the rotary pursuit tests. The dosages were by 15, 25 and 50 r increments, with totals from 25 to 200 r. Conclusions from observations of psychomotor skills following irradiation were:

"There was no evidence of a psychomotor decrement among the individuals who received these doses of radiation, whether it was administered over a period of a few minutes or over a period of a day in five different fractions of dose. In addition, there was no clinical evidence of radiation effects."

Animal studies have been conducted to determine if radiation exposures affected learning or retention (46, 75). For example, monkeys receiving median, or just lethal doses were tested for acquisition, retention, and transfer of multiple discrimination problems immediately after and 150 days post-exposure. No significant changes in score were observed and the only reported performance deficit was an increase in reaction time. Rats were irradiated and put through an

exhaustion-swimming test. Rats receiving 300 r (LD₅₀ rats = 700 r) had slightly less endurance than did the controls, while those receiving 500 r showed significant performance decrements. Performance proficiency gradually decreased, reaching its minimum during the third and fourth week post-exposure, then returned to normal by the ninth week post-exposure. This performance decrement was attributed to somatic malaise rather than any direct effects on neuro-motor functions (48).

In an experiment on animal personality, aggressive mice were exposed to lethal radiations and placed back in cages with their regular cage-mates. The irradiated mice maintained the aggressive behavior until death (90).

Furchtgott summarizes a review of animal behavioral studies with this statement:

"The published studies pertaining to the behavioral effects of ionizing radiations were reviewed. More studies have actually been performed in this area. The author knows of several additional ones, performed by himself and by others, but the negative results have discouraged the workers from publishing them."

"Underlying any discussion of the behavioral effects of radiation is the relative radioresistance of the adult nervous system. Total body doses in the median-lethal range do not seem to produce any gross neural dysfunctions. Except for the instances in which the body is shielded and the radiations are applied to the head only, death will intervene long before any neural changes can be observed. Thus, we will not find any significant behavioral changes in those activities which are mediated directly by the nervous system. We have reviewed several studies of learning by different investigators which seem to bear this out" (30).

These conclusions on radiation-behavior are consistent with evidence from radiation victims in Nagasaki and Hiroshima. Clinical data on observation of 49 victims at about 1,000 meters from ground zero (where the dose was greater than 1,000 rad) reported only one victim with visual disturbances late in the illness and one incident of delirium also late in the illness and assumed to be due to the high fever at the terminal stages of the illness (3).

However, a large and irrefutable body of recent research has shown that in a great number of species, radiation (at even relatively low doses) produces marked behavioral changes. The mechanism or mechanisms involved in the radiation induced alterations in behavior are still only speculative but the experimental evidence for the existence of the phenomenon is sound (32). It should be stressed that these changes are functional and may have no pathophysiological significance in the problem of radiobiological warfare.

Radiation Protection

The area of research concerning protection against the acute effects of radiation has proved to be of considerable academic and practical interest. Not only are these investigations directed toward elucidation of the fundamental phenomena involved in radiation damage, but they may also

offer promise of a method to ameliorate the threat from nuclear disasters. It is hoped that this research area will receive increased attention both by civilian and military research agencies.

A Brief History of Research in Radiation Protection

By 1860, five years after the discovery of X rays by Roentgen and natural radioactivity by Becquerel, 170 cases of radiation injury had been recorded. The use of medical X rays increased markedly during World War I without an attendant increase in knowledge about its hazards and by 1922, the death of about 100 radiologists had been attributed to over-exposure to ionizing radiation (88). Ironically, most of the early effects resulted from chronic rather than acute exposures, so it was difficult to correlate the conditions of exposure with biological effect. Public awareness of the general effects of radiation began to assume some degree of sophistication after the use of the A-bombs in 1945, but some of the most fundamental research in radiobiology had been reported before the first World War.

In 1929, Risse (94) suggested that the basic mechanism of radiation damage to the cell was through the action of highly reactive oxidizing radicals created from ionized intracellular water. Weiss described this notion in greater detail in 1944 (92). In 1949, Barron et al. (5) showed

that some of the sulfhydryl compounds administered to irradiated cell suspensions modified the usual response to lethal radiation by lessening cell mortality. In the same year, Patt (62) showed that the compound cysteine would decrease the mortality of irradiated rats. Soon after, glutathione was shown to exert a similar protective action (63). These observations plus other independent attempts to learn the fundamental mechanisms of radiation action led to the discovery that certain classes of chemicals and certain conditions of exposure modified the response to acute radiation, notably by extending survivability.

