

HEALTH ASPECTS
OF
CHEMICAL AND BIOLOGICAL
WEAPONS

Report of a WHO Group of Consultants



WORLD HEALTH ORGANIZATION

GENEVA

1970

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1. INTRODUCTION

On 29 January 1969, the Secretary-General of the United Nations requested the Director-General of the World Health Organization to co-operate with the United Nations Group of Consultant Experts on Chemical and Bacteriological (Biological) Weapons in the preparation of a report on this subject. WHO was asked to provide such information as the Organization considered useful for the United Nations report, which was to be transmitted to the Eighteen-Nation Committee on Disarmament,¹ the Security Council and the General Assembly, if possible by 1 July 1969, as requested in Resolution 2454 A (XXIII) adopted by the General Assembly on 20 December 1968 (see Annex 7).

In order to help WHO in this task, the Director-General appointed a number of consultants. In addition, liaison was maintained with the Disarmament Affairs Division of the United Nations (which serviced the Group of Consultant Experts appointed by the Secretary-General), the Food and Agricultural Organization of the United Nations (FAO), the Stockholm International Peace Research Institute (SIPRI), and the Pugwash Organization, in order to avoid unnecessary overlap in their respective contributions.

The possible development and use of chemical and bacteriological weapons and their destructive potentialities have been matters of concern to WHO for several years. In 1967, the Twentieth World Health Assembly, on a recommendation of the WHO Executive Board, adopted a resolution (see Annex 8) welcoming Resolution 2162 (XXI) of the United Nations General Assembly and calling upon all Member States of WHO to exert every effort to implement it. The Director-General was therefore glad to meet the request to assist the United Nations in this matter, and in late May 1969 an interim report was completed and forwarded to the Secretary-General. Some of the information contained in the WHO submission was incorporated into the final report of the United Nations Group of Consultant Experts on Chemical and Bacteriological (Biological) Weapons (hereafter referred to as "the United Nations report"),² which was released to the public on 2 July 1969 and transmitted to the Eighteen-Nation Committee on Disarmament for discussion during the summer of 1969 before being

¹ Renamed on 26 August 1969 the "Conference of the Committee on Disarmament".

² United Nations (1969) *Chemical and bacteriological (biological) weapons and the effects of their possible use. Report of the Secretary-General*, New York (United Nations Publication, Sales No : E.69.I.24).

considered at the Twenty-fourth session of the United Nations General Assembly later in the year.

The relatively short period of time available for the preparation of the WHO submission to the United Nations did not permit the health and related scientific aspects of chemical and biological warfare to be covered to the extent and in the depth merited by the importance of the subject. For this reason and in pursuance of resolution WHA22.58 (Annex 9) adopted by the Twenty-second World Health Assembly in July, 1969, a further study of the problem was undertaken with a view to expanding and revising certain sections of the interim report.

2. COMPARISON OF THE WHO AND UNITED NATIONS REPORTS AND THEIR CONCLUSIONS

The United Nations report presents a comprehensive review of the problem, and includes consideration of military aspects, plant and animal diseases, ecology, and economic and security aspects, along with implications to human health. The report was intentionally written in a style that would be easily understood by governments and by the lay non-specialist reader, and it does not attempt to present highly technical information or to provide a detailed analysis of public health considerations and medical effects.

The present WHO report, on the other hand, attempts to deal with the subject of chemical and biological warfare on a more technical level and to make quantitative estimates; it is addressed particularly to public health and medical authorities. Thus the WHO report and the United Nations report are complementary. Both arrive at essentially the same technical conclusions, although inevitably there are some differences with respect to the choice of emphasis and the assessment of possible effects on public health, which reflect the differing approaches and technical orientations of the groups that prepared the WHO and United Nations reports. It is hoped, therefore, that the present document will provide the Member States of WHO with the technical information that will enable them to appreciate more fully the public health implications of the possible use of chemical and biological weapons.

The following main conclusions emerge from the WHO analysis :

1. *Chemical and biological weapons pose a special threat to civilians. This is because of the often indiscriminate nature of such weapons, and because the high concentrations in which they would be used in military operations could lead to significant unintended involvement of the civilian population within the target area and for considerable distances downwind.*

2. *The large-scale or, with some agents, even limited use of chemical and biological weapons could cause illness to a degree that would overwhelm existing health resources and facilities.*
3. *Large-scale use of chemical and biological weapons could also cause lasting changes of an unpredictable nature in man's environment.*
4. *The possible effects of chemical and biological weapons are subject to a high degree of uncertainty and unpredictability, owing to the involvement of complex and extremely variable meteorological, physiological, epidemiological, ecological, and other factors.*
5. *Although advanced weapons systems would be required for the employment of chemical and biological agents on a militarily significant scale against large civilian targets, isolated and sabotage attacks not requiring highly sophisticated weapons systems could be effective against such targets in certain circumstances with some of these agents.*

These conclusions are in harmony with the conclusions of the United Nations Group of Consultant Experts on Chemical and Bacteriological (Biological) Weapons and with the hope for further action to deal with the threat posed by the existence of these weapons, as expressed by the Secretary-General, U Thant, in the foreword to the United Nations' report.

3. AIM AND SCOPE OF THE WHO REPORT

The present report attempts to analyse the health effects of the possible use of chemical and biological weapons on civilian population groups at different levels of social and economic development, and the resulting implications for WHO and its Member States. The assessment is confined to civilian populations, and no attempt is made to consider the purely military aspects of the problem, except insofar as they may relate to civilian populations as possible targets for attack. The military aspects of chemical and biological warfare are considered in the United Nations report and in a report being prepared by SIPRI. The report also makes qualitative and quantitative estimates of the health effects of selected chemical and biological agents employed under specified hypothetical conditions.

4. WORKING DEFINITIONS OF CHEMICAL AND BIOLOGICAL WEAPONS FOR THE PURPOSES OF THIS REPORT

Chemical agents of warfare include all substances employed for their toxic effects on man, animals, or plants.¹

Biological agents include those that depend for their effects on multiplication within the target organism, and are intended for use in war to cause disease or death in man, animals or plants.²

A *lethal agent* is one intended to cause death when man is exposed to concentrations well within the capability of delivery for military purposes.³

An *incapacitating agent* is one intended to cause temporary disease or to induce temporary mental or physical disability, the duration of which greatly exceeds the period of exposure.⁴

A *harassing agent* (or short term incapacitant) is one capable of causing a rapid disablement that lasts for little longer than the period of exposure.⁴

Casualties are deaths or disabilities.

5. SELECTION OF CHEMICAL AND BIOLOGICAL AGENTS AS MODELS FOR QUALITATIVE AND QUANTITATIVE ASSESSMENTS

There are many chemical and biological agents that are potentially suitable for use in war. A selection of some of the more likely candidates for possible use as lethal, incapacitating and harassing agents has been made

¹ This definition is intended to exclude chemicals now employed in warfare such as high explosives, smoke, and incendiary substances (e.g., napalm, magnesium, and white phosphorus) that exert their primary effects through physical force, fire, air-deprivation or reduced visibility.

² This definition therefore excludes toxins elaborated by some microbes (e.g., botulin toxin and staphylococcal enterotoxin) when they are preformed outside the target organism. In some discussions of chemical and biological weapons, such toxins are classified as biological agents because the technology of their production resembles that of biological agents rather than that of chemical agents.

³ In lower doses, such agents can cause severe and sustained disability and certain of them may act predominantly in this way when employed in combat.

⁴ No sharp line of demarcation can be drawn between lethal and incapacitating agents used in chemical and biological warfare, because incapacitating agents can be lethal or permanently disabling under certain circumstances (e.g., in the presence of malnutrition or pre-existing disease; in infants or the aged; or when there is exposure to unusually high doses, as in enclosed spaces or in close proximity to functioning chemical or biological weapons). For similar reasons, no sharp demarcation line can be drawn between harassing agents and other anti-personnel chemical agents; furthermore, harassing agents may be used in war in conjunction with high-explosive, fragmentation or other weapons to increase the lethal effectiveness of the latter—as distinct from their employment in riot control in order to reduce injuries and to save lives.

for the purposes of this report, based on published information as well as on theoretical considerations.

The chemical and biological agents described in Annexes 1 and 2 have been selected to illustrate possible varieties of usage and effects: aerosol exposure; sabotage of communal water supply; quick or delayed action; essentially non-spreading and spreading types of infective disease; vector introduction. Qualitative descriptions are given for all of them, and a number of representative types have been selected for quantitative assessments of the effects of their possible use.

6. BASES OF THE ESTIMATES OF CASUALTIES

The actions and toxicities of the chemical warfare agents considered are reasonably well known. For many, there are generally agreed estimates of lethal doses, although it should be kept in mind that often these are based on assumptions concerning the relative susceptibility of different animal species, and that susceptibility varies between individuals. The clinical symptoms, the prognosis, and the general methods of treatment and prevention, if any, can be assessed from commonly available information.

The agents chosen for discussion as possible biological weapons are those whose clinical effects are well known; for some of them data on approximate infective doses by inhalation or ingestion are also available, either from published information about laboratory accidents or from studies in human volunteers. However, little is known about the susceptibility of man to artificial aerosols of infective agents and about the consequences of exposure to very high doses. This report is confined to a discussion of known agents with a wide range of infectivity and lethality. Other agents could conceivably be developed. In spite of these uncertainties, it has been considered useful to attempt to predict the range of immediate effects of the agents dealt with in this report.

It is considered unlikely that the general conclusions reached in this study would have been greatly modified if it had been possible to consult classified information concerning chemical and biological agents, although the assessments concerning the feasibility of their use in particular circumstances might have been made more realistic.

The estimates of casualties recorded in Tables 8 and 10, Annex 3, are based on the number of individuals within a segment of a particular population group exposed to a given chemical or biological agent. The assumptions made and the variables taken into account are stated in Annex 3. These assumptions deal with delivery, dissemination, and persistence of the agents; meteorological conditions; effective concentrations and doses; human infective doses, attack and case fatality rates; and chemotherapy.

In the detailed analysis of hypothetical attack with tularaemia, pneumonic plague, and VX, the effects of the availability and use of health facilities on the outcome are considered (Annex 4). Annex 5 describes the possible effects of sabotage of a communal water supply with botulinum toxin, the typhoid bacillus and LSD.

The estimates of casualties that are given in Annex 3 are applicable to a surprise attack on an urban area that possesses no specific protection against attack with chemical and biological agents, and in which the buildings are freely ventilated. It will be seen that even where the target area is not very densely populated the effects of attack by a single aircraft could create health problems of unprecedented magnitude.

It is certain that the scale and effectiveness of an attack (and also the cost and feasibility) would depend upon military technology. To discuss this aspect in any depth is outside the terms of reference of this report. A limited attack on a civilian population using a pattern favouring the effectiveness of the weapons employed has therefore been chosen for consideration. In this way, it is hoped to illustrate the scale of the danger that could arise from the use of such weapons. Similar results could be produced by attacks on a larger scale if the circumstances were unfavourable for the pattern chosen.

7. LONG-TERM EFFECTS

A few general considerations regarding the possible long-term effects of chemical and biological agents should be noted. First of all, insufficient knowledge is available to allow reliable predictions to be made. In many cases, not much more can be done than to outline the various possibilities needing further study. Beyond that, there are problems of evaluation that, while still having a considerable technical component, also involve value judgements that are clearly beyond the scope of this report. For example, in comparison with the direct effects of a lethal chemical or biological attack, a limited risk of long-term harmful effects to health may seem relatively unimportant. On the other hand, the long-term effects of the military use of agents that are not directly lethal may be considered more important than their immediate effects. In the latter connexion it should be kept in mind that non-military experience with disease-causing organisms and chemicals present in the environment may not be a good guide to the effects of those same agents under the quite different conditions and in the generally higher doses involved in their military employment.

Possible long-term health effects of chemical and biological warfare include (1) chronic illness caused by exposure to chemical and biological agents (see specific descriptions in Annexes 1 and 2); (2) delayed effects in persons directly exposed to chemical and biological agents; (3) creation

of new foci of infective disease ; and (4) effects mediated by ecological changes.

Delayed effects of direct human exposure

There is wide concern at present regarding the possibility that exposure to both infective and chemical agents already present in the human environment may cause harmful effects of a delayed nature. The effects of greatest concern are :

(a) *Carcinogenesis.* Both viral and chemical agents have been strongly implicated in the causation of cancer in man. Whether infection by any of the viruses contemplated for possible military employment can be carcinogenic in man is not at present known. A limited amount of information is available on the ability of certain classes of chemicals to induce cancer, mainly in experimental animals. For example, many alkylating agents have been found to be carcinogenic. Some compounds of military interest, such as mustard, CS, and others, are alkylating agents. As discussed in Annex 1, there is evidence suggesting a significant increase in respiratory tract cancer among veterans exposed to mustard gas in the First World War, and a large increase in such cancers has been reported among workers engaged in the manufacture of mustard gas in the Second World War.

(b) *Teratogenesis.* Certain chemicals and infective agents can cause severe damage to the developing human foetus. Thalidomide and the rubella virus are particularly well known teratogens. It is not known whether any agents likely to be used in chemical or biological warfare would have teratogenic effects at the doses likely to be received by pregnant women in civilian populations under direct attack with or unintentionally exposed to such agents during wartime. In this regard, it may be noted that the use of 2,4,5-trichlorophenoxyacetic acid, an anti-plant chemical that has been extensively used for both military and non-military purposes, has recently been restricted by the United States Government because experiments have shown that relatively high oral doses of this compound are teratogenic in mice and rats.

