emia.[1-4] In all the families that we have observed only males have been afflicted,[7] and, in at least 1 family (Fig. 1, Family T), there is very suggestive evidence that this disease may also be transmitted as a sex-linked recessive trait in certain families. We have followed from birth 4 female infants born after the propositi in the families (Fig. 1), and they are all normal at their present ages of six months to two years. Two siblings, a male and a female, have been reported to us from Chicago to have died of the Swiss type of agammaglobulinemia,[15] and another communication concerning a Navajo Indian female infant who died of the Swiss type of agammaglobulinemia has been received.[16]

Summary

Thymic transplants did not restore immunologic competence in a Negro boy with the Swiss type of agammaglobulinemia. However, subsequent transplantation of maternal bone-marrow cells resulted in a rise of the peripheral blood lymphocytes to normal levels and transfer of delayed hypersensitivity. The infant ultimately died of overwhelming pulmonary infection.

We are indebted to Dr. David Carver, of the Albert Einstein College of Medicine, who brought this patient to our attention, to Dr. Park S. Gerald and Miss Susan Warner, of the Clinical Genetics Unit, for karyotyping the patient, to the Blood Grouping Laboratory for the red-cell typing, to Miss Ursula Ruefli, of the Hematology Research Laboratory, for technical assistance, to Dr. Luther Longino, of the Department of Surgery, for performing the transplants, and to Dr. Hugh M. Pyle, of the Protein Foundation Laboratories and the New England Deaconess Hospital, for carrying out the aspiration of bone marrow.

References

1. Hitzig, W. H., Biro, Z., Bosch, H., and Huser, H. J. Agammaglobulinämie und Alymphocytose mit Schwund des lymphatischen Gewebes. *Helvet. paediat. acta* **13**:551-585, 1958.
2. Hitzig, W. H., and Willi, H. Hereditäre lymphoplasmocytäre Dysgenesie. *Schweiz. med. Wchschr.* **91**:1625-1633, 1961.
3. Tobler, R., and Cottier, H. Familiäre Lymphopenie mit Agammaglobulinämie und schwerer Moniliasis: die "essentielle Lymphocytophthise" als besondere Form der frühkindlichen Agammaglobulinämie. *Helvet. paediat. acta* **13**:313-338, 1958.
4. Freycon, F., Jeune, M., Larbre, F., and Germain, D. La lymphocytophthisie essentielle: aplasie lymphoplasmocytaire du nourrisson avec alymphocytose et hypogammaglobulinémie. *Rev. franç. clin. et biol.* **6**:817-824, 1961.
5. Allibone, E. C., Goldie, W., and Marmion, B. P. Pneumocystis carinii pneumonia and progressive vaccinia in siblings. *Arch. Dis. Childhood* **39**:26-34, 1964.
6. Rosen, F. S., Gitlin, D., and Janeway, C. A. Alymphocytosis agammaglobulinaemia, homografts and delayed hypersensitivity: study of case. *Lancet* **2**:380, 1962.
7. Gitlin, D., and Craig, J. M. Thymus and other lymphoid tissues in congenital agammaglobulinemia. *Pediatrics* **32**:517-530, 1963.
8. Good, R. A., Martinez, C., and Gabrielsen, A. E. Clinical considerations of thymus in immunobiology. In Conference on the thymus, Minneapolis, 1962. *The Thymus in Immunobiology: Structure, function and role in disease: By 72 Authors.* Edited by R. A. Good and A. E. Gabrielsen. 778 pp. New York: Harper, 1964. Pp. 3-47.
9. Hitzig, W. H. Immunobiologische Reaktionen des cellularen und des humoralen Systems. *Schweiz. med. Wchschr.* **93**:1433-1444, 1963.
10. Hitzig, W. H., Kay, H. E. M., and Cottier, H. Familial lymphopenia with agammaglobulinaemia ("Swiss type of agammaglobulinemia"): attempt of treatment by implantation of foetal thymus. *Lancet* **2**:151-154, 1965.
11. Lepow, I. H. Personal communication.
12. Yunis, E. J., Hilgard, H. R., Martinez, C., and Good, R. A. Studies on immunologic reconstitution. *J. Exper. Med.* **121**:607-632, 1965.
13. Wilson, R. E. Technics of human bone marrow procurement by aspiration from living donors. *New Eng. J. Med.* **261**:781-787, 1965.
14. Hildemann, W. H., Linscott, W. D., and Morlino, M. J. Immunological competence of small lymphocytes in the graft-versus-host reaction in mice. In *Ciba Foundation Symposium on Transplantation.* Edited by G. E. W. Wolstenholme and M. P. Cameron. 426 pp. Boston: Little, Brown, 1963. Pp. 236-263.
15. Greaves, A. A. Personal communication.
16. Liftschitz, M. Personal communication.