It was also discovered that some portions of the body were more radiosensitive than others, so when these radiosensitive tissues and organs were protected, as by shielding, the animal had a better chance for recovery. Thus, it was found that shielding the spleen or marrow-producing bones permitted animals to withstand otherwise lethal exposures to X rays (44). Similarly, reducing the atmospheric oxygen tension to 5 per cent during the period of exposure to 1200 roentgens extended the 30-day survival of rats from zero per cent (for controls) to 100 per cent for experimental animals (22).

In consequence of such observations, a great deal of research has been directed toward developing techniques which will first, lessen the

severity of exposure, and second, treat directly those cellular defects which result from radiation absorption. This research is complicated by the fact that the exact mechanisms of radiation's action upon the living cell are still to be described, and similarly, the mode of action of the protective chemicals is not completely understood.

By 1960, more than 1000 compounds had been tested for their ability to exert a protective influence against radiation (53). Of these, the sulfhydryl-containing and aminoalkylisothiurea chemicals appeared to be particularly effective. The most prominent of these compounds are cysteine, glutathione, cysteamine, AET (aminoethylisothiurea), MEA (mercaptoethylamine), and MEG (mercaptoethylguanidine). Also effective are such compounds as PAPP (p-aminopropiophenone) and serotonin which appear to operate at the physiologic rather than the chemical level (37).

Principles of Radiation Protection

There are three fundamental ways to achieve radio-protection. One way is to avoid or reduce exposure through the use of shielding. The second way is to counteract or vitiate the detrimental effects once having been exposed and the third is to repair the damage which has already been caused by radiation.

Most or all of the current defense efforts in shelter design utilize the first principle of radio-protection: the reduction of exposure. Through the use of dense building materials and earth, intense external radiation will be reduced to very low levels when it reaches the confined personnel. It is also possible that some degree of individual protection against the gamma portion of fallout might be obtained from portable, partial shielding. While it is not possible to shield against all the radiation (gamma), partial shielding might provide enough of a dose-reduction-factor to be of biological significance.

The second general method for achieving radiation protection is to prevent (or reduce) the damage that results once radiation penetrates living tissue. As was described in detail earlier in this review, the so-called indirect effects of radiation are caused by the action of free radicals on critical bio-molecules, particularly those in the cell nucleus (78). If exogenous chemicals could quench or compete for these free radicals, it might be possible to decrease the amount of biological damage. This has been achieved with limited success since most demonstrated protective can at best only reduce the dose effect to about one half and the best dose reduction factor is about 1.7.

The third general means for achieving radiation protection is to replace those critical cells and tissues already destroyed by radiation. There are certain organ systems within the body that are sensitive to ionizing radiation, particularly the hematopoietic or blood forming tissues. Since the unimpaired function of the blood and circulatory system is central to all of the life processes, it is imperative to quickly remedy any defects that occur. Damage to the hematopoietic system may destroy the body's ability to maintain adequate concentrations of vital blood constituents. Under special circumstances it is possible to replace damaged blood-forming cells and repopulate destroyed areas.

It can be seen that there is a pattern into which these radioprotective techniques fall. First, means are sought to reduce exposure by the use of shielding. Second, if complete shielding cannot be effected, and if it is known that some radiation will be absorbed, it may be possible to counter the radiation effects at the chemical level within the cell before the biological damage occurs. Finally, if radiation damage does occur, and if this damage is critical, it should be possible to replace the damaged tissues by transplantation of healthy tissues.

Experimental Work - Partial Body Shielding

Partial body shielding is a technique used in research and clinical work to reduce or limit the radiation damage. As an experimental technique, shielding various portions of the body has permitted test animals to absorb large doses of radiation. In therapeutic and diagnostic clinical work, partial shielding is used routinely for protection of both the practitioner and the patient. While the notion of portable body shielding for military and civilian defense personnel is very attractive, it is obvious that an individual could not carry enough high density shielding material to offer complete protection against gamma radiation. However, it is possible for an individual to wear a limited amount of shielding. Therefore, it is worthwhile to examine some of the research with partial body shielding to see if, 1) partial shielding is significant for extending survivability in nuclear warfare, and 2) if it is significant, how a limited amount of shielding might best be utilized.