(c) *Mutagenesis.* Until recent years little attention has been given to the possibility that infectious diseases or chemicals in the environment might cause detrimental alterations in the human genome. Several chemicals are known to induce such changes in experimental organisms and in cultured human cells. Infection with certain viruses causes extensive chromosome breakage in man, but it is not known whether any heritable effect results. At least in the case of rubella it can be said that genetic damage is not massive, although the induction of a lower but nevertheless significant frequency of mutations cannot be excluded.

New foci of infective disease

As discussed in Annex 2, biological warfare would entail a risk that new foci of infective disease might be established, either in human populations or in lower animals, including vector arthropods. This possibility has been discussed in the United Nations report :

“ A bacteriological (biological) attack might lead to the creation of multiple and densely distributed foci of infection from which, if ecological conditions were favourable, natural foci might develop in regions where they had previously never existed or in areas from which they had been eliminated by effective public health measures.”

Effects mediated by ecological change

The possibility of the direct establishment of new foci of disease has been referred to immediately above. New foci might also be established as the result of ecological changes following the use of biological agents infective for man and animals. This possibility has also been discussed in the United Nations report :

“ ... the large scale use of bacteriological (biological) weapons might reduce populations of susceptible wild species below the level at which they could continue to exist. The elimination of a species or group of species from an area would create in the ecological community an empty niche which might seriously disturb its equilibrium or which might be filled by another species more dangerous to man because it carried a zoonosis infection acquired either naturally or as a result of the attack. This would result in the establishment of a new natural focus of disease.”

As for anti-personnel chemical warfare, it can at least be said that the massive dissemination of several chemical agents during the First World War has not apparently caused any major long-term ecological damage in Europe.

However, new foci of human disease may also be produced as a result of the use of anti-plant agents. Extensive damage to the flora over large areas may create conditions favouring the establishment of new vectors or reservoirs of disease infective to man. One example of the way in which damage to plant life can create new health hazards is cited in the United Nations report :

“ When a forest in a state of ecological equilibrium is destroyed by cutting, a secondary forest regenerates, which contains fewer species of plants and animals than were there originally, but larger numbers of those species which survive. If secondary forest is replaced by grassland, these changes are even more marked. If one or more of the animal species which increases in numbers is the host of an infection dangerous to man (a zoonosis) then the risk of human infection is greatly increased. This is

exemplified by the history of scrub typhus in south-east Asia, where the species of rat which maintains the infection and the vector mite are much more numerous in secondary forest, and even more so in grassland, so increasing the risk of the disease being transmitted to people as forest is cleared.”

Finally a profound long-term adverse effect on human health could result from any major reduction in the quality or quantity of the food supply. This could occur directly from the use of anti-crop agents or indirectly through ecological changes that might result from chemical or biological warfare.

8. SUMMARY

A. *Qualitative considerations*

Chemical and biological agents that might be considered for possible use in warfare are described in Annexes 1 and 2, and pertinent assumptions and other background factors are considered earlier in this text and in Annexes 3, 4, and 5. Also of importance, although more difficult to assess, are the possible long-term effects referred to in section 7, and the psychosocial consequences associated with the problem of chemical and biological weapons (see Annex 6).

The rapid action of the lethal *chemical agents* (see Annex 1) would preclude any large reduction of mortality by specific treatment. Possible protection by gas masks or shelters requires a highly disciplined and prepared population, a condition that is not fulfilled in most countries today, and it would pose serious economic and psychosocial problems if such a defence programme were to be implemented.

The outstanding characteristics of *biological weapons* (see Annex 2) for potential use in warfare are the following :

(a) The large variety of biological agents and the possible combinations available for such purposes.

(b) The possibilities for manipulating currently circulating strains of micro-organisms for warfare purposes, by producing antigenically modified or antibiotic-resistant types (tularemia, plague, anthrax, influenza) that would by-pass available prophylactic or therapeutic procedures.¹

(c) The unpredictability of the direct effects. A biological attack intended to be highly lethal might prove relatively ineffective, whereas an attack intended to be merely incapacitating might kill an unexpectedly

¹ Mass immunizations would be of doubtful protective value because of the multiplicity of agents and strains that might be employed, quite apart from the adverse immunological side-reactions to be expected.

large proportion of the target population. Also, certain agents (anthrax, coccidioidomycosis) could persist for long periods in a resistant spore form, which could be spread over very large distances by wind carriage in the course of time.

(d) The unpredictability of secondary effects such as the likelihood of contagion and the danger that epidemics might be initiated. There is the additional danger that epidemics might occur unintentionally through escape of virulent strains being purposely sought in laboratories.

(e) Although biological agents themselves are easy to produce, complex production and delivery systems are needed if even minimal reliance is to be placed on the outcome of an attack, except perhaps where the intention is simply to produce social disruption by a limited sabotage effort (e.g., the introduction of smallpox).

Of the above characteristics, (a) and (b) would favour the attacker, whereas (c) and (d) would reduce the value of biological weapons from a military point of view.

B. *Quantitative estimates* (Tables 8, 9 and 10, Annex 3)

1. Assessments have been made of the primary effects of possible small-scale airborne attacks on cities of 0.5-5 million population in industrially developed and developing countries. The postulated mode of attack consisted of one or a few bombers dispersing specific chemical or biological agents along a 2-km line perpendicular to the direction of the wind. On the basis of the particular assumptions employed, the following conclusions have been reached :

(a) Of the known chemical warfare agents, only the nerve gases, and possibly botulinal toxin, have a casualty-producing potential comparable to that of biological agents.

(b) Under atmospheric conditions favourable to the attacker, an efficiently executed attack on a city with 4 tons of sarin (requiring some 15-20 tons of weapons) could cause tens of thousands of deaths in an area of about 2 km². Even in unfavourable conditions there could be thousands of deaths. If 4 tons of VX were used in such an attack, the casualties would not be appreciably greater in unfavourable meteorological conditions, but in favourable conditions this small attack would affect an area of about 6 km² and could cause anywhere between 50 000 and 180 000 deaths.

(c) If a suitably stabilized botulinal toxin or a fine aerosol of VX (particles of 5 μ diameter) were developed and 4 tons were employed, several hundreds of thousands of deaths could result because of the greater coverage possible with such agents—12 km² for botulinal toxin and 40 km² for monodispersed VX aerosol. A larger total weight of weapons, perhaps

2-3 times that needed for the agents in (b) above, would have to be used to deliver these forms of botulinal toxin and VX.

(d) If a biological agent such as anthrax were used, an attack on a city by even a single bomber disseminating 50 kg of the dried agent in a suitable aerosol form would affect an area far in excess of 20 km², with tens to hundreds of thousands of deaths. A similar attack with any one of a number of other more labile biological agents could affect from 1 km² to more than 20 km², depending upon agent used, with tens to hundreds of thousands of casualties and many thousands of deaths.

2. Limited sabotage of a communal water supply with the typhoid fever bacillus, LSD, or a stable botulinal toxin, could cause considerable disruption and deaths in a large city (see Annex 5), affecting tens of thousands of people.

3. Sabotage-induced or open attacks, causing the secondary spread of epidemics of yellow fever, pneumonic plague, smallpox or influenza, might under certain conditions ultimately result in many millions of illnesses and deaths (see Annex 2).

4. The numbers of potential casualties and deaths recorded in this report represent the possibilities arising out of a very small and limited attack already well within the capabilities of a number of nations, with the possibility that an ever-increasing number of countries will acquire similar capabilities. With technologically advanced weapons and a larger scale of attack, achievable without too much difficulty by militarily advanced powers, the magnitude of destructiveness attendant upon the use of chemical and biological weapons would be considerably increased.

9. IMPLICATIONS FOR THE WORLD HEALTH ORGANIZATION AND ITS MEMBER STATES

According to Art. 2 (c) of WHO's Constitution, WHO shall "... furnish appropriate technical assistance and, in emergencies, necessary aid upon the request or acceptance of Governments". The use of chemical and biological weapons would unquestionably result in extensive health and medical emergencies, including mass illnesses, deaths and epidemics, that WHO might be called upon to help overcome. An attempt to assess the magnitude of public health problems with respect to a minimal attack with selected examples of agents (tularaemia, plague, VX) is contained in Annex 4. This limited assessment, supported by analyses made in other parts of this report and in the United Nations report, reveals the very large and essentially wasteful effort that would be involved in undertaking elaborate measures for defence against specific agents. Also, as pointed out in Annex 6, such measures could well add credibility to projected fears of

annihilation in other countries. The resultant reciprocal fears between nations might contribute in turn to a proliferation of chemical and biological weapons and an accelerated arms race, resulting in vastly increased danger of accidental or deliberate release of chemical and biological agents.

Certain measures could, however, be taken within the framework of existing needs and resources that would redound to the benefit of health and preventive medical activities currently underway, and would not give rise to fears of this kind. These measures include the improvement of rapid detection and diagnostic facilities for air pollution and for communicable diseases, which would obviously be of value for health and laboratory services in general; improved medical management for natural disasters, including decontamination procedures; and the wider use of safety features in buildings (ventilation filters) and for communal water supply systems (see Annex 5). While such measures might act as a partial deterrent to irresponsible groups and might significantly reduce casualties from a very small attack or from the spreading effects of an attack on a neighbouring country, they cannot be relied upon to afford major protection to a country subjected to a determined attack.

As long as chemical and biological research directed specifically to military use is continued, it will be considered necessary by some countries to continue research towards detection of and protection against such agents. This research could in itself point to agents more destructive than those now existing. In view of the power of existing agents in conditions favourable to their use and the possibility of developing new and even more dangerous weapons, it is imperative to find ways of abolishing any presumed need for this militarily orientated research as soon as possible.

It is therefore clear that in the last analysis the best interests of all Member States and mankind in general will be served by the rapid implementation of the resolutions on chemical and biological warfare adopted by the United Nations General Assembly and the World Health Assembly (Annexes 7 and 8), and by any additional steps that would help ensure outlawing the development and use in all circumstances of chemical and biological agents as weapons of war.

Finally, there is the possibility that WHO might be called upon by the United Nations to help deal with allegations of use of chemical and biological weapons between nations and to assist in the limitation of chemical and biological weapons, and disarmament. The technical resources of WHO ¹

¹ An example of such technical resources is the collection of epidemiological information on communicable diseases that has been made by WHO for many years, through its serum banks and its surveillance programmes involving specific diseases. This information provides an invaluable background and potential for determining changes in communicable disease patterns, as well as for obtaining knowledge of diseases already existing in a community. Apart from its general epidemiological value, expansion in the accumulation of such data could be very useful for investigating any possible future allegations of use of biological weapons.

could contribute greatly to the resolution of many of the difficulties that are associated with these problems and are now being discussed within the framework of the the United Nations.

ACKNOWLEDGEMENTS

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ANNEX I

CHEMICAL AGENTS

Classification and definitions

The number of substances that have been examined as candidate chemical warfare agents runs into hundreds of thousands. During the First World War, virtually every known chemical was screened, and much of the work done then was repeated during the Second World War; in addition, a high proportion of the new compounds that had been synthesized or isolated from natural materials during the interwar years were examined. Since the Second World War, the major laboratories engaged in such work have probably been carrying out a systematic check on all compounds whose properties suggest any utility in chemical warfare, however remote.

The requirements that must be satisfied by candidate chemical warfare agents in respect of production cost and physical, chemical and toxicological properties are severe, and the number of chemicals that have actually been used in chemical warfare or stockpiled in quantity for such use is small, probably not more than sixty. Of these, about two-thirds were used during the First World War, when the battlefield fulfilled many of the functions of modern chemical warfare proving grounds. Less than a dozen were at all efficacious.

From a military point of view, chemical warfare agents have been developed with three quite different tactical functions in mind:

- (1) "lethal agents", used either to kill an enemy or to injure him so severely as to necessitate his evacuation and medical treatment;
- (2) "incapacitating agents", used to put an enemy completely out of action for several hours or days, but with a disablement from which recovery is possible without medical aid; and
- (3) "harassing agents", used to disable an enemy for as long as he remains exposed.