SPECIAL ARTICLE

CHEMICAL AND BIOLOGIC WEAPONS — A PRIMER*

Victor W. Sidel, M.D.,† and Robert M. Goldwyn, M.D.‡

BOSTON

THE increasing development and stockpiling of chemical and biologic weapons have been well documented, and facts are available to all citizens.[1-3] Because these agents injure, incapacitate and kill, and because their manufacture and possible use present grave ethical considerations, physicians in particular not only must be familiar with their existence and their properties but also must stand firm in questioning the moral and even practical justification of their use.

*From the Physicians for Social Responsibility.

†Associate in preventive medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital; fellow, Medical Foundation (Boston); faculty fellow, Milbank Memorial Fund.

‡Instructor in surgery, Harvard Medical School; junior associate in surgery, Peter Bent Brigham Hospital; associate in surgery, Beth Israel Hospital.

History

The origins of modern chemical and biologic warfare can be found in antiquity.[4] Poisoned arrows, still used among some aborigines, were commonly employed in ancient Asia and Western Europe. Hannibal threw bottles of venomous snakes onto the vessels of Eumenes II of Pergamus to cause panic. Around 400 B.C., during the siege of Athenian cities, the Spartans burned sulfur and pitch to form the irritating gas sulfur dioxide. The Greeks, the Carthaginians and the armies of the Middle Ages frequently poisoned wine, food and water supplies. Occasionally, the gross tactic of throwing dead human and animal bodies into water wells was employed.

The debut of modern chemical warfare occurred during World War I.[5] The French, in 1914, hurled grenades filled with tear gas, and the Germans retaliated with tear-gas artillery shells.[6] The first major attack with lethal gas was launched at Ypres in 1915 by the Germans, who released chlorine gas from cylinders. On subsequent occasions the belligerents employed phosgene, chlorine and mustard gas. Biologic agents, however, played an insignificant part in the military strategy of World War I.

The next reported use of chemical agents was by Mussolini in Ethiopia in 1936. A year later the Chinese claimed that the Japanese had attacked them with gas. In World War II explosives, smoke, flame and incendiaries were used but not toxic chemicals, and "chemical warfare," as the term is commonly used, was avoided. Recently, in South Vietnam the United States has supplied defoliating and crop-destroying substances[7,8] and irritating but nonlethal gases (tear and nausea gases of the type sometimes employed by police)[9-11] for use by the South Vietnamese against the Viet Cong; these have been labeled by the world's press as forms of chemical warfare.[12]

Chemical Agents

The term "chemical warfare" will be restricted, as it is in current usage, to the employment of chemicals toxic to men, animals or plants. This definition excludes such weapons as explosives, smoke, flame and incendiaries, which are also chemicals, but to include these in "chemical warfare" dilutes the term so much that the problems and issues are blurred.

Chemicals toxic to plants, such as defoliants and crop-destroying agents, which are forms of chemical warfare, will also be omitted from this review since they are of only indirect concern to physicians. The agents recently used for defoliation and destruction of food supplies[7,8] in South Vietnam were examples of these weapons. The remaining chemical weapons, all toxic or noxious to man, fall into 6 arbitrary categories.[1,4,13] The first three groups to be discussed are incapacitating but usually nonlethal, although they can kill under certain circumstances: extremely high concentration of agent or highly susceptible victim, such as the very young, the very old or the very sick. The remaining 3 categories of chemical agents are lethal.

Irritating Agents

These gases usually apply to riot control but have been employed in combat. Effects include conjunctival irritation, lacrimation, cough, dyspnea, nausea and vomiting. Examples of these weapons are as follows[10,11]: DM (diphenylaminochloroarsine), a pepper-like agent that incapacitates for periods of half an hour to two hours; CN (chloroacetophenone), a form of "tear gas" that may also irritate the skin and incapacitates for about three minutes; and CS (O-chlororbenzalmalononitrile), a more recently developed lacrimatory and nausea-inducing agent that incapacitates for five to ten minutes. Specific first aid against these agents requires the victim to avoid rubbing his eyes and to face into a wind free of the agent.