The survivability pattern of partially shielded mice given acute exposures to radiation are similar to those percentages obtained from chemical protection against acute exposure. For example, Jacobson et al (42) showed that by exteriorizing the spleen and completely shielding it while the mouse received a whole body exposure, it was possible for three-quarters of the test animals to survive an exposure to 1025 roentgens

for at least 4 weeks. In fact, 27 percent of these mice survived a 1300 r exposure for the same period. The LD_{50/30} for mice is about 5 5-600 r. It was also observed that the spleen-protected mice displayed less drastic hematopoietic symptoms than the unshielded controls. In another experiment (82), the gastrointestinal tract was exteriorized and shielded during the period of irradiation. Following irradiation, the animals received a transfusion of isologous bone marrow. With this combined treatment, a third of the animals survived for 30 days after an acute exposure of 1400 r.

Bone marrow shielding during acute exposure has not been as effective a technique as might be hoped, especially against the higher exposures. The reason for this is that although the protected marrow serves in some way to accelerate the repair of unshielded hematopoietic tissue, intestinal death intercedes before the marrow restoration is complete. Therefore, survival at the higher exposures is correlated not only with marrow shielding, but also with gut shielding (82).

As opposed to experimental work protecting specific critical organs of the body, other research has shown that against lower acute exposures (650 r), shielding any portion of the body offers some protection, even shielding portions of skin or muscle (10, 81).

Partial body shielding has also been used as protection against chronic exposures. In the first of a series of experiments (19), non-shielded mice were exposed to 50 roentgens per day until death. A few deaths occurred by 15 days, 50 per cent were dead by 38 days, and all control mice died by 48 days. By contrast, the animals which had either the head or pelvis covered with a 0.5² cm thick lead shield enjoyed a significant increase in survivability. For example, 50 per cent of the pelvis-shielded mice were alive at 48 days (all control mice were dead by 48 days) and about 10 per cent were alive at 60 days. Of the head-shielded animals, 50 per cent were still alive at 60 days. The most interesting results were seen from the abdomen- and thorax-shielded mice. About 85 per cent of these animals were alive at 60 days, after having accumulated 3000 roentgens.

When the exposure was increased to 100 roentgens per day, the results were similar. At 100 roentgens per day, mortality for control animals was very abrupt. Deaths began to occur in two weeks, and all animals were dead by 21 days. By contrast, some of the pelvis- and head-shielded animals did not succumb until 40 and 55 days, respectively. However, 50 per cent of the abdomen- and thorax-shielded mice were still alive at 60 days, after having accumulated 6000 roentgens (35).

²A 0.5 cm lead shield at the X ray energy used in these experiments, 250 Kev, reduces the radiation to about 10 per cent of its original dosage (31).

In the second experiment, the conditions were similar except that the partial body shields had been increased in thickness from 0.5 cm to 0.64 cm. Again, the abdomen- and thorax-shielded mice lived longer than the head- or pelvis-shielded animals. At 50 roentgens per day, 50 per cent of the thorax-shielded mice lived at least 160 days, and 70 per cent of the abdomen-shielded mice lived at least 160 days. These 160 day-plus survivors had been exposed to a total of 8000 roentgens (77).

When the exposure was increased to 100 roentgens per day, a breakoff point for lethality became evident. By 120 days, only about 10 per cent of the thorax- and abdomen-shielded mice had survived. It should be noted, however, that these animals had been exposed to a total of slightly more than 12,000 roentgens before death (77).

Additional literature (11, 43) about partial body shielding reveals comparable results: some increase in survivability results from shielding almost any portion of the body. In fact, Hansen (33) reports that in a case of human exposure where only the upper thorax and head were exposed, the radiation syndrome and prognosis were considerably modified (for the better) as compared to those effects from a whole-body exposure. There is little question that partial body shielding would offer protection to exposed personnel, both for acute and chronic exposure. The basic

question to be answered is how much shielding could be worn practically, where it should be worn, and does partial shielding offer significant protection against chronic exposure.