The above classifications are not toxicological categories, for the effects of a chemical warfare agent depend as much on the way it is used as on its toxicological properties. If too much of an agent intended for harassment is used, it may kill or severely injure. Likewise, if a low concentration

TABLE 1. SOME PROPERTIES OF SELECTED CHEMICAL WARFARE AGENTS

1	Sarin	VX	Hydrogen cyanide	Cyanogen chloride	Phosgene	Mustard gas	Botulinum toxin A	BZ	CN	CS	DM
2	Lethal agent (nerve gas)	Lethal agent (nerve gas)	Lethal agent (blood gas)	Lethal agent (blood gas)	Lethal agent (lung irritant)	Lethal and incapacitating agent (vesicant)	Lethal agent	Incapacitating agent (psycho-chemical)	Harassing agent	Harassing agent	Harassing agent
3	Vapour, aerosol or spray	Aerosol or spray	Vapour	Vapour	Vapour	Spray	Aerosol or dust	Aerosol or dust	Aerosol or dust	Aerosol or dust	Aerosol or dust
4	All types of chemical weapon		Large bombs	Large bombs	Mortars, large bombs	All types of chemical weapon	Bomblets, spray-tank	Bomblets, spray-tank	All types of chemical weapon		
5	1 000 kg	1 000 kg	1 000 kg	1 000 kg	1 500 kg	1 500 kg	400 kg	500 kg	750 kg	750 kg	750 kg
6	100%	1-5%	100%	6-7%	Hydrolysed	0.05%	Soluble	?	Slightly soluble	Insoluble	Insoluble
7	12 100 mg/m ³	3-18 mg/m ³	873 000 mg/m ³	3 300 000 mg/m ³	6 370 000 mg/m ³	630 mg/m ³	Negligible	Negligible	105 mg/m ³	Negligible	0.02 mg/m ³
8 (a) (b)	Liquid Liquid	Liquid Liquid	Liquid Liquid	Solid Vapour	Liquid Vapour	Solid Liquid	Solid Solid	Solid Solid	Solid Solid	Solid Solid	Solid Solid
9 (a) (b) (c)	¼-1 h ¼-4 h 1-2 days	1-12 h 3-21 days 1-16 weeks	Few minutes Few minutes 1-4 h	Few minutes Few minutes ¼-4 h	Few minutes Few minutes ¼-1 h	12-48 h 2-7 days 2-8 weeks	— — —	— — —	— — —	— 2 weeks for CS1; longer for CS2 —	— — —
10	> 5 mg-min/m ³	> 0.5 mg-min/m ³	> 2 000 mg-min/m ³	> 7 000 mg-min/m ³	> 1 600 mg-min/m ³	> 100 mg-min/m ³	0.001 mg (oral)	100 mg-min/m ³	5-15 mg/m ³ concentration	1-5 mg/m ³ concentration	2-5 mg/m ³ concentration
11	100 mg-min/m ³	10 mg-min/m ³	5 000 mg-min/m ³	11 000 mg-min/m ³	3 200 mg-min/m ³	1 500 mg-min/m ³	0.02 mg-min/m ³	?	10 000 mg-min/m ³	25 000-150 000 mg-min/m ³	15 000 mg-min/m ³
12	1 500 mg/man	6 mg/man	—	—	—	4 500 mg/man	—	—	—	—	—

KEY: 1. Common name
 2. Military classification
 3. Form in which the agent is most likely to be disseminated
 4. Types of weapon suitable for disseminating the agent
 5. Approximate maximum weight of agent that can be delivered effectively by a single light bomber (4-ton bomb load)
 6. Approximate solubility in water at 20°C
 7. Volatility at 20°C
 8. Physical state (a) at -10°C
 (b) at 20°C

9. Approximate duration of hazard (contact, or airborne following evaporation) to be expected from ground contamination:
 (a) 10°C, rainy, moderate wind
 (b) 15°C, sunny, light breeze
 (c) -10°C, sunny, no wind, settled snow
 10. Casualty-producing dosages (for militarily significant injuries or incapacitation)
 11. Estimated human respiratory LC₅₀ (for mild activity: breathing rate approx. 15 litres/min)
 12. Estimated human lethal percutaneous dosages

of a lethal agent is disseminated, its effects may be only incapacitating or harassing.

The properties of some of the most important agents are summarized in Table 1.

A. LETHAL AGENTS

A variety of tissue irritants and systemic poisons have been developed into lethal chemical warfare agents. The former group includes the lung irritants (asphyxiants) and the vesicants (blister agents); the latter includes the blood gases and the nerve gases.

Historical introduction

Asphyxiants were first used during the First World War in the spring of 1915 when a series of massive surprise attacks with chlorine caused many thousands of casualties. As respirators became available, the trend was at first towards finding agents more toxic than chlorine. This soon led to the widespread use of phosgene, trichloromethyl chloroformate, and hydrogen cyanide. The physical properties of hydrogen cyanide could not be brought under sufficient control for practical use during the First World War, but phosgene proved highly effective. Another trend was towards the development of substances such as chloropicrin whose physical and chemical properties made their retention by respirators difficult. The third trend, and certainly the most important one for the future development of chemical warfare, was towards the development of agents like mustard gas and the arsenical vesicants that damage the skin, thereby circumventing the protection of the respirator.

During the 1920s and 1930s, many new candidate chemical agents were given serious consideration. These included such congeners of phosgene and chloropicrin as bis(trichloromethyl) oxalate and the tetrachlorodinitroethanes; disulfur decafluoride; a variety of arsenical vesicants, the nitrogen mustards and the higher sulfur mustards; metallic carbonyls; cadmium, selenium and tellurium compounds; fluoroacetates; carbamates; and many others. Although a few of these appeared to have some advantages over existing chemical warfare agents in certain tactical situations, and were eventually manufactured for possible war use, none exceeded phosgene or mustard gas in general utility, and these two agents formed the bulk of the stockpiles at the start of the Second World War, just as they had at the end of the First.

A significant development in lethal agents came during the Second World War with the secret manufacture by one of the belligerent nations of the first series of nerve gases, the G-agents. These included tabun, sarin and soman. Tabun had been discovered at the end of 1936, and pilot plant

production facilities were working when the war broke out. By 1945, massive quantities were available. It is much more poisonous than phosgene and is quicker acting. In addition, it can produce casualties by penetration of the eyes or skin, albeit at much higher dosages, as well as by inhalation.

After the war, when details of this nerve gas work were published, the G-agents were developed further. Sarin emerged as the most attractive of these for military purposes, and production methods were elaborated in a number of countries to overcome the difficulties that had prevented its manufacture on a large scale during the war.

In 1955, a further class of nerve gases was discovered in a commercial insecticide laboratory. These new substances are now known as the V-agents and their development has produced what appear to be exceptionally powerful chemical weapons.

Estimates of the respiratory lethal dose of phosgene in man are generally around 50 mg, while that of sarin is around 1 mg, so that in terms of agent toxicity the potentialities of chemical weapons increased by more than an order of magnitude with the discovery of the G-agents. With the V-agents there came another sharp increase, for the respiratory lethal dose of these substances in man is thought to be of the order of 0.1 mg. But more important is their increased percutaneous toxicity: something like 5 000 mg of mustard gas or 1 000-2 000 mg of sarin are probably needed to kill a man through his skin, whereas with a V-agent such as VX perhaps only 5 mg are needed. A person's skin had thus become nearly as vulnerable a target as his lungs. As it is harder to protect a man fully against a contact hazard than a respiratory one, and as the V-agents are persistent and so call for elaborate decontamination measures (which need to be a great deal more efficient than those for mustard gas) the V-agents represented not only an increase in effectiveness in a given situation, but also an increase in the number of military situations where chemical weapons might be effective. It is since 1955 that it has come to be recognized that chemical weapons are not historical leftovers but could be useful components of a modern military arsenal.

At the present time, it is unlikely that any substance appreciably more toxic than the V-agents has been developed into a practical chemical warfare agent, even though a large number of such substances exist. They include a variety of animal, vegetable and bacterial toxins, notably saxitoxin, tetrodotoxin, bobatrachotoxin, ricin, abrin and the toxins of *Clostridium botulinum* and *Cl. tetani*. Most of these are proteins of high molecular weight that are expensive to extract and difficult to disseminate undetoxified. Special circumstances might conceivably permit their use as chemical warfare agents, but it is unlikely that they would ever be stockpiled in preference to the V-agents. When their toxicology is better understood, it is possible that their toxic principles may be incorporated into more tractable substances, but this seems unlikely to happen in the near future.

Specification of toxicity of chemical agents

The precise specification of toxicity in terms of LD_{50} and LCt_{50} is explained in Annex 3.

It is important to understand that there is no sharp demarcation between lethal and non-lethal doses : there is a gradual increase in the probability of causing death as the dose increases. Precise specification of the relation between this probability and the dose calls for experiments on large numbers of animals. The necessary data are not always available for lower animals, and are never available for man.

In consequence, often the only published information available is that a particular dose may kill or incapacitate. This dose may be described as the "lethal dose" or the "incapacitating dose", but it is often impossible to determine with any precision what proportion of those receiving this dose would be killed or incapacitated. Since this report relies on published information it can only be correspondingly imprecise.

1. Lung irritants

The lung irritants, sometimes also referred to as asphyxiants or choking gases, are substances that cause physical injury to the tissues of the respiratory tract. The protective membranes lining the air passages may be damaged, thus increasing susceptibility to microbial infection and possibly leading to bronchopneumonia or similar diseases. In addition, the lung capillaries through which oxygen is taken up into the circulation may be damaged, and the resultant oedema may eventually prevent uptake altogether.

The majority of the lethal chemical agents employed during the First World War were lung irritants, and it is estimated that they were responsible for more than 80% of the deaths due to gas during the war. Since the discovery of the nerve gases, the importance of lung irritants has greatly declined. None the less, some of them are widely available commercial chemicals and may still remain attractive as chemical warfare agents in cases where nerve gases are not obtainable. This applies especially to phosgene, the properties of which are reviewed below.

(i) *Phosgene* (carbonyl chloride, $COCl_2$)

Except in cold weather, phosgene is a colourless gas. In low concentrations, it has a rather sweet, not unpleasant odour resembling that of new-mown hay, but it becomes more pungent and irritating in higher concentrations. Its vapour is three times as dense as air. It is rather rapidly decomposed into carbon dioxide and hydrogen chloride when dissolved in water, and more slowly in moist air. It has many industrial applications, and in some countries it is produced at a rate of more than 100 000 tons per year.

Toxicology

On inhalation, the initial effect of a dangerous quantity of phosgene is a transient irritation of the mucous membranes, especially of the eyes and respiratory tract. This may be too mild to warn the exposed person against further inhalation, even though attack on lung tissue will already have begun. Depending on the dosage, this may lead successively to bronchiolar constriction, acute pulmonary inflammation, pulmonary oedema, emphysema, destruction of the alveolar epithelium, occlusion of the pulmonary circulation by intravascular clotting and haemolysis, and bronchiolar and bronchial necrosis (Tobias et al., 1949; American Industrial Hygiene Association, 1968; Everett & Overholt, 1968). Symptoms are not generally experienced for some hours after inhalation. Typically they begin with increasing breathlessness, progressing through cough, dyspnoea, sense of suffocation, thirst, vomiting, and pain in the chest. As the oedema builds up in cases of severe poisoning, the symptoms culminate in cyanosis, frothing at the mouth, extreme weakness, mental disorientation, coma, convulsions, and death from acute cardiac failure (Wirth et al., 1967; Everett & Overholt, 1968; von Oettingen, 1958).

Sublethal dosages will generally give rise to chronic sequelae. The damaged lung tissue may take some time to heal: even a quite small dose can produce a pneumonitis that is identifiable for several weeks or months after exposure. The probability of microbial infection will be greatly increased and the overall clinical picture may be complicated by chronic bronchitis and bronchiectasis.

Exposure of the eye to high phosgene concentrations causes severe conjunctivitis and, although at first the cornea appears to be unaffected, corneal turbidity and visual disturbances may develop later (von Oettingen, 1958).

The respiratory LC_{50} in man (see Annex 3 for explanation) is estimated to be about 3 200 mg-min/m³. Dosages of about 1 600 mg-min/m³ produce what is described as a "militarily significant incapacitation" (US Department of the Army, 1963). In animal experiments, it has been shown that repeated exposure to sublethal concentrations of phosgene is not cumulative (Box & Cullumbine, 1947).

Therapy

It has been suggested that the initial biochemical lesion in phosgene poisoning might be the acylation of certain essential lung constituents (Tobias et al., 1949). It has also been suggested that the pulmonary oedema may be of the neuroparalytic type, mediated by reflex action with resultant sympathetic paralysis and severe pulmonary vasoconstriction (Ivanhoe & Myers, 1964). These considerations, however, have not yet led to an

effective antidote for the poisoning, and the treatment of phosgene victims remains essentially palliative and supportive.

In many patients who recover, there appears to be no permanent residual disability (Sax, 1963). Recovery requires weeks to months (Thienes & Haley, 1964).

Use as a chemical warfare agent

Since phosgene can be easily liquefied under pressure, it can be used conveniently to set up rapidly lethal concentrations of heavy gas over large areas without the need for a large weight of weapons. In addition, quite low field concentrations may produce effects that, although not fatal, are nevertheless severely incapacitating. Its disadvantages lie in the delay before it produces its toxic effects and its rather low toxicity compared with the nerve gases. Its toxicity is almost certainly too low to suggest its use in preference to explosives or incendiaries in attacks on civilian targets when the object of such attacks is anything other than terrorization. As it has no percutaneous action, respirators provide complete protection against its effects.

2. Blood gases

The designation "blood gas" is used to denote those lethal chemical warfare agents that interfere with cell respiration; it is an allusion to the supposed mechanism of action of these substances, which is thought to involve either a blockage of oxygen uptake from the blood, or a blockage of the exchange of carbon dioxide between the blood and the tissues, and between the blood and the air in the lungs.

The important members of the class are hydrogen cyanide and cyanogen chloride, and their properties are reviewed below.

(i) Hydrogen cyanide (hydrocyanic acid, HCN)

Hydrogen cyanide, like phosgene, is a widely available commercial product used in the manufacture of a variety of organic chemicals.

At room temperature, it is a highly volatile, almost colourless liquid. It is completely soluble in water. Its vapour is less dense than air.

Toxicology

Although massive doses of hydrogen cyanide can produce percutaneous intoxication, in warfare it would be used for respiratory effect; it is readily absorbed into the circulation through the lungs.