Weapons of this type, according to Secretary of Defense Robert S. McNamara,[10] have been used "only two or three times" in Vietnam, "most recently on January 27 [1965] after Communist guerrillas took refuge in a village in Phuyen Province."*

Vesicant Agents

Agents of the blistering type used in World War I included sulfur mustard ("mustard gas" or H), which caused about 25 per cent of the casualties in the American Expeditionary Force, and lewisite (L), an arsenical. A new distilled mustard (HD) and 2 kinds of nitrogen mustards (HN-1 and HN-3) are available for military use.[14] Low concentrations of sulfur mustard will irritate conjunctivas severely and the skin mildly. Moderate concentrations will burn the eyes and will produce skin blisters, which can be deep and may require weeks or months of healing. High concentrations will have systemic effects such as nausea and vomiting, cardiac arrhythmia and shock. The victim who survives the initial effects may later show aplasia of the bone marrow, dissolution of lymphoid tissue and ulceration of the gastrointestinal tract.[15] The nitrogen mustards, used for their cytotoxic effects in patients, are nitrogen analogues of sulfur mustard.

The vesicant agents in their gaseous phase are more insidious than the irritants, because their effects may not be noted for several hours; the victims will unknowingly remain in the atmosphere until severe damage is done. Furthermore, *liquid* mustard — the "gas" is a liquid at room temperature — penetrates leather, clothing, plastics and other materials. Since the liquid material may evaporate very slowly it can cause casualties several weeks later. First-aid measures include blotting the liquid mustard off exposed skin and using a protective ointment within five minutes after detection of its characteristic garlic odor.

In World War II the British discovered that the toxicity of the arsenical vesicants such as lewisite depends upon their ability to react with thiol groups

*The *New York Times* (October 11, 1965, p. 59) reports the following developments since this paper was submitted: "On Sept. 25 Gen. William C. Westmoreland, United States Commander in Vietnam, announced that there would be no disciplinary action against a marine officer who chose to use tear gas rather than lethal flame throwers or grenades to remove women and children from a series of Vietcong tunnels. On Oct. 8 United States paratroopers used tear gas in combat under specific authorization from General Westmoreland and officials said the tactic would be repeated in 'selected circumstances.'"

in proteins.[16] Attention was then focused on thiols, which block the action of the toxic arsenical, and the dithiol 2,3-dimercaptopropanol was found to be the most effective. American investigators, learning of the British development, termed it British antilewisite (BAL). This drug, whose generic name is dimercaprol, has also been used in man as an antagonist against the effects of certain heavy metals.

Psychochemicals

These agents, also known as hallucinogens, lead to mental derangements that are usually reversible.[17] The substance most frequently discussed is d-lysergic acid diethylamide (LSD-25).[18] This compound is odorless, tasteless and colorless, and effective in extremely small amounts. LSD may produce a wide spectrum of psychopathologic reactions and psychoses, including an inability to concentrate, severe anxiety and manic states and complete catatonic withdrawal. An additional hazard of these agents, in contrast to the biologic agents and other chemicals, is that the victim may be unaware of his altered behavior. An investigating congressional committee viewed a film that "demonstrated that troops exposed to one of these agents were not even conscious of their abnormal condition which was so changed that they were unable to follow simple commands and perform normal tasks with acceptable accuracy. Only an outsider not exposed and coming upon them would recognize their behavior as eccentric."[19]

Agents Producing Pulmonary Edema

This group includes the World War I gases chlorine and phosgene (CG). Of these only phosgene is still considered a weapon for possible use in warfare, and it too has been rendered relatively obsolete by the newer lethal nerve gases. The military disadvantages of phosgene are its low toxicity, the high concentrations required, its telltale odor of newmown hay and the delay in its pathologic effects (several hours to twenty-four hours).

Agents Affecting Oxidizing Enzymes

These agents, an example of which is hydrocyanic acid ("prussic acid" or AC), are very rapidly acting poisons and have been used as fumigation agents and for executions in "gas chambers." Cyanide reversibly inhibits cellular oxidizing enzymes containing iron in the ferric state. So far as is known, these gases are not being seriously considered for use in warfare. First aid, to be effective, must be given immediately upon the discovery of the characteristic bitter-almond odor. Treatment of cyanide poisoning involves the immediate intravenous injection of 2 agents, sodium nitrite and sodium thiosulfate.[20] The use of these procedures in any large group of people under emergency conditions would be difficult, if not impossible.