Experimental Work - Anti-Radiation Chemicals

The experimental work using the protective chemicals to extend survivability of irradiated test animals has provided some significant results. Representative of the more prominent protective compounds is AET. Untreated mice acting as experimental controls could not survive more than two weeks after a single, whole body, acute exposure of 700 roentgens. When AET was administered just before radiation, more than 90 per cent of the AET-treated mice were able to survive at least 30 days after the 700 roentgen exposure. When the exposure was increased to 1000 roentgens, a third of the treated mice survived for at least 30 days. The dose-effect curve (where per cent mortality is plotted against the radiation dose) for AET is interesting for it shows that AET gives proportional protection throughout the range of exposure from 500 to 1000 roentgens (18). This would suggest that the compound AET offered protection to at least one critical organ system, probably the hematopoietic, to such an extent that other dependent organ systems were able to function until the insult at higher exposures became overwhelming.

One of the pressing problems associated with the administration of protective compounds is that most are toxic. Consequently, it is necessary to carefully control not only the dosage amounts, but the time of administration as well, because these compounds quickly enter into biological reactions. Therefore, for maximum effectiveness they must be used just prior to radiation exposure (37). However, combinations of the protective compounds have been used to improve effectiveness and reduce toxic effects. It was found, for example, that another of the protective compounds, glutathione, antidotes the toxicity of MEA without reducing MEA's protective action(36). Thus, a natural follow-on experiment was to administer combinations of protective chemicals, such as glutathione and MEA, hoping to compound the protective action. There was also a second reason for administering two or more chemicals in combination and that was to take advantage of their individual modes of protective action (on the assumption that they are different). A sulfhydryl compound such as MEA may form temporary mixed-disulfides which absorb much of the radiation normally slated for the sulfur groupings on the biological molecules. In essence then, the sulfhydryls may insulate the critical molecules against the radiation effects. Serotonin, cysteine, or

glutathione on the other hand, are believed to offer protection indirectly through physiologic action, namely the production of local tissue anoxia at sensitive tissues (57). Because the oxygen concentration is lowered under conditions of anoxia, less oxygen is available to react with water ions to form such radicals as H O^{\bullet} . The most dramatic of the experiments using chemical combinations was one where cysteine and MEA pretreatment allowed mice to survive an acute exposure of 1200 roentgens for at least 30 days (36). MEA plus serotonin extended the survival of a few mice exposed to 1400 roentgens to about 20 days (35).

Most of the work done with the anti-radiation chemicals, such as the reports cited above, has been done with acute exposures. It is also important to determine if these chemicals are effective against chronic exposure. In the next series of experiments, mice were exposed to fractionated X ray doses of 50 and 100 roentgens per day until death. Combinations of AET, MEA, serotonin, and PAPP did little to extend the survivability of these animals much beyond the control period of three weeks. The authors felt that there were two reasons why these compounds had little protective influence against high level chronic exposure. First, they believed that some of the compounds had a cumulative toxicity. Thus, any protective action would have been obscured by a toxicity reaction. Second, they believed that an organ system other than the hematopoietic, probably the liver, was involved in chronic exposure (20). While it

seems fairly certain the above-mentioned chemicals protect the hematopoietic system against acute effects, it has not been indicated that they operate similarly to protect the liver against chronic exposure. For these reasons, and others not yet clarified by research, certain combinations of the protective compounds have not yet been demonstrated effective against high chronic exposures.

Another of the problems in radiation-protection research is that of equating post-irradiation survival with specific actions of the chemicals on critical organs and tissues. In some instances, the administration of these protective chemicals has maintained the enzyme level of a critical tissue at normal amounts (as opposed to drastic changes induced by radiation), yet it has not been possible to correlate survival with enzyme protection (36). Probably these compounds operate at several physiologic sites throughout the body so that single indices of effectiveness are not meaningful in the evaluation of a particular compound. This also suggests that more than one protective compound will eventually be used in order that several modes of protection be exerted. The research to date on the anti-radiation chemicals is not hampered so much by a lack of favorable experimental results but rather by a lack of understanding of the fundamental modes of action by radiation and by the chemicals. Also, there is no readily available data on human application of the protective compounds.

However, as the research in this area progresses simultaneously with the uses of radiation therapy for malignancy, more data may become available.

Variables Associated with Chemical Protection

Significant among the many variables associated with the experimental conditions of radiation protection is the fact that all of these protective compounds are toxic to the body. In order to counter the effect of radiation, these compounds must operate at the chemical level in and around the cell. They must operate in intimate proximity with the molecular structure of very complex and precise biological molecules. It is inevitable therefore that, in the absence of radiation disturbances, these protective compounds enter into biological reactions and thereby compete for some vital process within the cell. In addition, most of these compounds are short-lived within the body, being neutralized, combined, and/or detoxified at a rapid rate. For these reasons, the timing of administration of these compounds is very critical. They must have time to reach the appropriate cells before radiation is absorbed and they must have time to exert a protective influence before being inactivated. Therefore, the protective chemicals appear to have been most effective when administered some minutes before irradiation (37, 53).