At high respiratory doses, hydrogen cyanide may produce, without warning, sudden loss of consciousness and prompt death from respiratory arrest. With smaller but still lethal doses, the illness may be prolonged for

one or more hours. In these cases an immediate and progressive sensation of warmth over the entire body, due to vasodilatation, with visible flushing, is the first symptom; this is followed by prostration, then nausea and vomiting, often with headache, and then by difficulty in breathing, with a sensation of tight bands around the chest; and finally unconsciousness supervenes, swiftly succeeded by asphyxial convulsions (Sollman, 1957; Gleason et al., 1957).

The lethal effect of inhaled hydrogen cyanide varies greatly with its concentration in the air, because the body rapidly destroys this poison. When the concentration is 60 mg/m³, a 60-minute exposure may cause no serious symptoms. When the concentration is 200 mg/m³ death may follow exposure for 10 minutes. When the concentration is 5 000 mg/m³ death may follow exposure for 1 minute (Paulet, 1960; Manufacturing Chemists' Association Inc., 1961).

Therapy

Two types of therapy for hydrogen cyanide poisoning are available: the administration of nitrites, such as amyl nitrite, and the use of substances that can destroy absorbed hydrogen cyanide in the very short time before its effects have run their course. The latter compounds include thiosulfates, which convert hydrogen cyanide to thiocyanate, a reaction that is catalyzed by an enzyme present in the blood.

If therapy is begun in time, recovery from hydrogen cyanide poisoning may be very swift.

Use as a chemical warfare agent

The attractions of hydrogen cyanide as a chemical warfare agent lie in the extreme rapidity of its toxic effects if it can be disseminated in sufficiently high field concentrations. However, this is more difficult to achieve than with phosgene owing to the low vapour and liquid densities of hydrogen cyanide and its tendency to inflame when disseminated by explosive burst. As with phosgene, its low toxicity as compared with G and V agents (see below) does not make it an obvious choice for attacks on large civilian targets. Respirators can provide virtually complete protection against it, although it is easier to saturate charcoal filters with hydrogen cyanide than with most chemical warfare agents.

(ii) *Cyanogen chloride (ClCN)*

Like hydrogen cyanide, cyanogen chloride is a widely available commercial product, having applications as a fumigant and as an industrial intermediate. It was in limited use as a war gas during the First World War. When inhaled at a sufficiently high concentration it kills rapidly, with a toxic action similar to that of hydrogen cyanide.

At room temperature it is either a gas or a highly volatile colourless liquid. Unlike hydrogen cyanide, its vapour is strongly irritating to the eyes and respiratory passages at low concentrations. It is readily decomposed by moisture into hydrogen cyanide and hydrochloric acid. Its liquid and vapour densities are greater than those of hydrogen cyanide and it is much less inflammable.

Toxicology

The signs and symptoms of its toxic effects are a combination of those produced by hydrogen cyanide and a lung irritant. Its systematic action first stimulates the respiratory centre and then rapidly paralyses it.

All concentrations of cyanogen chloride, from about 10 mg/m³ onwards, produce immediate eye irritation and lachrymation. When it is inhaled, cyanogen chloride causes in addition irritation of the nose and throat, coughing, and tightness in the chest. Dizziness, increasing dyspnoea, convulsions, retching, and involuntary urination and defecation may then occur. Unconsciousness is followed by respiratory failure and death within a few minutes.

If these effects do not result in death, signs and symptoms of pulmonary oedema may develop (persistent cough with much frothy sputum, pulmonary rales, severe dyspnoea, and marked cyanosis (US Department of the Army, 1968).

The respiratory lethal dosage in man has been estimated to be about 11 000 mg-min/m³; on this basis, therefore, it is less than half as toxic as hydrogen cyanide.

Therapy

Treatment of cyanogen chloride poisoning is palliative and supportive. In severe cases the same methods may be used as for hydrogen cyanide intoxication. In addition, it may be necessary to treat the eyes and respiratory airways as in the case of phosgene poisoning.

Use as a chemical warfare agent

In chemical warfare, cyanogen chloride would be used in the same way as hydrogen cyanide, over which it has the advantage that its tendency to ignite is much lower. Its lower toxicity is counterbalanced to a large extent by its higher volatility, and the greater densities of its liquid and vapour.

3. Vesicants

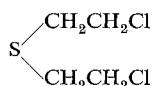
The vesicants, or blister agents, are general tissue irritants with an additional systemic action. Contact with skin tissues provokes blistering in the affected region after some delay. Contact with the eyes causes more

rapid injury and leads to inflammation and possible temporary loss of sight. Injury to the respiratory tract is similar to that caused by the lung irritants described above.

The two main groups of vesicants are the dichloroarsine derivatives and the so-called "mustards". The latter are militarily more important as they lack the initial irritant effect of the former group and have much less readily detected odours, so that they are well adapted to insidious attack. All the mustards contain at least two 2-chloroethyl groups, attached either to thioether residues (the "sulfur mustards") or to amine residues (the "nitrogen mustards").

Mustard gas was employed on a massive scale during the First World War and was the most extensively stockpiled chemical agent of the Second World War. Its properties are reviewed below.

(i) *Mustard gas (Yperite, Lost : bis(2-chloroethyl) sulfide)*



Mustard gas is a colourless to amber oily liquid of neutral reaction, freezing at 14°C when pure and boiling at 217°C with slow decomposition. At high concentrations, it has a pungent odour resembling that of horseradish, onions or garlic, much of which may be due to contamination with ethyl sulfide and similar by-products of its synthesis. Toxic concentrations of mustard gas can generally be smelt in the air, but may often not be sensed by untrained persons (Dickel et al., 1952). It is only slightly soluble in water, but may dissolve in organic solvents and fats. Chemically and physically, it is a relatively stable substance. It gradually hydrolyses in water and is quickly oxidized to its sulfoxide, a less toxic compound, by chlorinated lime. These reactions may be incomplete under some circumstances : a mustard gas accident in Germany in 1950 showed that soil that had become contaminated by mustard gas, although thoroughly and repeatedly treated with water and chlorinated lime, still contained traces of mustard gas 2 weeks after contamination (Dickel et al., 1952).

Toxicology

Mustard gas produces acute toxic effects only at supralethal dosages : central nervous excitation leads to convulsions and rapid death. Under field conditions without protection, the development of symptoms is usually in the following order : no effects are felt immediately on exposure, except to high concentrations, when there may be a tendency to sneeze, with or without smarting of the eyes. Haemorrhage, especially from the nose, is a common early symptom. The first definite symptoms generally occur in the eyes between a half and three hours after exposure, starting with a feeling

of grittiness, progressive soreness and a bloodshot appearance, and proceeding to oedema and all the phenomena of acute conjunctivitis. There is increased nasal secretion, sneezing, sore throat, coughing and hoarseness. Within 4-16 hours after exposure, these symptoms become much more marked and distressing: the eyes begin discharging and are very painful, the nasal discharge is more purulent, and the voice is husky or suppressed. Nausea, retching and vomiting, associated with epigastric pains, occur in a large proportion of subjects and may recur at frequent intervals for several hours. In severe cases, they may become intense and prolonged. Diarrhoea may set in, but is rather exceptional. The skin may begin to itch during this period and skin rashes may show as a dusky erythema of the exposed parts of the body and in the axilla and genitals, with blisters beginning to appear. At the end of 24 hours all these symptoms may have increased in severity, but death almost never occurs during the first day. During the second day, the inflammation of the respiratory tract becomes conspicuous in severe cases. The expectoration becomes abundant, mucopurulent, sometimes with large sloughs of tracheal mucosa. This is complicated by secondary infection of the necrotic respiratory membranes. Fever sets in, with rapid pulse and respiration. The infection may terminate in bronchopneumonia, with death at any time between the second day and the fourth week.

Mustard gas produces militarily significant effects over a wide range of dosages. Incapacitating eye injury may be sustained at about 100 mg-min/m³. Significant skin burns may begin at 200 mg-min/m³. The respiratory lethal dose is estimated at 1 500 mg-min/m³. 4-5 g of liquid mustard gas on the bare skin may constitute a lethal percutaneous dosage, while droplets of a few milligrams may cause incapacitation.

Blisters caused by mustard gas may heal in 2 or 3 weeks, and ulcerations after 6 or 8 weeks. The blisters are often followed by a crop of furuncles or pustules, generally on and around the burned area. The site of healed mustard burns is hypersensitive to other trauma. Moreover, there seems to be a general lowering of resistance after mustard gas poisoning, and therefore increased susceptibility to infections such as influenza, bronchitis, pneumonia and tuberculosis (Sollman, 1957). It is not uncommon for chronic bronchitis and emphysema to outlast the acute poisoning (Wirth et al., 1967).

Several instances of delayed keratitis of the eye have been ascribed to mustard gas exposures some forty years earlier (Amalric et al., 1965).

The demonstration of mutagenic, carcinogenic and teratogenic actions of the mustards has recently aroused considerable interest. Both sulfur and nitrogen mustards have been shown to be strongly mutagenic when tested on *Drosophila* and other lower organisms (Auerbach, 1949). A teratogenic action has been demonstrated in chickens and rats (Szirmai, 1966; Salzgeber, 1968). A carcinogenic action has been demonstrated with both sulfur

and nitrogen mustards after parenteral administration as well as after inhalation in mice (Heston, 1953a, 1953b). In man, chronic exposure of factory workers to mustard gas has also produced a marked excess of pulmonary tumours within the lung at the same site as in mice and of the same histologic type (Yamada, 1963). A tenfold increase (30 cases against about 3 expected) in respiratory tract cancer (mainly lung) was observed in such workers employed in Japanese factories during the Second World War (Wada et al., 1968). An examination of the mortality data on 1 267 British war pensioners who suffered from mustard gas poisoning in the 1914-18 war, and who were still alive on 1 January 1930, showed that almost all (over 80%) had chronic bronchitis at that date. In subsequent years an excess of deaths attributed to cancer of the lung and pleura was observed amongst them (29 deaths found compared with 14 expected) (Case & Lea, 1955.) Furthermore, observations on American veterans of the First World War suggest that the incidence of lung cancer was slightly increased in men who had been subjected to mustard gas poisoning (Beebe, 1960).

Therapy

Treatment is palliative and supportive. The vesication may be treated in much the same way as skin burns.

Use as a chemical warfare agent

In chemical warfare, mustard gas would probably be used to create long-lasting contact hazards. For this purpose it would be disseminated as a liquid spray to contaminate the ground, vegetation, and equipment. During the travel of the spray, it would create a short-term air-borne skin hazard as well. In warm weather there would be appreciable evaporation of the spray fallout, and as the vapour has little smell and its vesicant action is delayed, it would be possible for anyone in the area to absorb a casualty-producing dose without being aware of any exposure. This would rarely be lethal, but as mustard gas can produce damaging effects at dosages as low as 100 mg-min/m³, this insidiousness has considerable military attractions. Airborne concentrations of mustard gas that would very probably be lethal are unlikely to be set up except by weapons disseminating aerosols (Vocci et al., 1963).

Occupation of ground contaminated with mustard gas at a density of 10-60 mg/m² would be hazardous without protection or decontamination measures. Yet the acute hazard would be less severe than with VX (see below) even at these higher densities, because the lethal percutaneous dosage of mustard gas required is so much greater and because the toxic effects are generally milder and more delayed.

4. The nerve gases

The designation "nerve gas" is used to denote organophosphorus compounds that inhibit tissue cholinesterase in man at small dosages; it is an allusion to the mode of action of these substances, which consists essentially of a disruption of nerve impulse transmission. At the present time, two families of nerve gas are important for military purposes: the G-agents, consisting of alkyl esters of methylphosphonofluoridic acid or of dialkylphosphoramidocyanidic acids, and the V-agents, consisting of alkyl esters of *S*-dialkylaminoethylmethylphosphonothiolic acids. It will be noted that these two families theoretically include several hundred different chemical substances.

Chemically and toxicologically, the nerve gases are similar to many of the commercial organophosphorus pesticides and, while information on severe nerve gas poisoning in man is rather limited, there are considerable data on human exposure to some of these pesticides. Insecticides, such as tetraethyl pyrophosphate (TEPP) and parathion, have caused a number of fatalities as a result of misuse or accidental poisoning. In Japan there were more than 6 000 cases of parathion poisoning within a five-year period (Namba & Hiraki, 1958) and the use of this compound and of some other organophosphorus insecticides of similar toxicity has been curtailed or abolished in several countries.

There is no shortage of data in the unclassified literature on what appear to be the most attractive of the G-agents for military uses. Thus, detailed information is available on the toxicological, chemical and physical properties and methods of preparation of the following:

ethyl <i>N,N</i> -dimethylphosphoroamidocyanidate	(tabun, GA)
isopropyl methylphosphonofluoridate	(sarin, GB)
1,2,2-trimethylpropyl methylphosphonofluoridate	(soman, GD)

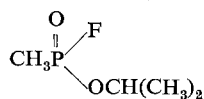
There is rather less information on certain other G-agents that are believed to be attractive as chemical warfare agents, notably on cyclohexyl methylphosphonofluoridate (GF). The properties of sarin are reviewed below.

On the V-agents, there is much less information. Their general structural formula as published in the literature is $\text{RO} \cdot \text{CH}_2\text{P}(\text{O}) \cdot \text{SCH}_2\text{CH}_2\text{NR}'\text{R}''$, where R, R' and R'' are alkyl groups. What has not yet been published are the individual structures of those members of this large family that are regarded as most attractive by the armed forces, so that substances like VE, VM and VX are known only by code names.