Nerve Gases

Of the chemical weapons these are the newest, the most effective and the most likely to be used. They are colorless and odorless organic phosphates that enter the body as gases via the lungs or as liquids through the skin and act by blocking cholinesterase; the presence of anticholinesterase prevents the breakdown of acetylcholine at nerve endings. Low concentrations of these agents lead to coryza, miosis and dyspnea; higher concentrations produce nausea, vomiting, muscular fibrillation, convulsions, respiratory paralysis and death.

These weapons were developed and stockpiled by the Germans in World War II but were never used. The German names for the volatile agents of this type were Tabun, Sarin and Soman, and the corresponding American codes for these "G agents" are GA, GB and GD.[21] Other, less volatile, substances of the same type are the V agents, particularly a liquid called VX. GB has been produced and stockpiled in the Rocky Mountain Arsenal in Denver, and it, or another of the nerve gases, was produced as recently as April, 1964, at a plant in Newport, Indiana.[3] The size of the stockpiles is unknown, but the magnitude of the stockpiling operation may be surmised from the *Washington Post* disclosure that the Indiana facility, with 300 civilian employees, has been operating for twenty-four hours a day for over three years. The final products of the assembly line in this plant are chemically filled rockets, land mines and artillery shells. The officer in charge of the plant states that "from Newport, the rockets and artillery shells are shipped in normal Army channels." Army Field Manual *FM3-10* gives detailed instructions to field commanders for tactical use of these weapons.[22]

These newer gases possess almost all the qualities that make an excellent chemical-warfare agent. Being odorless and colorless, they give no warning; they act rapidly and effectively in low concentrations, being about thirty times as toxic as phosgene, and fourteen times as toxic as sulfur mustards.[23] A few inhalations can cause a blood concentration sufficient to kill in one or two minutes, and, at the concentrations attainable under field conditions, even a single inhalation can kill. Immediate masking and protective clothing remain the only effective defense. Administration of atropine is supportive, but the effects of the atropine must be titrated against the effects of the nerve gas. Respiratory assistance may be required.

Biologic Weapons

Biologic warfare is the intentional employment of living organisms or their toxic products to cause death, disability or disease in man, animals, plants or food supplies.[24] Theoretically, a multitude of bac-

teria, viruses, rickettsiae, fungi or toxins could be used. Some of those most likely to be employed against personnel are given in Table 1.[25]

Characteristics essential to an effective antipersonnel biologic agent are as follows[26]:

The agent must be lethal or incapacitating, and should be capable of being produced economically in adequate quantities from available materials. This requirement is easily satisfied by a great number of biologic materials.

The agent must maintain its virulence or infectivity during production, storage and transportation. This attribute is important in war and separates the dependable from the nondependable killers. Anthrax, for example, lives for years in spore stage, whereas the spirochete causing syphilis quickly dies upon exposure to air. Bacteria with capsules have a greater potential for survival. To simulate capsule protection, microbiologists have used imbedding proteins such as milk, blood and serum in addition to lyophilization. By these measures, a dry-powered material is obtained that will remain stable for years in airtight vials.

The agent must be easily and effectively disseminated. The 2 principal methods of dispersal are covert contamination of air, food or water and overt attack with a cloud of pathogens or toxins. Biologic weapons are extremely suitable for covert use, such as sabotage. They work by delayed action; they are difficult to detect, and only a small quantity is needed. It has been pointed out that 1 person could easily incapacitate part of a metropolitan population by introducing pathogens into the water or ventilating systems. Drug and food industries are also readily accessible to effective sabotage. The chief limitation to the covert use of biologic agents is the fact that only a limited number of people are affected. To harm more, multiple simultaneous attacks would be necessary, and detection would be more likely.

Overt attack can be accomplished through the delivery of aerosols in the form of sprays, shells, missiles, bombs or detonated mines floating off shore. Particle size is critical. Particles that are too large will fall to the earth before affecting the target area. Those larger than 5 microns will be removed from the air in the upper respiratory tract and may be less effective than particles 1 to 5 microns in size, which will reach the alveolar bed. For example, to infect a guinea pig with *Brucella suis* requires six hundred times as many 12-micron as 1-micron particles.[27] Particles smaller than 1 micron tend to be exhaled without injury to the host.