Within limits, the amount of protection is closely associated with the amount of the chemical present in the body. Therefore, it would seem that if a means could be found to permit extra-toxic doses to be administered without harm, protection would be extended proportionally. This has not been so, at least for one of the more spectacular compounds tested, MEA. Earlier it was mentioned that serotonin was given simultaneously with MEA in order to reduce the toxicity of the latter and also to compound the protective effects. It was found that increasing the MEA concentration beyond its normal maximum amount did not increase the degree of protection. In other words, there appears to a maximum amount of protection which these compounds afford, at least under the specified experimental conditions. There is also some possibility that these compounds have an accumulated toxic effect over long-term administration against chronic exposures to radiation (23). However, there have not been enough toxicity studies to make satisfactory generalizations.

As mentioned earlier, many of the compounds appear to be less effective against the effects of chronic exposure. In some instances the cumulative toxicity may have obscured any protective influence, but it is generally felt that different mechanisms of damage are operative

at the chronic level and that some of the compounds simply do not operate at this level of radiation effect.

Still another problem exists in extrapolating the positive findings of the animal research to human applications. There are enough similarities among mammals to warrant considering the inter-species application of experimental results. However, the ever-present fact of biological variability tends to make extrapolation of animal studies to human studies a frustrating process. The attempt to apply results even from lower primates to human beings (or vice versa) carries its own hazard. For this reason, it is hoped that as soon as enough basic information has been collected and understood, a greater number of the anti-radiation chemical studies can be conducted with simian species. It would then also be possible in higher mammal and primate experiments to study the interplay of supportive techniques used in conjunction with the protective chemicals. Most of the experimental studies made so far have permitted the animals to eat and drink ad libitum after exposure, and usually no antibiotics or transfusions were given to help the animal over crises. Some of the work with combined treatment has yielded very interesting results (11, 37).

There is a unique planning problem associated with the possible use of the protective compounds in their present form. If they are short-lived and both chronically and acutely toxic within the body, it would be

difficult to determine exactly when they should be administered to personnel anticipating exposure. It might be possible in the future to obviate this timing problem by using a vehicle for these chemicals such that their release into the cells would be prolonged over a period of several hours, or better still, the release would be proportional to the degree of radiation exposure. There are some physiologic cues that might be used to signal the release of the compounds (1, 49) such as the transient acidosis and subsequent alkalosis that follows radiation exposure. A carrier vehicle or substrate may be discovered which is inert until radiation products begin to appear in the tissues and cells. However, these latter notions are purely speculative and there is little or no indication in the literature that they are techniques promised for the near future.

Summary of Chemical Protection

Results from studies on the interaction of radiation and living matter together with what is known about chemical protection can be summarized briefly:

1. The physical and chemical effects that occur following the interaction of ionizing radiation with matter are completed in about a millionth of a second. Consequently, if any of

the radio-protective agents are to be effective during the physical or chemical stages of radiation interaction, they must be present at the time of exposure.

2. The end product of radiation interaction is the creation of ions. When these electrically unstable products restabilize themselves and/or form free radicals, there are nuclear transformations which produce atoms and molecules that are of a different chemical identity than the original atom or molecule. Some of the theories about the mechanisms of chemical protection hold that the protective compounds begin operating during this period before the biological stage. While it is not possible to reduce the number of ion pairs produced by radiation, it is desired to recombine these ions and radicals before they attain biological significance.
3. The biological stage is not well understood. In some instances, biological manifestations do not become obvious for years, whereas sensitive cells may die within hours after exposure. It is important to know, first, whether the biological reactions occur within microseconds, over a period of hours, days, or even years. It is also

important to know whether any of the biological reactions are reversible. It is now known that there is a correlation between a) the normal life span of a cell, b) the ratio of its cytoplasm to nucleoplasm, c) the cell's metabolic rate, and d) its histological character and the manner in which the cell will respond to radiation (38). For example, cells with a long life span and a slow metabolic rate, such as the transparent cells of the cornea, show their reaction to radiation after a period of years. By contrast, young lymphocytes with large nuclei are especially vulnerable and die within hours after exposure (27). The answer to the questions about the variability of cellular response will undoubtedly show that a great number of conditions ultimately determine the exact manner in which a particular cell will react to a specific quantity and type of radiation. As these conditions become better understood, research in chemical protection will be facilitated.