Of the individual V-compounds for which data on toxicological, physical and chemical properties are to be found in the unclassified literature, one that appears to be particularly suitable for use as a chemical warfare agent is that in which R is an ethyl group, and R' and R'' are methyl groups.

According to Julea & Popa (1966), this compound is referred to as VX ; its properties are reviewed later.

(i) *Sarin, GB : (isopropyl methylphosphonofluoridate)*



Sarin appears to be one of the most important of the G-agents. When pure, it is a colourless liquid that is volatile at ordinary temperatures, giving off a colourless and odourless vapour. The freezing point is -56°C and the boiling point 147°C .

Sarin is miscible with water in all proportions. In strongly alkaline solutions of pH 12 or higher, it is hydrolysed extremely rapidly, yielding non-toxic products, while between pH 4 and 7 the hydrolysis takes place at such a slow rate as to be of little practical significance, for example, in decontamination procedures.

Toxicology

Sarin, like all nerve gases, may be absorbed through any body surface. When dispersed as a vapour or aerosol, or adsorbed on dust, it is readily absorbed through the respiratory tract or conjunctivae. The route through which absorption is most rapid and complete is the respiratory tract.

Signs and symptoms of nerve gas poisoning as listed by Grob (1956) are given in Table 2. The time course of their appearance varies with the degree and route of absorption. After inhalation, bronchoconstriction and respiratory distress appear before pronounced symptoms involving the gastro-intestinal tract develop.

People with a history of infections of the upper respiratory tract would probably show more pronounced interference with respiration. Exposure to sarin vapour concentrations that were just lethal would probably result in death within one to a few hours and exposure to several times the lethal concentration would probably be fatal within several minutes to half an hour (Grob, 1956 ; Grob & Harvey, 1958).

It is possible that persistent paralysis—a neurotoxic effect due to demyelination of axon sheaths seen in poisoning by some organophosphorus compounds—might develop among victims surviving many times the lethal dose of sarin. Although this effect has not been reported in man, it has been experimentally produced with sarin in hens, a species similar to man in its response to the neurotoxic effect of organophosphorus compounds (Davies et al., 1960).

In volunteers, a single oral dose of 0.022 mg/kg produced mild symptoms and an additional 0.008 mg/kg administered within 8 hours resulted in

TABLE 2. SIGNS AND SYMPTOMS OF NERVE-GAS POISONING *

Site of action	Signs and symptoms
	<i>Following local exposure</i>
<i>Muscarinic</i>	
Pupils	Miosis, marked, usually maximal (pin-point), sometimes unequal
Ciliary body	Frontal headache; eye pain on focusing; slight dimness of vision; occasional nausea and vomiting
Conjunctivae	Hyperaemia
Nasal mucous membranes	Rhinorrhoea; hyperaemia
Bronchial tree	Tightness in chest, sometimes with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion; cough
Sweat glands	Sweating at site of exposure to liquid
<i>Nicotinic</i>	
Striated muscle	Fasciculations at site of exposure to liquid
	<i>Following systemic absorption</i>
<i>Muscarinic</i>	
Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion; dyspnoea, slight pain in chest; increased bronchial secretion; cough; pulmonary oedema; cyanosis
Gastrointestinal	Anorexia; nausea; vomiting; abdominal cramps; epigastric and substernal tightness (? cardiospasm) with "heartburn" and eructation; diarrhoea; tenesmus; involuntary defecation
Sweat glands	Increased sweating
Salivary glands	Increased salivation
Lachrymal glands	Increased lachrymation
Heart	Slight bradycardia
Pupils	Slight miosis, occasionally unequal; later, more marked miosis
Ciliary body	Blurring of vision
Bladder	Frequency; involuntary micturition
<i>Nicotinic</i>	
Striated muscle	Easy fatigue; mild weakness; muscular twitching; fasciculations; cramps; generalized weakness, including muscles of respiration, with dyspnoea and cyanosis
Sympathetic ganglia	Pallor; occasional elevation of blood pressure
<i>Central nervous system</i>	Giddiness; tension; anxiety; jitteriness; restlessness; emotional lability; excessive dreaming; insomnia; nightmares; headache; tremor; apathy; withdrawal and depression; bursts of slow waves of elevated voltage in EEG, especially on hyperventilation; drowsiness; difficulty in concentrating; slowness of recall; confusion; slurred speech; ataxia; generalized weakness; coma, with absence of reflexes; Cheyne-Stokes respiration; convulsions; depression of respiratory and circulatory centres, with dyspnoea, cyanosis, and fall in blood pressure.

* After Grob (1956).

moderate symptoms. The estimated oral lethal dose was 0.14 mg/kg (Gob & Harvey, 1958).

Sarin splashed in the eye may be lethal at about 0.05 mg/kg (Kondritzer et al., 1959).

The toxicity of sarin applied to the skin has been variously estimated at 100-200 mg/man (FOA, 1967) and 1 700 mg/man (US Department of the Army, 1963). Sarin vapour is not appreciably absorbed through the skin

(Grob & Harvey, 1953) and only to a limited extent through the eyes (Albanus et al., 1966). Respiratory LCT_{50} estimates for sarin vapour or aerosol include figures of 50-100 mg-min/m³ (FOA, 1967) and, for breathing rates of about 15 litres per minute, 100 mg-min/m³ (US Department of the Army, 1963). Increased lethality of sarin, particularly through the skin, was demonstrated in experimental animals when they were kept at an elevated environmental temperature (38°C) (Craig et al., 1959).

Therapy

The effects of both nerve gases and organophosphorus insecticides have been related to the inhibition of tissue cholinesterases at synaptic sites, and to an accumulation of excessive amounts of acetylcholine in effector organs. This is responsible for the production of the muscarinic, nicotinic and central nervous system symptoms described in Table 2. Deaths from sarin poisoning can be attributed to respiratory and circulatory failure.

The inhibition of acetylcholinesterase rapidly becomes more or less irreversible and the effects of repeated daily exposure are cumulative to some extent.

Because the originating biochemical lesion in nerve gas poisoning has been identified, it has become possible to elaborate therapeutic procedures from first principles, and many of these procedures are comparatively effective.

The toxic effects of accumulating acetylcholine may be partly countered with anticholinergic drugs,¹ such as atropine, and for this purpose individual soldiers of the more sophisticated modern armies are equipped with auto-injectors for self-administration of the drugs as soon as the effects of nerve gas poisoning begin to be felt.

Anticholinergic drugs are not capable of reactivating inhibited acetylcholinesterase. They can counter only the muscarinic effects of nerve gas poisoning. Reactivators are available, however, that can counter some of the nicotinic effects, including the paralysis of the respiratory muscles. In the absence of such reactivators, the only way of maintaining respiration is by the use of positive-pressure artificial respiration. At present, the best reactivators are certain oximes, particularly salts of pralidoxime iodide and obidoxime; some armies include these in their autoinjector atropine preparations. Their principal drawback lies in their inability to penetrate the blood-brain barrier, so that they are unable to counter the effects on the central nervous system. In addition, with most nerve gases, the inhibited acetylcholinesterase undergoes a chemical change after taking up a nerve

¹ Anticholinergic drugs are generally highly poisonous substances in their own right. As the dosages in which they are effective against nerve gas poisoning are usually higher than their own toxic dosages, they can be employed as antidotes only with considerable care and expertise.

gas residue, which greatly impedes its reactivation by oximes. With some agents, such as soman (but not sarin or VX), this change may occur so rapidly that it becomes impossible to administer oximes in time. Atropine and prolonged artificial respiration then become the only possible therapy at present available.

If exposure to many times the lethal dose has occurred, or if treatment has been too long delayed, death may occur in spite of all efforts to save the patient. Even if recovery from sarin poisoning occurs, irreversible central nervous system damage can ensue because of anoxaemia.

Use as a chemical warfare agent

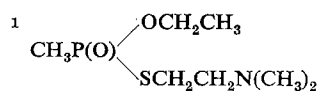
In chemical warfare, sarin could be used to create short-term respiratory hazards. In warm climates it is sufficiently volatile for lethal vapour concentrations to be readily attainable, but the airborne concentration would generally be increased by disseminating it as a rapidly evaporating aerosol. This can be done quite simply by including a heavy explosive charge in the weapon. Weapons based on this principle have apparently been developed for almost all delivery systems. Any sarin that is not immediately vaporized or aerosolized would soon precipitate to form a contact hazard on the ground, and thereafter evaporate, at a rate determined mainly by the ground temperature, to reinforce the respiratory hazard.

(ii) *Agent VX*

VX appears to be the most important of the V-agents. These were first prepared in 1955 as candidate insecticides and were a logical development of the Amiton-type insecticides described by Ghosh & Newman (1955).

The unclassified literature contains little information on the V-agents themselves, but it is reasonable to assume that their toxicological properties are qualitatively similar to those of the dialkyl *S*-dialkylaminoethyl phosphorothiolate esters (the Amiton-type insecticides). Most of the accessible data are contained in a study by Aquilonius et al. (1964) of the toxicology of a group of V-agents, Amiton derivatives and "Tammelin esters".

Ethyl *S*-dimethylaminoethyl methylphosphonothiolate¹ (referred to as VX by Julea & Popa (1966) was found by Aquilonius et al. (1964) to be the most toxic of the compounds they studied and considerably more toxic than sarin, the intraperitoneal LD₅₀ values in mice being determined as 0.05 and 0.45 mg/kg respectively. They announced that in future papers the mode of action following various routes of administration would also be described "with special regard to percutaneous absorption". Since



then, however, no publication has been traced in the unclassified literature on this subject.

VX is a non-volatile liquid at room temperatures, with a boiling point of 80°C at 0.06 mm Hg (Tammelin, 1957). Its solubility in water is between 1% and 5% at room temperature. The V-agents as a class are more resistant to hydrolysis than sarin, particularly in alkaline solution (FOA, 1967).

Toxicology

The toxicology of the V-agents is essentially the same as that of other nerve gases (see sarin). It may be noted however that, in contrast to sarin, they are unaffected by phosphoryl phosphatases (Tammelin, 1958), the enzymes responsible for the hydrolysis of many organophosphorus compounds in the body, and display a slightly slower onset of symptoms (Aquilonius et al., 1964). In addition, they generally cause gastro-intestinal pains preceding bronchoconstriction as the initial symptom, in contrast to the G-agents (FOA, 1967).

FOA (1967) give the following ranges of figures for the estimated lethal dosage of the V-agents in man: 2-10 mg of liquid on the skin for the dermal absorption route, and 5-10 mg-min/m³ of aerosol in the air for absorption through the respiratory tract.

Therapy

The therapy of V-agent poisoning is essentially the same as for the G-agents (see sarin above).

Use as a chemical warfare agent

In chemical warfare, VX could be used to create long-term contact hazards by contamination of ground, vegetation and equipment, or to create short-term respiratory hazards. For the latter, it would have to be disseminated as a fine aerosol, as it lacks the volatility to provide a lethal field concentration of vapour. A coarse liquid spray would be highly effective for ground contamination or skin attack, but would not be a respiratory hazard unless the spray included very fine droplets. It can be assumed that appropriate weapons have been developed for the different purposes.

A fine aerosol of VX would probably not be effective in skin attack: the small droplet size would mean a poor impaction efficiency on the skin, as compared with the larger droplets contained in a spray.

Occupation of ground contaminated with VX at a density of 0.5-5 mg/m² would be extremely hazardous without protective clothing or decontamination measures.

5. Other lethal chemical warfare agents

Two other groups of chemical agents of potential military application should be mentioned ; both of these attracted considerable attention during the Second World War.

The first is the family of aryl carbamates structurally related to the alkaloid physostigmine. They are anticholinesterase agents, some of which have toxicities comparable to those of the G-agents. The fact that they are solids and that chemically they are not too stable greatly detracts from their use as chemical warfare agents, and they are mentioned here only as examples of easily synthesizable chemicals embodying the toxic principle of a poisonous naturally occurring substance. One of the more extensively studied members of the family is 3-diethylaminophenyl *N*-methylcarbamate methiodide, whose inhalation toxicity in man has been estimated at around 100 mg-min/m³.

The second is the group of naturally occurring, toxic proteins of high molecular weight, exemplified by ricin and botulinal toxin. The shortcomings of the group as chemical warfare agents have been mentioned earlier, but nevertheless these two in particular have military advantages that are not negligible.

Ricin is potentially available on a large scale as a by-product of castor bean processing. Comparatively successful weapons were developed during the Second World War to disseminate it as a chemical warfare agent. The human lethal dosage of aerosols of the crude toxin has been estimated to be about the same as that of sarin ; for a more highly purified material it would not be unreasonable to expect a toxicity exceeding that of VX. While a nation that could produce nerve gases in bulk would probably not be interested in ricin as a chemical warfare agent, particularly as its toxic effects are delayed, a nation that lacked such a manufacturing capability might well be attracted by it. Detailed information has recently become available in the patent literature, both on production methods for extracting it in a form explicitly suited to chemical warfare and on the design of weapons for its dissemination.

The botulinal toxins, being among the most toxic substances known to man, have long been regarded as potential chemical warfare agents. Their properties are reviewed below.

(i) *Botulinal toxins*

The toxins of *Clostridium botulinum* are the causative agents of botulinal food poisoning (botulism).

Cultivation of the bacterium (a sporulating saprophyte) and purification of the neurotoxic proteins extractable from the culture are straightforward processes and make it possible to produce toxins on a fairly large scale in bacteriological laboratories.