Very small numbers of organisms are required to infect the human victim. Q fever can be produced by inhalation of a single organism.[28] Other diseases that can be transmitted by aerosols are influenza, tuberculosis, anthrax, glanders, psittacosis, undulant fever, tularemia and plague.

Against the agent there must be no widespread natural or acquired immunity. For example, against the population in the United States, the anthrax bacillus would be a more effective agent than the diphtheria bacillus.

Some form of protection must be available to the user. Unless the attacker has developed immunization or therapeutic agents he will most probably seek his protection in masks, in special clothing and in distance from the area of dispersal.

In addition to the essential characteristics listed, desirable attributes of a biologic agent include difficulty in its detection, predictable persistence in a stricken population and ability to enter the body through more than one portal.

TABLE 1. *Possible Agents for Antipersonnel Bacteriologic Warfare.*[24]

BACTERIAL	
Anthrax, cutaneous	Plague, bubonic
pulmonary	pneumonic
Bacillary dysentery	Salmonella food poisoning
Brucellosis	Tuberculosis
Cholera	Tularemia
Diphtheria	Typhoid fever
Glanders	Paratyphoid fever
Melioidosis	
RICKETTSIAL	
Q fever	Typhus, epidemic
Rocky Mountain spotted fever	murine
	Scrub typhus
VIRAL	
Dengue fever	Russian Far East encephalitis
St. Louis encephalitis	Infectious hepatitis
Eastern equine encephalomyelitis	Influenza
Western equine encephalomyelitis	Psittacosis
Venezuelan equine encephalomyelitis	Smallpox
Japanese B-type encephalitis	Yellow fever
FUNGAL	
Coccidioidomycosis	Nocardiosis
Histoplasmosis	
TOXINS	
Botulism	Staphylococcus enterotoxin

EARLY DETECTION OF AND PROTECTION AGAINST BIOLOGIC WEAPONS

Because biologic agents are invisible, odorless and tasteless and usually produce no immediate physiologic damage, their early recognition would most probably be impossible. Another reason for the delay in recognition of the aggressive use of a biologic agent lies in the fact that physical detection from samples of air, food and water would take days and even longer, especially if the organism were foreign to the affected population. The early detection of a biologic attack on a population would be likely only if the enemy were seen spraying clouds or using mists or by identification of a new vector.

Protection against biologic agents is extremely difficult, but a few means are discussed below.[29,30]

Physical Protection

Protection of human beings against airborne agents is chiefly by air filtration since the organisms are carried in particles, either liquid or solid. This filtration would generally be accomplished by masks, but could be done by means of filters in ventilating systems. This latter method would be impractical and expensive and would help only a small segment of the population. Protective boards for rooms and shelters have been devised. These incorporate activated charcoal, which absorbs chemical and biologic agents but allows carbon dioxide and moisture within the enclosed space to escape.

Decontamination

This mode of protection will not be easy to achieve. For example, the *Emergency Manual Guide on Biological Warfare* (1959) states: "Decontamination of extensive areas is not considered practical. Rather, natural decay, assisted by sunlight, temperature and air movement must be relied on."[31]

Sanitary Measures

In a population sick or dying the usual sanitary measures not only must continue but must be made better: control of sewage and waste, proper disposal of corpses, control of insects and rodents and the provision of safe water, food and drug supplies.

Immunization

A population would be better protected if it has been immunized actively or passively before biologic attack. After the attack only passive immunization would be useful since an enemy would select an agent against which active immunity would be delayed or unlikely. Thus far it has been impossible to have available a multitude of vaccines capable of being dispersed and administered to a large population. Also, there are as yet no effective vaccines against certain diseases.

Medical Treatment

The disease inflicted upon a population by an attacker would require the treatment commonly employed in a nonwarfare situation. Under wartime conditions these standard measures would be extremely difficult to carry out for a large number of victims.

Discussion

Certain general features of chemical and biologic weapons should be considered.

In the first place, these weapons are likely to be used against noncombatant populations. As Major General Thomas J. Hartford[32] has stated in an editorial in *Military Medicine*:

> It appears from the information available in this symposium and elsewhere that this weapons system [biologic warfare] would be used primarily for strategic rather than tactical purposes. It would be an excellent means of producing noneffectiveness without causing damage to material things. Thus it is possible that the civilian and not the military population might be the prime target. If an enemy were attacking the New York-New Jersey coastal area he would be more interested in producing disability in the millions of industrial workers than in the few thousand military personnel stationed in the target area. . . .