4. Some chemical compounds do appreciably extend the survivability of lower mammals. AET, MEA, serotonin, and PAPP all extend life under conditions of acute exposure. It is not clearly understood whether some of the compounds simply

act at a chemical level to counter the disruptive effect of the ions and radicals or whether other of the compounds actually promote a physiological process of repair. In all probability, both of these situations occur (37). There is another consideration: that certain of the protective chemicals are effective only in specific tissues. Therefore, attempts are being made to discover additional compounds that are operative in tissues as yet unprotected. And finally, there is an indication that the biological effects of chronic and acute radiation exposure are different. It may be that the compounds already tested are only effective against acute effects and that residual damage to the organism has not yet been corrected.

5. Several theories have been proposed to explain the mechanism of radioprotection by chemicals within the cell. These chemical compounds may operate singly or by any combination of the following mechanisms (1, 37, 53):
 - a. The chemicals serve as trapping agents for the free radicals created by radiolysis of water. In this manner a percentage of the free radicals would be quenched before they entered into chemical reactions

- with critical macromolecules.
- b. The chemicals may form temporary combinations at vulnerable sites on the biological molecules thereby preventing free radicals and ions from affecting these vital sites.
 - c. Compounds such as serotonin may cause vasoconstriction, thereby lowering tissue oxygen tension. By decreasing the available oxygen, the yield of HO_2^\bullet free radical, and H_2O_2 would be decreased.
 - d. Some of these compounds may accelerate the rate of repair so that the remaining normal cells rate of replacement balances the effect of those cells damaged by radiation.

Marrow Therapy for Radiation Damage

In the previous section of this report, research was reviewed describing a chemical method for reducing damage caused by the absorption of ionizing radiation. This section includes a review of an experimental method for replacing critical cells already damaged by radiation. Individuals exposed to 750 to 1000 rads will die as a result of damage to the hematopoietic system although exposures at the lower end of this

range may only cause temporary nausea plus transient fluctuations in the composition of the blood, exposures nearer 1000 rads will cause death due to hematopoietic failure and the subsequent failure of normal body defense mechanisms (42).

With present knowledge, there is little that can be done for victims of CNS or G I syndrome. The insult has been so heavy that many organ systems have been involved and the damage is compounded. However, the class of victims having only hematopoietic involvement may respond to both supportive and corrective treatment. Because this class contains victims who display the range of effects from no-obvious-symptoms to death, it is possible that protective techniques would be able to extend survivability closer to what now constitutes a lethal exposure. Among the most significant of these protective techniques is bone marrow transplantation, a technique which attempts to replace those vital cells destroyed by radiation.

Immunology in Tissue Transplants

Tissue transplantation, the method by which exogenous cells or tissues are administered to replace those destroyed through some traumatic event, is an area of biological research which has received active interest and participation for many decades. The central problem

in tissue transplantation arises when a host receives donor cells (54). The host's immunologic system regards these donor cells as being alien and then seeks to rid the host of these cells. Thus, the tissue is invariably rejected. Normally, the immune response developed and acquired by an individual serves to protect him against toxic and infectious agents. However, the immunologic response is apparently unable to distinguish between toxic and nontoxic, or between infectious and noninfectious, agents. In fact, under some experimental conditions of tissue transplantation, the body can develop a generalized immune response to its own tissues, i. e., auto immunization (72).

There are two principal phases of the immune response. The first is the typical rejection of donor tissue which usually occurs within two or three weeks after transplantation. This primary response can be suppressed by heavy exposure to penetrating radiation. Because portions (or all) of the immune response are associated with the white blood cells and hematopoietic tissues, when these latter cells and tissues are destroyed by poisons or radiation, the intensity of the primary response decreases. It is possible to make a successful transplant of tissues between individuals of the same species if the radiation exposure approaches the lethal range. However, if the individual survives the radiation exposure for a period of one to three months, he still encounters the secondary

immune response. Here, the donor tissue, in this case, bone marrow, would probably be producing cells of its own antigenic character (rather than producing cells of the host's character). The secondary response then develops very precipitously, to the ultimate embarrassment of the host (54). Some experimental work has been done with x-irradiation and marrow poisons in order to suppress both the primary and the secondary response. It seems, however, that in order to suppress the initial response completely, lethal doses of x-ray are required and even then the secondary response may appear in full strength. If the x-ray dosage is increased even further, hopefully to attack the secondary response, other tissues will become so involved, especially the gastro-intestinal tract, that the cure literally is worse than the affliction (85, 86).