Every strain of *Clostridium botulinum* produces one specific antigenic neurotoxin which can be isolated, identified, and labelled (A, B, C, D, E or F); type A has been crystallized. The toxins are chemically and antigenically different. The molecule of type A toxin appears to comprise a single polypeptide chain. Type A toxin crystals are white and odourless, of unknown taste.

The botulinal toxins are destroyed by boiling for 5 to 10 minutes; they are detoxified by formaldehyde and precipitated by their specific anti-toxin (Lamanna & Carr, 1967). In cold, stagnant water, they are stable for a week. In food, they may persist a long time, provided air is excluded (US Department of the Army, 1965).

Toxicology

Botulinal toxins can cause poisoning following absorption through any mucous membrane surface, e.g., the digestive tract or bronchial or conjunctival mucosa; only healthy normal skin prevents absorption. The lethal doses are generally largest by the oral route, smaller by inhalation, and smallest by parenteral administration. In the case of oral administration, a large fraction of the ingested toxin becomes ineffective as a consequence of enzymatic breakdown (Lamanna & Carr, 1967). Nevertheless, the mortality rate in most outbreaks of botulism is high (estimated by Dreisbach, 1969, as being approximately 60% and by Wirth et al., 1967, as being 15-90%).

The basic process of poisoning is believed to be the same for all types of toxin after their absorption. To be effective, the toxins must reach the circulatory system, which carries them until they find their specific receptors at the neuromuscular junction.

Once there, they produce an effect that renders the junction incapable of releasing acetylcholine in quantities sufficient to evoke a contraction of the muscle fibre. Nerve conduction *per se* is not impaired in peripheral nerves by the toxin, and the postsynaptic excitability of muscle fibres remains normal. These facts have been established in man (Tyler, 1963). The consequent muscular weakness is observed in all voluntary muscles innervated by peripheral nerves that are cholinergic in character, both preganglionic and postganglionic autonomic fibres being affected, and in skeletal muscles innervated by somatic nerves. Evidence for a central effect of the toxin is not yet conclusive (Lamanna & Carr, 1967), although a specific and primary action at the autonomic ganglia is believed by some to be of the greatest importance.

The symptomatology in man following inhalation of botulinal toxin aerosols has not been described, but that following ingestion is well reported. Early signs and symptoms appear usually within 6-48 hours, but sometimes later. The most consistent are a combination of extreme weakness,

malaise, dry skin, dilated and unresponsive pupils, blurred vision, dry coated tongue and mouth, and dizziness when upright. As the patient becomes worse, he develops progressive muscular weakness with facial paralysis, and weakness of arms, legs and respiratory muscles. He may die of respiratory failure unless artificial respiration is applied. There may be associated cardiac arrest or complete vasomotor collapse.

For the type A toxin, the intraperitoneal injection of less than 3×10^{-8} mg has been shown to kill a mouse. This extraordinary toxic potency would account for the capacity of the protein to act as an oral poison in spite of its sensitivity to proteolytic enzymes. For man, the fatal oral dose may be 1 000 times, and for monkeys 750 times, the parenteral dose. Man is believed to be the most sensitive of known species; the estimated oral lethal dose is 7 000 mouse intraperitoneal lethal doses, and the estimated respiratory lethal dose is 7 such mouse units (Lamanna & Carr, 1967; Herrero et al., 1967). However, until quantitative studies have been made to define a realistic basis of comparison, available data are insufficient to make a scientific judgement of the true LD_{50} for man (Lamanna, 1959). Further estimates of the human lethal respiratory dose have recently appeared in the literature; one such estimate for type A toxin is 0.0003 mg (Markkula, 1967), corresponding to an inhalation dosage of 0.02-0.05 mg-min/m³.

In the case of rhesus and squirrel monkeys, very steep dose-response curves have been obtained in toxicity determinations by intravenous injection of the type A toxin (Herrero et al., 1967). For the significance of this finding, see Annex 3, p. 85.

Therapy

The botulinal toxins elicit an immune response from the body, and toxoid immunoprophylaxis is feasible. Polyvalent antisera (at least against types A, B, C, D and E) are also available, either for prophylactic use or for administration after intoxication. With suitable supportive treatment (Hill & Chesney, 1966; Wirth et al., 1967), surviving patients generally recover in about a week.

Use as chemical warfare agents

Botulinal toxins have been openly discussed since before the Second World War as potentially among the most dangerous substances for use in chemical warfare. Although highly toxic, it is not at all certain that they have in fact been developed as chemical warfare agents, in view of their chemical and physical instability. Such difficulties are probably not insurmountable and, with continued research on this problem, their dissemination as aerosols or through communal water supplies could become feasible, if it is not so already. (Estimates of effects by both routes, aerosol and

water carriage, are given in Table 9, Annex 3, and Annex 5.) Preventive immunization is feasible, but therapeutic measures could be applied only to very small numbers of exposed individuals with little effect on the overall mortality that could be expected. Decontamination of the environment would be required, and all food would have to be heat sterilized before consumption.

B. INCAPACITATING AGENTS

Introduction

The idea of "incapacitating" agents is an old one, and the possibilities of such substances for waging a "humane" war have been discussed at least since the nineteenth century. Only recently, however, have compounds been discovered that are potentially suitable for this purpose. Although a great number of chemicals exist that can produce a non-fatal and prolonged but temporary incapacitation under controlled conditions, very few, if any, can be expected to do so in extensive conflict situations. Apart from the usual conditions that govern the selection of compounds for possible use in chemical warfare, two other difficulties are involved. First, the agent must be one whose incapacitating inhalation dosage is sufficiently far removed from the lethal inhalation dosage to make it unlikely that fatalities will occur, even in the immediate vicinity of the disseminating device. Secondly, the agent must be one that will disable groups of people to an extent that is both significant from the military point of view and predictable. Neither of these difficulties appears to have been fully overcome in the two groups of substances at present available that seem to be most suitable for use as incapacitating agents.

1. Bacterial enterotoxins and related substances

Many bacterial toxins can produce acutely incapacitating effects at dosages that are far below their lethal ones. Typical effects of this type are pyrexia, emesis, and diarrhoea: these may occur with sufficient violence and persistence to immobilize a subject completely for periods of several hours. However, although certain toxins are capable of producing these effects in man at microgram dosages, a few milligrams of the same substances have killed laboratory animals, and it is thus to be expected that some fatalities would result from their military use. But this consideration may be outweighed by the comparative cheapness, ready availability, and speed of action of the toxins. The properties of one group are reviewed below.

(i) *The staphylococcal enterotoxins*

The acutely incapacitating nature of staphylococcal food poisoning suggests the use of staphylococcal enterotoxins in chemical warfare. It is

known that the effects of their use in aerosol form have been studied in experimental animals in military chemical warfare establishments. The subject of the staphylococcal enterotoxins has recently been reviewed by Lamanna & Carr (1967).

Staphylococcal cultures generally contain a considerable number of biologically active compounds, which may sometimes include one or more types of enterotoxin. Four distinct antigenic types of the enterotoxin have been described (types A, B, C and D), and it is likely that others will be discovered as more staphylococcal strains are screened; a given strain may provide more than one antigenic type of toxin (Casman et al., 1963).

Staphylococcal enterotoxins have been shown to be simple proteins. The most extensively studied is the type B toxin (SEB) which, although not yet crystallized, has been purified (Schantz et al., 1965) to a stage permitting a complete aminoacid analysis (Spero et al., 1965) and biophysical characterization of the molecule (Wagman et al., 1965). The rest of this section will be mainly concerned with the type B toxin.

SEB has a molecular weight of around 35 000. It appears to be a more stable substance than the botulin toxins, for example, and has a remarkable heat resistance. Thus, ordinary cooking cannot be relied upon to render heavily contaminated foods harmless: the enterotoxins can withstand boiling water for 30 minutes (US Department of the Army, 1965).

Toxicology

SEB is active both orally and parenterally. Its toxicity has been studied when administered via the oral, intraperitoneal, and intravenous routes and, as an aerosol, via the respiratory route. Emetic doses are generally smaller by the intravenous than by the oral route. In view of this it seems likely that the primary site of action of SEB lies outside the intestinal lumen: it is thus probably not strictly an enterotoxin. Nevertheless, there may be some direct irritant action on the mucosa of the gastrointestinal tract. It has been suggested that SEB evokes its characteristic vomiting response in cats and monkeys by stimulating the vagal and sympathetic nerves (Clark et al., 1962). The nature of the inciting stimulus in the gut remains obscure.

Fatal effects from aerosol inhalation in monkeys have been observed. These have been shown to arise chiefly from pulmonary oedema (Lamanna, 1961).

No clinical studies of the effects of inhalation of SEB in man have been published, although there is extensive literature on staphylococcal food poisoning. In the latter, symptoms normally begin within ½-6 hours (generally around 3 hours) after ingestion of the contaminated food, often quite suddenly and violently. The onset time may well be shorter if SEB enters the body via the respiratory route. The heralding sign is increased salivation, which is followed by nausea, vomiting, abdominal pain, watery

diarrhoea, and prostration. Pyrexia and hypotensive effects have been observed in some cases. Recovery generally occurs within 24 hours. Mortality from staphylococcal food poisoning ranges from 0-5% in different outbreaks, and death occurs only when the dehydration is excessive, particularly in infants or the debilitated (US Department of the Army, 1965 ; Morse, 1965).

The literature contains no estimates of the human incapacitating or lethal doses of SEB, either by the oral or the respiratory route, and it is known that large differences in susceptibility exist among individuals. Figures have been obtained with monkeys, cats and mice (Lamanna & Carr, 1967). Inhalation of 0.03 mg was sufficient to cause emesis in rhesus monkeys (Lamanna, 1961).

Therapy

SEB is able to induce the production of neutralizing antibodies. An anatoxin (toxoid) can be prepared by formaldehyde treatment that has demonstrable immunizing capacity in the rhesus monkey. The use of anti-toxin or toxoid in man has yet to be fully evaluated. Treatment is supportive.

Use as a chemical warfare agent

Because the staphylococcal enterotoxins are more stable, they would presumably be rather easier to disseminate effectively in aerosol form than the botulin toxins, so it can probably be assumed that their military use in this form would not present insuperable technical problems.

The prostrating, but generally short-lived, effects of staphylococcal food poisoning suggest that the enterotoxins involved might make effective incapacitating agents, particularly as they have a rather rapid onset of action. But in view of their rather high toxicity, even though their incapacitating dosage may be very low, their use in aerosol form or as water contaminants would almost certainly lead to an appreciable proportion of deaths, a proportion that would be unpredictable in the present state of knowledge.

2. Psychochemicals

The other main group of potential incapacitating agents comprises certain highly potent psychotropic drugs. By affecting the central nervous system in a variety of ways—the precise pharmacological mechanisms at work are unclear—these drugs can so upset a subject's pattern of behaviour as to suggest that exposed soldiers might become incapable of carrying out their military functions.

The relationship between the behaviour of an isolated subject under controlled conditions and the behaviour of groups of exposed soldiers in combat situations is extremely obscure. In the first place, drug-induced

behavioural changes in an individual may be strongly influenced by the behaviour of other individuals in his group. With LSD, for example, it has been demonstrated that drugged soldiers may behave in an apparently normal manner within a unit containing undrugged soldiers. On this count, it would seem that the effects of a psychochemical on a group could be accurately predicted only if its members could all receive doses that would produce similar behavioural changes. This would require a foreknowledge of the responses of each individual to dosages of the drug, together with equipment for ensuring that each individual received the dosage suited to him.

But there is a more fundamental uncertainty, one which is quite unresolvable : that resulting from the influence of individual motivations. With a sufficiently powerful motivation a subject may accomplish quite complicated tasks even though he is obviously severely drugged and behaving irrationally. It is thus possible that if individual reactions to drug-distorted perceptions (there is no evidence to suggest that LSD is abnormal among psychotropic drugs in this respect) happened to coincide with some useful military activity and were sufficiently strongly motivated, the performance of a fighting unit might increase rather than diminish under the influence of a psychochemical. Instances of this are known in history. But the nature of individual motivations and the physical responses to them are not predictable : a combat unit may be as likely to excel itself as to behave in an uncoordinated manner or to relapse into a stupor. Furthermore, motivations in war cannot be simulated in peacetime with any degree of confidence. The likely military effects of psychochemicals can thus be guessed at but never accurately predicted.

With some psychochemicals, behavioural disturbances may be complicated by physical incapacitation. These may include such effects as blurred vision, fainting, and vomiting. The combined incapacitating effect may be sufficiently great to suggest possible military applications.

The properties of two psychochemicals are reviewed below. Other possible agents include certain cannabinoids, amphetamines, and phenothiazines.

(i) *LSD ((+)-N,N-diethyllysergamide)*

LSD (sometimes known as LSD 25) can be prepared from lysergic acid, which is obtained by fermentative processes from naturally occurring substances. The crystalline free base is practically insoluble in water. The tartrate, which has been produced for medical use, is readily soluble in water and maintains its activities over long periods of time (Hofmann, 1968 ; Hollister, 1968.) A 0.5% solution is tasteless.

LSD is reported to be sensitive to heat and light and to be readily destroyed by oxidizing agents, including the chlorine in superchlorinated water.

Toxicology

LSD is highly active when administered orally or parenterally, and presumably also by inhalation.