Secondly, the effects of chemical and biologic warfare cannot be completely predicted. Beyond the immediate consequences there may be ecologic, medical and social results impossible to foresee. A biologic agent introduced into a susceptible population may cause epidemic disease or mortality on a scale not visualized by the attacker. An example is the measles virus, which, although usually relatively benign, can cause an extremely high fatality rate under certain conditions — for example, in an unprotected population such as the Fiji Islanders, of whom 20 to 25 per cent died from measles or its consequences in 1875, or in a population weakened by war such as the women and children in Boer concentration camps in 1900.[33] In contrast to other weapons, biologic agents may make the human being not only a victim but also a propagator of the disease.

Finally, since the production and the delivery of these weapons are relatively inexpensive, they can easily be manufactured by countries with limited industrial potential. The stockpiling of these weapons by one nation encourages their production and stockpiling in centers throughout the world; control thus becomes increasingly difficult.

These general features and the information already presented on the current status of chemical and biologic weapons indicate that physicians can do very little about the effects of such agents once they are used. As in other areas of medicine, the major emphasis must be prevention.

Although the French and Germans as long ago as 1675 agreed to ban the use of poisoned bullets no general agreement to outlaw germ or gas warfare exists today.[34] Some countries, including the United States, never ratified the Hague Convention of 1899 or the Geneva Protocol of 1925, both of which prohibited such warfare. The United States did sign and ratify a treaty on the Limitation of Naval Armaments in 1921 that banned the use of poison gas. The treaty never became legal because France objected to the phrasing of the restriction pertaining to submarines.

During World War II, President Franklin D. Roosevelt[35] made the following statement:

> Use of such weapons [biologic and chemical] has been outlawed by the general opinion of civilized mankind. This country has not used them, and I hope that we never will be compelled to use them. I state categorically that we shall under no circumstances resort to the use of such weapons unless they are first used by our enemies.

Recently, however, military spokesmen have increasingly stressed the "humane aspects" of certain of these weapons and the tactical advantages of their employment. For example, when Congressman Robert W. Kastenmeier (Democrat, of Wisconsin) introduced a resolution into the House of Representatives in September, 1959 ("Resolved . . ., That the Congress hereby reaffirms the longstanding policy of the United States that in the event of war the United States shall under no circumstances resort to the use of biological weapons or the use of poisonous or obnoxious gases unless they are first used by our enemies"[36]) this resolution was opposed by the Department of Defense, with the statement: "As research continues there is increasing evidence that some forms of these weapons, differing from previous forms, could effectively be used for defensive purposes with minimum collateral consequences."[11] The resolution was defeated.

The current position of the Department of Defense and, therefore, a published position of the United States of America on this matter is stated in Army Field Manual *FM27-10* "The Law of Land Warfare": "The United States is not a party to any treaty, now in force, that prohibits or restricts the use in warfare of toxic or nontoxic gases, of smoke or incendiary materials, or of bacteriological warfare."[37]

Many other nations, similarly, have made no commitment that restricts the manufacture or use of these weapons.[38] Japan, Brazil and Argentina, for example, have never ratified the Geneva Protocol of 1925; Italy, which had ratified the Protocol, used gas against Ethiopia in 1936. The only nations that have made agreements restricting their manufacture of such weapons since World War II are Italy and West Germany, as a condition of membership in the Western European Union, and Austria, as a part of the state treaty that re-established her as a sovereign power.

In addition, other nations are believed to be capable of using these weapons — for example, the United States Army "credits the Soviets with the ability to wage chemical and biological warfare on a large scale, with an especially large capability in chemical warfare."[39] Unfortunately, evaluation by neutral observers of the capability of individual nations in this area of warfare does not exist.

International tensions have thus far made prohibition or adequate control of these weapons impossible. Scientists from 8 nations, including the United States and the Soviet Union, meeting at the Fifth Pugwash Conference in 1959, discussed the severe difficulties inherent in the control of these weapons and made the following recommendations[40]: each nation should renounce official secrecy controls over microbiologic, toxologic, pharmaceutical and chemical-biologic research; and a general international agreement should be negotiated to prohibit the use of such weapons.