As will be seen later in this section, therapeutic doses of x-rays have been delivered to leukemia patients in attempt to suppress the malignant hematopoietic tissues and to suppress the primary immune response t so that normal donor marrow may be accepted.

The Use of Autologous and Homologous Tissues

The following canine study gave a fairly representative picture of the difference between the use of autologous and homologous marrow transplants following irradiation. The median lethal dose for normal dogs is around 300 to 400 roentgens, the LD 100 is about 600 r (41).

Dogs receiving post-irradiation transfusions of several billion viable cells of their own marrow taken before irradiation were able to survive 700 r for a period of 2 to 15 months. Dogs receiving homologous transfusions fared no better than the untreated controls (45). In another experiment, dogs received a homologous transfusion of several billion marrow cells plus splenic transplants after exposure to 1000 r. The transplants were only able to confer marginal protection (two or three days extension of survivability) (45). In a study by Longerbeam, et al, (52), an autologous spleen suspension was used to demonstrate a protective influence. Dogs were splenectomized prior to being exposed to 500-700 roentgens. After exposure, a suspension of the spleen cells was administered intravenously. The treated animal showed marked improvement and were more alert, had no vomiting, and ate voluntarily. By the 14th day the bone marrow began to regenerate and by three weeks it was normal.

Another study was conducted on monkeys using homologous bone marrow treatment post-irradiation. In the control group, animals exposed to 650 r died within 7 to 13 days but two of the 8 animals in the experimental group survived well beyond the two week control period (522 and 1265 days respectively). A third group exposed to 800 r received antibiotics plus 2 billion homologous marrow cells. These animals lived only about 2 weeks after irradiation, but 6 of the 8 animals showed evidence of bone marrow regeneration. Whether or not the

regenerating marrow was the host's own tissue or the donor's was not stated. Also, the experimental animals showed less severe symptoms of radiation sickness and had less hemorrhagic tendency (16).

Marrow Transplants in Humans

In contrast with the experimental data for chemical protection against radiation, the literature on marrow transplants contains considerable data on human studies. All of the individuals in these reports were victims of malignant disease, mostly leukemia. Attempts were made to destroy the malignant bone marrow with x-irradiation or marrow poisons, then to add normal marrow with the hope that the leukemia would be sufficiently suppressed such that the transplanted normal cells would repopulate the marrow bones and begin production of formed elements in proper proportion. Typically, when leukemia victims were considered for irradiation and marrow transplants, they had failed to respond to less radical treatment. Two typical case histories are as follows. A 30-year old male leukemia victim had shown no response to marrow toxins. He was then exposed to 1,768 roentgens. After irradiation he was weak and experienced occasional vomiting but could eat and was ambulatory. A liver, splenic tissue, and marrow suspension was administered to this man in a total dose of 28.5 billion cells over a 12-day period after irradiation. In addition, the patient received whole blood transfusions.

Despite these measures, he died 13 days after irradiation, succumbing to a massive blood stream infection of Escherichia coli. Another leukemia victim was exposed to 2,016 roentgens. He received a total of 9.6 billion marrow cells from a twin brother. This individual retained a fever during the post-irradiation period, plus localized infections. On the 20th post-irradiation day, this patient died of generalized infection. However, at autopsy there was no evidence of leukemia and there was some regeneration of the bone marrow (83, 84, 85, 86).