The following three characteristic types of symptoms have been reported :

Somatic symptoms—dizziness, weakness, tremors, nausea, drowsiness, paraesthesiae, blurred vision

Perceptual symptoms—altered shapes and colours, difficulty in focusing on objects, a sharpened sense of hearing and, rarely, synaesthesiae

Psychic symptoms—alterations in mood (happiness, sadness or irritability at varying times), tension, distorted time sense, difficulty in expressing thoughts, depersonalization, dreamlike feelings, and visual hallucinations.

Physical effects are relatively few, dilated pupils, hyper-reflexia, increased muscle tension, incoordination, and ataxia being the most common. Effects on pulse rate and blood pressure are variable, as are changes in appetite and salivation. The clinical syndrome tends to follow a sequential pattern with somatic symptoms first, perceptual and mood changes next, and finally psychic changes, although there is considerable overlap between these phases. Specific types of reaction, such as paranoid ideation, are probably a matter of personal predisposition.

Many of the emotional and behavioural effects of LSD are due to an excitatory effect of the drug, interpreted and elaborated by the subject. The emotion experienced, and the ensuing behaviour, may vary widely from person to person and from situation to situation. In a group comprising others in the same circumstances, the heightened arousal might well be expressed in greater talkativeness and animation and be interpreted as elation. In a strange setting, with unfamiliar people, where some nervousness may be already present, anxiety is perhaps more likely (Smart et al., 1967).

With oral administration, the first signs of intoxication may be expected 30-60 minutes after ingestion, the symptoms reaching a peak after 3-5 hours (Hollister, 1968). An intoxication usually lasts about 12 hours (Council on Mental Health and Committee on Alcoholism and Drug Dependence, 1967). There is no indication that children react generally to LSD in a different way from adults. The risk of severe reactions to LSD is increased by the presence of cardiovascular diseases, pregnancy or epilepsy (Hollister, 1968). Recent studies suggest that LSD may cause chromosomal damage and the possibility of a teratogenic action has been discussed (Council on Mental Health and Committee on Alcoholism and Drug Dependence, 1967 ; Smart et al., 1968).

An oral dose of 0.2-0.4 mg of LSD taken by a person who has not acquired tolerance will often induce fairly complete disorganization. Some physical effects are experienced with doses as low as 0.03 mg, but as the dose increases so do confusion and intellectual impairment (Hollister, 1968).

Tolerance to LSD develops rapidly, but is usually lost in 2-3 days. Some chronic users have built up their LSD doses to 1 or 2 mg over a period of 3 days (Council on Mental Health and Committee on Alcoholism and Drug Dependence, 1967 ; Hollister, 1968).

LSD can be expected to be equally active by practically every route of introduction, including inhalation and injection. A degree of incapacitation that could have military significance has been reported following inhalation of dosages in the 10-100 mg-min/m³ range (FOA, 1967).

The lethal dose of LSD is controversial, and a variety of widely divergent estimates have been made. Death might occur as a consequence of behavioural disorders, as well as of intoxication.

Therapy

Contradictory reports on the biochemical effects of LSD allow no conclusive statement on its mechanism of action, and it is still too early to specify the chain of events leading from biochemical changes to the behavioural disturbances.

Depressants may be used to counter some of the effects of LSD intoxication. Effective antagonists include the phenothiazines, triflupromazine, prochlorperazine, thiopropazate, and barbiturates. Promazine and promethazine are ineffective, while reserpine aggravates the LSD state (Hollister, 1968).

Use as a chemical warfare agent

In chemical warfare, LSD might be used either as a water contaminant or to produce a short-term inhalation hazard, with a threat of delayed incapacitating effects. Its use as a water contaminant is considered in some detail in Annex 5.

To create an airborne hazard, LSD could be disseminated as an aerosol, but because it is a solid and comparatively thermolabile substance, it would be difficult to do this without elaborate aerosol generators. This fact, together with its relatively high cost and the unpredictability of its effects on groups, may make it unattractive as a chemical warfare agent, despite its potency.

(ii) *Agent BZ*

BZ is a psychochemical that has been developed specifically as an incapacitating agent for chemical warfare. It is an anticholinergic agent closely related chemically and pharmacologically to such benzilates and

other glycolates as Ditran and aprofen. Its chemical structure is a military secret, but it is believed to be a phenylglycolate ester of an aminoalcohol, such as 3-quinuclidinol.

BZ is a white crystalline solid, whose physical and chemical properties and thermal stability permit effective aerosols to be generated from pyrotechnic compositions.

Toxicology

BZ is apparently intended primarily for use in aerosol form to create a respiratory hazard. Effective doses can also be absorbed through the skin from suitable liquid formulations of the agent, although this must almost certainly be a far less efficient process than inhalation of the aerosol.

The signs and symptoms of BZ poisoning are increased heart rate, dry skin and mouth, mydriasis and blurred vision, ataxia, disorientation, and confusion progressing to stupor. Small doses of BZ cause sleepiness and decreased alertness. The casualty can be recognized by an elevation in heart rate, dry skin and lips, and elevated skin temperature. Large inhaled concentrations will produce a progressive intoxication in the untreated casualty as follows (US Department of the Army, 1967):

1-4 hours : tachycardia, dizziness, ataxia, vomiting, dry mouth, blurred vision, confusion and sedation progressing to stupor

4-12 hours : inability to respond effectively to environmental stimuli or to move about

12-96 hours : increasing activity, random unpredictable behaviour ; gradual return to normal 2-4 days after exposure.

In the case of percutaneous intoxication, symptoms may take as long as 36 hours to appear (US Department of the Army, 1968).

The EC_{50} of BZ that produces a militarily significant degree of incapacity in man has been reported to be 110 mg-min/m^3 , and the EC_{30} to be 90 mg-min/m^3 (Klose, 1968). No information is available on estimates of lethal dosages or on experimental data with laboratory animals.

Therapy

Most of the physically incapacitating effects of BZ intoxication can be explained adequately in terms of cholinergic blockade, and the central effects resemble those of known anticholinergic psychomimetic drugs. Its mechanism of action is thus very similar to that of atropine, although it is far more potent than the latter in its effects on the central nervous system, where it is capable of disturbing the higher integrative functions of memory,

problem solving, attention and comprehension (US Department of the Army, 1968). Like atropine, it inhibits the sweating mechanisms, and if used in hot, dry climates it may thus induce severe heat-stroke.

Just as anticholinergic drugs can counter some of the effects of anticholinesterase agents, anticholinesterase drugs can counter some of the effects of anticholinergic agents. Physostigmine, for example, is an effective antagonist of BZ poisoning. However, anticholinesterase drugs containing quaternary ammonium groups, such as pilocarpine, neostigmine, and prostigmine, are ineffective antagonists, as they are incapable of penetrating the blood-brain barrier (US Department of the Army, 1968).

Anticholinesterase drugs are highly poisonous materials and their correct use requires considerable skill. Atropine or other nerve gas antidotes should be held in readiness to cope with any overdose.

Use as a chemical warfare agent

BZ apparently possesses the physical and chemical properties that are essential for potential use in chemical warfare, and its cost is considerably less than that of LSD. Effective field concentrations for military purposes seem to be feasible, and weapons have been designed to disseminate it. As an incapacitating agent, the principal drawbacks of BZ seem to be unpredictability of its effects on troops in the field, and the severe or even fatal injuries that may result from its use in hot, dry weather. There is no information on the risk of directly lethal dosages being set up in the field, but this is unlikely to be negligible.

C. HARASSING AGENTS (SHORT-TERM INCAPACITANTS)

Introduction

Harassing agents may be defined as chemical agents that are capable, when used in field concentrations, of rapidly causing a temporary disablement that lasts for little longer than the period of exposure. They may be distinguished from such incapacitating agents as the so-called psychochemicals in that the effects of the latter have a delayed onset and persist for a period greatly exceeding that of exposure. A distinction between these two classes of chemical warfare agent may also be drawn on physiological grounds: psychochemicals and allied incapacitating agents are centrally acting substances, while harassing agents are sensory irritants. Their harassing effects, which arise from the reflex responses of the body to sensory irritation, include lachrymation, sternutation, vomiting, and pain.

Any sensory irritant can provoke all these responses, to a greater or lesser extent, depending on the body tissues with which it comes into contact. The conjunctivae of the eyes may be particularly sensitive towards some irritants: the predominant response would then be the secretion of tears, and the irritant would be classed as a "lachrymator". Towards other irritants, the inner surfaces of the nose or upper respiratory tract might be particularly sensitive, and these agents would be classed as "sternutators". Finally, if dispersed as a gas or as particles of approximately 0.3-0.5 μ diameter, an irritant will penetrate to the deeper recesses of the respiratory tract.

If enough of a sensory irritant is inhaled, it may produce the same sort of damage as that caused by a lethal lung irritant, such as phosgene.

Harassing agents were the first type of chemical warfare agent to be employed during the First World War, and by the end of the war some 13 000 tons of various types had been used, which was rather more than the amount of mustard gas expended. By mid-1915, harassing agents were being used mainly to force an enemy to wear gas masks, and so to reduce his fighting efficiency: they were also used to force him out of cover and so make him face capture or hostile fire, to deny him access to other terrain, or to upset his firing efficiency. With an enemy carrying respirators, the latter objectives were not often attained. None the less, at the time of the Second World War, when respirators were greatly improved and had been issued in large numbers, considerable stockpiles of harassing agents, mainly CN (a lachrymator) and DM or adamsite (a sternutator), were accumulated by most of the belligerents, amounting to some 12 000 tons for the German, Japanese and United States armies alone.

Harassing effects can also be achieved with skin irritants, and some pruritogens and algogens (such as phosgene oxime) have been described as possible chemical warfare harassing agents. However, few of the skin irritants available have a sufficiently powerful action to be attractive *per se* for military purposes, and with the more potent ones, the risks of severe lung damage on inhalation are likely to be unacceptably high for their use solely as cutaneous harassing agents. Thus, skin irritation is unlikely to be considered to render a substance suitable for use as a harassing agent unless combined with other harassing effects, as in the case of some lachrymators and sternutators. Where the aim is prolonged exposure, however, as in the case of organoarsenical vesicants, skin irritation could be an undesirable property.

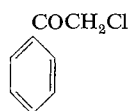
Military experience with harassing agents has encouraged the use of such compounds in domestic police operations, such as the control of civil disorders. Many of the military harassing agents are in fact quite unsuited to police use, either because the risk of fatalities is too high or because they may easily cause exposed individuals to become totally incapacitated, whereas the main reason for their use by the police is to get rioters or potential law-breakers moving out of a particular area.

Ideally, a "police-type irritant" (or "riot-control agent") should be characterized by a combination of physical and toxicological properties that will ensure that lethal exposures will be extremely rare and that the harassing effects will be relatively benign. It is doubtful whether these requirements are fulfilled by the agents at present being used in some countries. If used without restraint in situations where airborne concentrations may persist, their effects will not remain relatively benign, and may be lethal.

Some fifteen sensory irritants have been used in war as harassing chemical warfare agents.

The three agents whose properties are summarized below have all been extensively employed in war. The devices developed for their dispersal are essentially the same; they include hand grenades and rifle grenades; projectiles for automatic launchers and rocket launchers, for both ground and aircraft use; mortar bombs; gun and howitzer projectiles; high-capacity dusting apparatus, both portable and for mounting in trucks or helicopters; and aircraft bombs, cluster bombs, and bomblet dispensers.

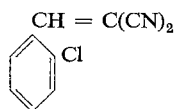
(i) *CN* (*o*-chloroacetophenone)



CN is a solid, generally disseminated as a particulate aerosol. It is essentially a lachrymator. Exposure to a concentration exceeding about 0.5 mg/m³, induces a copious flow of tears in less than a minute. At higher concentrations, or with prolonged exposure, intense irritation is experienced in the nose and upper respiratory tract, soon followed by an itching and burning of moist areas of exposed skin, which may even lead to blistering. Allergic reactions may also result (Jolly & Carpenter, 1968). On cessation of exposure, recovery is swift, but at high dosages, such as might be experienced within an enclosed space, serious lung damage may occur. A number of deaths have been reported in the literature, due mainly to pulmonary oedema.

The field concentration needed to produce harassing effects of military significance is above about 10 mg/m³. The human lethal inhalation dosage, extrapolated from animal data, is estimated at around 11 000 mg-min/m³ (US Department of the Army, 1963), which is about the same as that for the lethal agent cyanogen chloride.

(ii) *CS* (*o*-chlorobenzal malononitrile)



CS was developed in the 1950s as a replacement for CN for police use. It was the culmination of a search for a compound having a more potent irritant action than CN but less likely to cause complete incapacity than such agents as the arsenical sternutators. After being successfully tried out by police forces, it has been used as a military harassing agent.

Its effects are qualitatively rather similar to those of CN, but are even more rapid, and are brought about at lower field concentrations. Militarily significant harassment occurs at concentrations above about 1 mg/m³, so that on this basis CS is about 10 times as potent as CN. Thus a device charged with CS is likely to be considerably more effective over a greater area than a similar device charged with CN.

Three forms of CS have been developed for war use: the commercial product itself, for dissemination by distillation from pyrotechnic compositions; CS1, a micronized powder formulation containing 5% of silica gel, for dissemination by explosive burst or dusting apparatus; and CS2, to be used in the same way as CS1, and consisting of the latter microencapsulated with silicone to improve its flow properties and weather resistance. Spread on open terrain under normal weather conditions, CS1 is effective for about a fortnight; CS2 is considerably more persistent (US Department of the Army, 1969).