Some physicians may accept warfare as a permanent feature of man's activities and may regard chemical and biologic warfare as the most "humane" type yet evolved,[41-43] particularly when contrasted with napalm, saturation bombing or nuclear warfare. There are 2 principal objections to the "humane" argument:

> This position assumes that once Pandora's box of chemical and biologic weapons is opened, only the most benign will come forth. Most of the agents now available either are benign and relatively ineffective or are lethal, permanently crippling and therefore quite effective. From the types of weapons that have been stockpiled for which instructions for offensive tactical use have been issued, it appears more likely that military commanders will select the most effective and therefore the most lethal.
>
> Even if a "humane weapon" is developed its "humanity" will require the delivery, as in the laboratory, of a precisely measured dose to a standard victim. Both these requisites have thus far been impossible to attain in the field. Chemical and biologic weapons are notoriously uneven in their dispersal and therefore in the amount absorbed by each recipient; to ensure that every person receives an incapacitating dose, some will have to receive an overdose. Furthermore, the young, the elderly and the infirm will be the particularly susceptible victims.

There has been remarkably little public debate, particularly among physicians, on the advisability of developing, stockpiling and using chemical and biologic weapons. Some of these issues, admittedly, are complex, controversial and uncomfortable. The physician, however, has a specialized knowledge about chemical and biologic agents. No nation could develop or protect against this kind of warfare without aid from its doctors. In addition to his particular competence, the physician must be concerned with chemical and biologic weaponry because of his fixed commitment to the health of individuals, singly and collectively. He must therefore be actively concerned with the medical consequences of chemical and biologic warfare.

Since the physician may be asked to develop these weapons he must carefully evaluate his own attitudes toward his rights and duties as a citizen and as a doctor. Although there should be no conflict in these roles, conflicts may arise, as the Nazi medical experience testifies, as stated in an editorial in the *Journal of the American Medical Association*[44]:

> Perhaps most serious of all is the failure of German medical organizations and societies to express in any manner their disapproval of these widely known experiments.

> Physicians have a right to expect that men trained in the traditions of medicine would refuse to participate in any way in such acts of inhumanity and brutality. In some instances the defense has been offered that these experiments were conducted under the highest authority of the German state. That cannot possibly be considered in the slightest an extenuation of the failure of these physicians to act in accordance with the principles and traditions of their profession.

As Rosebury[45] has commented: ". . . ethical principles are not a luxury . . . the essence of ethics — concern for the value of man — is indispensable for the survival of medicine as a profession and doubtless also for the survival of mankind as a species."

Through centuries physicians have labored to eradicate the afflictions now being considered for possible release on alien populations. To condone such a prospect seems a tragic reversal of medical progress and a disquieting rejection of Hippocrates's[46] admonition: ". . . I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong-doing. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course . . ."

We are indebted to Drs. Daniel Deykin, Frank Ervin, Cavin Leeman, Bernard Lown and Charles Magraw, and other members of the Executive Committee of Physicians for Social Responsibility, for criticisms and suggestions.