One recent article contained a review of 56 patients receiving bone marrow and radiation therapy for acute leukemia. The age of the patients was 5 months to 61 years. The exposure dosages ranged from 210 r to 2014 r. The period of survival was 4 hours to 10 months; (some of the patients received homologous bone marrow suspension of several billion cells, some received in addition whole blood, and probably all received antibiotics). In 4 cases there was evidence of the secondary immune response. The conclusions drawn by the authors of the above article were that if the leukemic patient is lethally irradiated, the administration of homologous transplants may delay death. However, if the victim persists for several months, the secondary response invariably appears with fatal consequence. Also, the leukemia patient,

already predisposed to infection, is acutely susceptible after irradiation. In a few remote instances, there have been long periods of post-irradiation survival (several months) but either the original disease returned, the patient died from associated failures, or the case history could not be completed. More encouraging is the fact that many of the histological examinations of hematopoietic and lung tissue showed no evidence of a primary immunologic response to the donor tissue. Also, the transfused marrow cells migrated to the normal histological site and, in instances where the patients lived for several weeks or more, there was a definite restoration of marrow and lymphatic function even though the individual would eventually succumb to the secondary immune response. The larger transfusions seem to restore function more quickly and also seem to lessen the severity of radiation sickness (86).

Part of the beneficial effect of post-irradiation marrow treatment may be due to the assist the intestinal tissues receive from the transplanted cells. Following higher radiation exposures, the defenses of the intestinal mucosa are lessened (due to radiation damage) and this deficiency not only paves the way for invasion of pathogens from the intestinal lumen into the blood stream, but also the body's over-all balance of functions is easily disrupted by unfavorable alterations in the alimentary canal (79). Thus,

any supportive or corrective treatment promoting and restoring the integrity of the gut tissues will greatly benefit the individual.

Summary of Marrow Therapy

1. Sub-lethal exposures to ionizing radiation make their first effects readily apparent in the hematopoietic system. As the acute exposure increases in intensity, the problem becomes increasingly critical. Not only do formed elements in the blood stream suffer lethal effects, but the vital formative tissues also sustain serious damage. As marked deficiencies in the vascular system develop, the mechanism of clotting and resistance fails to pathogenic organisms. However, it has been demonstrated that devitalized hematopoietic tissue can be replaced and that the rate of regeneration can be accelerated by the transplantation of exogenous blood-forming cells.
2. A major limitation to this transplantation technique is the fact that a host is only prepared to permanently accept his own cells even though another donor's cells might have temporary acceptance. Consequently, if cell transplantation were to be effected in anticipation of major disaster, those critical cells would have to be extracted, preserved, stored,

and reserved for each individual (61).

3. The human studies with marrow transplants for irradiated leukemic patients have met with limited success, but also with limited failure. That is, despite the fact that most of these patients were unable to resist infections or suffered a relapse of the original disease, both to a fatal consequence, some of the transplantations showed some evidence of take.
4. Marrow transfusion has been used as a therapeutic technique in conjunction with the protective techniques summarized earlier in the paper to give dramatic increases in the survivability of heavily irradiated animals (11).

A very interesting prospect for future research is combined treatment. It has been shown that the combination of AET, bone marrow, and antibiotic therapy has permitted some mice to survive 2600 roentgens for at least two months after exposure (11). This is twice the amount of protection that was available from any single mode of protection and is a good indication of how the acute trauma from radiation can be ameliorated. When radiation protection research achieves the next higher level of understanding, undoubtedly combined forms of protection will be manipulated to meet the specific conditions of exposure.

At the present state of knowledge, there is a limitation to each of the protective procedures such that they must be initiated before the individual (or experimental animal) is exposed to ionizing radiation. In the case of the chemicals, many of the more effective compounds must be present within the cell at the time radiation is absorbed because of the brevity of the physical and chemical stage of radiation interaction. Therefore, in order to counter radiation at the chemical level, it is necessary to administer the compounds before exposure. There is a similar problem with respect to tissue transplantation. The recipient is prepared immunologically to accept only his own tissues. Therefore, if a radiation victim were to require healthy marrow cells, these cells would have to be his own and would have to be harvested before exposure. More promising than the use of autologous tissue is the possible use of homologous tissue for transplantations. This would permit any healthy individual (or fresh cadaver) to be a potential donor. This, however, will require further research in immunology (53).

The partial body shielding technique is, as previously mentioned, a promising area of research. The shielding properties are well known for all of the good energy absorbers, but what is lacking is pertinent biological information. How can limited amounts of shielding best be used? For acute exposures, probably critical hematopoietic tissues would

be selected for protection, whereas for chronic exposure, it might be most effective to protect the entire lower torso. This remains to be clarified.

In conclusion, radiation protection is a very pertinent area of radiation research with respect to survivability planning. Despite the difficulty in studying some of these biological phenomena at their most basic level, great advances have been made in the last decade.

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