References

1. Carlat, L. E. Germs and Gases. *Nuclear Information* **5**(4):1-11, February, 1963.
2. Rothschild, J. H. *Tomorrow's Weapons, Chemical and Biological.* 271 pp. New York: McGraw-Hill, 1964.
3. Polk, J. R. U. S. assembly lines turn out deadly nerve gas for military. *The Washington Post* (April 22), 1964. P. 1.
4. United States Senate, Committee on Foreign Relations. *Chemical-Biological-Radiological (CBR) Warfare and its Disarmament Aspects.* XI, 43 pp. Washington, D. C.: Government Printing Office, 1960. Pp. 2-6.
5. Langer, W. L. *Gas and Flame in World War I.* 120 pp. New York: Knopf, 1965.
6. United States Senate, Committee on Foreign Relations.[4] P. 3.
7. Error destroys crops of model Viet village. *The Washington Post* (May 26), 1964.
8. Raymond, J. Weed killers aid war on Vietcong. *New York Times* (March 28), 1965. P. 1.
9. Frankel, M. U.S. Reveals use of nonlethal gas against Vietcong. *New York Times* (March 23), 1965. Pp. 1 and 2.
10. Raymond, J. Decision on gas made in Saigon, White House says. *New York Times* (March 24), 1965. P. 1.
11. *Idem.* Gas as weapon: pro and con. *New York Times* (March 28), 1965.
12. *Le Monde* (March 22), 1965. Quoted in *New York Times* (March 23), 1965. P. 2.
13. United States Department of Health, Education, and Welfare. *Effects of Chemical Warfare Agents.* 17 pp. Washington, D. C.: Government Printing Office, July 31, 1959. Pp. 10-13.
14. United States Senate, Committee on Foreign Relations.[4] P. 11.
15. Goodman, L. S., and Gilman, A. *The Pharmacological Basis of Therapeutics: A textbook of pharmacology, toxicology, and therapeutics for physicians and medical students.* Second edition. 1831 pp. New York: Macmillan, 1955. P. 1415.
16. *Idem.* P. 940.
17. Lieberman, E. J. Psychochemicals as weapons. *Bull. Atomic Sc.* **18**:11-14, 1962.
18. Rothschild.[2] P. 39.
19. United States House of Representatives, Committee on Science and Astronautics. *Research in CBR.* 14 pp. Washington, D. C.: Government Printing Office, 1959. P. 10.
20. Goodman and Gilman.[15] P. 933.
21. Rothschild.[2] Pp. 39-43.
22. United States Army. *Chemical and Biological Weapons Employment.* 110 pp. Washington, D. C.: Department of Army, February 20, 1962. (Field Manual FM3-10.)
23. Rothschild.[2] P. 33.
24. United States Department of Health, Education, and Welfare. *Effects of Biological Warfare Agents.* 28 pp. Washington, D. C.: Government Printing Office, July 31, 1959. P. 1.
25. *Idem.* P. 5.
26. *Idem.* Pp. 3-11.
27. Rothschild.[2] Pp. 64 and 65.
28. *Idem.* P. 236.
29. United States Department of Health, Education, and Welfare.[24] Pp. 15-19.
30. Defense against biological warfare: symposium. *Mil. Med.* **128**:81-146, 1963.
31. United States Department of Health, Education, and Welfare.[24] P. 17.
32. Hartford, T. J. Medical defense against biological weapons. *Mil. Med.* **128**:145, 1963.
33. Brincker, J. A. H. Historical, epidemiological, and aetiological study of measles (morbilli; rubeola). *Proc. Roy. Soc. Med.* **31**: 807-828, 1938.
34. United States Senate, Committee on Foreign Relations.[4] P. 6.
35. United States Senate, Committee on Foreign Relations.[4] P. 43.
36. United States House of Representatives, 86th Congress, 1st. Session. *House Concurrent Resolution 433,* September 3, 1959.
37. United States Army *The Law of Land Warfare.* III, 236 pp. Washington, D. C.: Department of the Army, July, 1956. (Field Manual *FM27-10.)*
38. Rothschild.[2] P. 194.
39. United States Senate, Committee on Foreign Relations.[4] P. 19.
40. United States Senate, Committee on Foreign Relations.[4] P. 35.
41. Rassweiler, C. F. What's so terrible about germ warfare. *Saturday Evening Post* (January 30), 1965. Pp. 12 and 16.
42. Pleasants, J. Gas warfare. *Commonweal* (May 7), 1965. Pp. 209-212.
43. Schneir, W. Campaign to make chemical warfare respectable. *The Reporter* (October 1), 1959.
44. Editorial. Brutalities of Nazi physicians. *J.A.M.A.* **132**:714, 1946.
45. Rosebury, T. Medical ethics and biological warfare. *Perspectives in Biology and Medicine* **6**:512-523, 1963.
46. *Source Book of Medical History.* Edited by L. Clendening. 685 pp. New York: Hoeber, 1942. P. 14.

MEDICAL PROGRESS

THE STATISTICAL METHOD*

JANE WORCESTER, DR. P.H.†

BOSTON

ARTICLES in the medical literature increasingly present statistical tests of significance. Too frequently one has the feeling that these have been added only after bitter correspondence between the author, the editors and a consulting statistician. Used in this way, tests of significance add little to the report of an investigation. However, if early in the design of the study, the investigator considers, with the help of a statistician if he plans eventually to consult one, the methods that will be used in the analysis of the data, the result is apt to be an improved investigation focused on a specific hypothesis with the observations

*From the Department of Biostatistics, Harvard School of Public Health.

†Professor of biostatistics and epidemiology, Harvard School of Public Health.