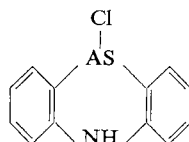
Experimental LC₅₀ values have been obtained in a variety of laboratory animals. For CS aerosols made up of particles of 1.5 micron mass median diameter, these range from 8 300 mg-min/m³ for guinea-pigs up to 43 000 mg-min/m³ for mice (Punte et al., 1962). The published estimates of lethal doses for man vary from 25 000 mg-min/m³ up to 150 000 mg-min/m³.

In this connexion, it may be noted that estimates of lethal doses for man are likely to be more unreliable for the harassing agents than for any other CW agents. They can be made only by extrapolation from results obtained with laboratory animals. Human volunteers can withstand only minute dosages, and there are no indicators of the kind provided by cholinesterase levels in nerve gas intoxication. Lethality data from industrial accidents or suicide autopsies are unlikely to be obtainable, and the estimation of lethal doses on the basis of deaths occurring when CS is used in police operations or for military purposes can only be extremely imprecise.

No studies have yet been published on the long-term effects in man of exposure to CS, despite the increasing use of this agent by police and military forces throughout the world. Thus, while there appears to be no evidence to suggest that CS is either carcinogenic or teratogenic, there is also no evidence to show that it lacks these properties.

It must be accepted as a strong possibility that in individuals suffering from asthmatic disorders or chronic bronchitis, these conditions will be exacerbated by exposure to CS (Himsworth et al., 1969).

(iii) *DM (adamsite : 10-chloro-5,10-dihydrophenarsazine)*



DM is a sternutator developed during the First World War. At low aerosol dosages it causes severe irritation to the upper respiratory tract, the peripheral sensory nerve endings, and the eyes ; it also irritates the skin but to a smaller extent ; at higher dosages it attacks the deeper respiratory passages. The irritation begins as a tickling sensation in the nose, followed by sneezing, with a flow of viscous mucus, similar to that which accompanies a bad cold. The irritation then spreads down into the throat, and coughing and choking set in until finally the air passages and the lungs are also affected. Headache, especially in the forehead, increases in intensity until it becomes almost unbearable, and there is a feeling of pressure in the ears and pains in the jaws and teeth. These symptoms are accompanied by an oppressive pain in the chest, shortness of breath, nausea (which soon causes violent retching and vomiting), unsteady gait, a feeling of vertigo, weakness in the legs, and trembling all over the body. Mental depression may occur as the symptoms progress. The agent begins to take effect 2 or 3 minutes after exposure begins. Recovery is usually complete in 1-2 hours. At very high dosages, the lungs may be damaged, and instances of death have been reported (US Department of the Army, 1968).

The field concentration of DM needed to produce harassing effects of military significance is about the same as that for CS. The human lethal inhalation dosage is estimated to be around 15 000 mg-min/m³ (US Department of the Army, 1963).

D. ANTI-PLANT AGENTS

Chemical anti-plant agents have come into use in warfare since the Second World War and their employment has increased rapidly over the past few years. Something of the order of fifty thousand tons of anti-plant agents have been sprayed in military operations over about 10 000 km² of Viet-Nam (Tschirley, 1969 ; McCarthy, 1969). They are used to destroy the enemy's food supply and to deny him concealment by foliage or vegetation.

No attempt will be made here to detail the modes of action of these substances or to discuss their military uses. They are relevant to the present report insofar as they may create public health problems and they are considered below from this aspect.

Currently employed anti-plant agents

Chemical anti-plant agents being used in warfare today fall into two groups. The first group contains the herbicides, plant growth regulators and desiccants that are applied directly to plants or trees to kill or defoliate them. The second group contains the soil sterilants that are used to contaminate soil and prevent or retard growth within it.

In the first group, there are at present four principal anti-plant agents :

2,4-Dichlorophenoxyacetic acid (2,4-D). This has been employed in a variety of salt and ester formulations, generally in admixture with other anti-plant agents.

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T). This has generally been employed in combination with 2,4-D in ester formulations.

Dimethylarsinic acid (cacodylic acid). Generally employed as an aqueous solution of the sodium salt.

4-Amino-3,5,6-trichloropicolinic acid (picloram). Generally employed in a salt formulation in admixture with 2,4-D.

In the second group, there are two principal agents :

5-Bromo-3-sec-butyl-6-methyluracil (bromacil), employed either in dust formulations, or in aqueous or fuel oil solutions.

3-(p-Chlorophenyl)-1,1-dimethylurea (monuron). Generally employed in dust formulations of its trichloroacetate salt.

The following figures show the ranges of application rates generally used with these agents for defoliation, crop-destruction or soil-sterilization. The formulations given are those in current use in Viet-Nam (US Department of the Army, 1969).

<i>Formulation</i>	<i>Application rate of the active ingredient (kg/ha)</i>
2,4-D/2,4,5-T (1:1) (agent orange)	15-50
Picloram/2,4-D (1:4) (agent white)	8-15
Cacodylic acid (agent blue)	3- 8
Bromacil formulations	15-30
Monuron formulations	20-30

Toxicological properties

As regards their acute toxicity, the anti-plant agents listed above are only moderately toxic to warm-blooded animals (Tschirley, 1969). Some experimental LD₅₀ values obtained with them are listed below :

Agent	Acute oral LD ₅₀ in rats (mg/kg)	Reference
2,4-D	375	Rowe & Hymas, 1954
2,4,5-T	500	"
Picloram	8200	House et al., 1967
Cacodylic acid	1350	Canada, Department of Agriculture, 1968
Monuron	3600	"
Bromacil	5200	"
Agent white	3080	House et al., 1967
Agent blue	2600	Tschirley, 1969
Agent purple ^a	566	House et al., 1967

^a Agent purple is a 2,4-D/2,4,5-T formulation almost identical with agent orange.

Very much less is known about the chronic toxicity or long-term effects of anti-plant agents, for example, their teratogenicity or carcinogenicity. In this connexion it must be borne in mind that the military employment of anti-plant chemicals may lead to their intake, by humans, in water and food, in dosages far higher than those experienced when the same chemicals are used for agricultural and other purposes. While it would be untrue to say that the possibility of chronic toxicity has been entirely ignored, it cannot be said that it has received anything approaching adequate study. However, the results of a preliminary laboratory study of the teratogenicity of one of the anti-plant agents listed above have recently become known. It was found that offspring of mice and rats given relatively large oral doses of 2,4,5-T showed a higher number of deformities than expected. While no attempt was made to correlate these findings with the possible effects of 2,4,5-T in man, the US Government has nevertheless been led to take action to restrict the use of the agent (see also *Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health*, US Department of Health, Education, and Welfare, 1969).

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ANNEX 2

BIOLOGICAL AGENTS

INTRODUCTION

In contrast to chemical weapons, there has fortunately been no authenticated use of biological agents in modern warfare. A large number of potential agents for use against human targets exists, and choices can be made to suit particular purposes and circumstances. Table 4 contains a list of the candidates that are considered most likely to be used because of their microbiological and epidemiological characteristics. Some of these agents are described later.

Many other agents not discussed here are worth mentioning briefly. They include the viruses of lymphocytic choriomeningitis; mumps, the parainfluenza group, poliomyelitis, rabies, measles and rubella; the bacteria that cause diphtheria, leptospirosis, listeriosis, meningococcal meningitis, pneumococcal pneumonia, streptococcal infections and tuberculosis; the agents of several mycotic infections—blastomycosis, cryptococcosis, histoplasmosis, nocardiosis; and protozoa that cause diseases such as amoebic dysentery and malaria. Almost any of these agents could be used in defined circumstances, e.g., in combination with other agents or weapons, but they are considered of lesser importance than many of those selected for discussion below because of the many other variables that would have to be taken into account to obtain any sort of predictable quantitative effect. Such variables would include levels of pre-existing immunity, difficulties in dissemination because of the lability of the micro-organism, and lack of knowledge of human infective doses.

The following descriptions of individual diseases and micro-organisms involve many in which man-to-man transmission is relatively unimportant. Several diseases considered here, however, notably influenza and pneumonic plague, are highly infectious to man; while others, such as those caused by arboviruses (yellow fever, Venezuelan equine encephalitis, tick-borne and Japanese encephalitis) and rickettsial diseases (epidemic typhus, Rocky Mountain spotted fever, Q fever) usually require an intermediate vector (mosquitos, ticks, lice, fleas, etc.). Quantitative estimates have been attempted in Annex 3 for primary cases resulting from a biolo-

gical weapons attack ; secondary effects from spread are described in the annex.

Military consideration would appear to be given generally to the possible use of agents characterized by little tendency to spread. Such a tendency could very well change and virulent new strains could emerge from human or animal populations exposed to them in war or in field tests. An additional hazard is the creation of new or increased animal reservoirs.

Another point worthy of emphasis is that the military use of many of the micro-organisms discussed would involve an atypical route of entry, namely, the lungs through aerosol exposure.

Human infection by the respiratory tract has been achieved experimentally for some of these diseases (yellow fever, Rocky Mountain spotted fever, tularaemia) and is known to occur naturally in exceptional instances for others (e.g., Venezuelan equine encephalitis, Rift Valley fever, tick-borne encephalitis, typhus fever). It is not known whether atypical infection of man through the respiratory tract, which can by-pass such normal protective mechanisms as local inflammatory processes, would increase the case fatality rate¹ of diseases ordinarily of low lethality, such as Venezuelan equine encephalitis. By analogy with other infections of man where respiratory entry is exceptional (pneumonic plague, respiratory anthrax), this should be regarded as a strong possibility.

While large-scale laboratory production of all the agents discussed here is feasible in most advanced microbiological laboratories, the drying, processing and delivery of most of them as military weapons require sophisticated technology. Some of them, however, such as smallpox virus, can be produced and used as weapons with relatively simple techniques.

A. VIRAL INFECTIONS

1. Arthropod-borne (arboviruses)

There are some 200 viruses belonging to the arbovirus group, transmitted to vertebrate hosts by blood-sucking arthropods such as mosquitos and ticks. About 75 of these viruses have been shown to produce diseases in man ; most of these are relatively mild and non-fatal but they also include such lethal diseases as yellow fever and tick-borne and Japanese encephalitis. The descriptions that follow are designed to illustrate the variety of effects associated with the possible employment of different members of this group as biological agents for warfare.

¹ Case fatality rates, as used in this report, represent the percentage of deaths in clinically ill persons.

(i) *Yellow fever*

Between the 17th and 19th centuries yellow fever was one of the great scourges of large parts of the world, wiping out populations and paralysing commerce. Its main habitats were the Americas and Africa and it was periodically introduced into Europe. Since the early part of the 20th century the disease has not appeared in North America and Europe, although it has continued to affect large parts of Central and South America and Africa. In recent years epidemics have occurred in Nigeria (1951-1954), Trinidad (1954), Central America (1948-1957), French Equatorial Africa (now Congo (Brazzaville)), the Belgian Congo (now the Democratic Republic of the Congo) (1958), Sudan and Ethiopia (1959-1962), and Senegal (1965).

Yellow fever is caused by a virus (Group B of the arboviruses) that is transmitted by a variety of mosquitos, mainly *Aedes aegypti* in urban areas and *Aedes* and *Haemagogus* species in forest areas. The disease has now been successfully controlled in most urban communities, especially in the Americas, where the man-mosquito-man cycle is operative. It is now mainly confined to forest and contiguous areas that favour the cycle of monkey-mosquito-man characteristic of jungle yellow fever. Sporadically the virus is reintroduced into the man-mosquito-man cycle in towns and villages and urban outbreaks of yellow fever result.

Apparently the disease has never occurred spontaneously in Asia, a fact that has long puzzled epidemiologists because all the requisites seem to be present: mosquito vectors, susceptible humans and monkeys, and considerable traffic between infected areas in Africa and south-east Asia. There is understandably a great fear of the introduction of yellow fever on the part of the health authorities in Asian countries, and considerable precautions are taken with respect to the disinsection of incoming aircraft and the vaccination of travellers who have recently visited countries where the disease is endemic.

The virus can easily be propagated in large amounts in eggs or tissue culture and freeze dried.

The disease in man has an incubation period of 3-6 days, and the blood is infective for mosquitos shortly before and during the first 3 days of illness. Infected mosquitos require a period of 9-12 days before they are capable of transmitting the virus to man, so that the initial cases are usually sporadic and often missed. There is then a gradual build-up of infected mosquitos in an area, after which explosive outbreaks occur in man. This has resulted in very extensive epidemics during the past 300 years, yellow fever being perhaps the most feared disease during recent history in the Western Hemisphere as far north as the USA.

In man the disease has a sudden onset, with fever, headache, backache, prostration, nausea and vomiting. As it progresses, epistaxis, bloody

vomitus and jaundice occur. Case fatality rates up to 30-40% are not uncommon in unvaccinated individuals living in urban or rural areas when the disease is newly introduced. New outbreaks require emergency epidemic measures, including mass vaccination with living attenuated vaccines, vigorous and sustained anti-mosquito control measures and special diagnostic services. Monkey reservoirs in forest areas cannot be eradicated and thus the disease continues indefinitely. The severe nature of the disease taxes to the limit any medical services available. It is evident therefore that, if yellow fever was introduced into the Asian continent and took foothold there, the results could well be catastrophic.

Use as a biological agent

Aerosol transmission of yellow fever has been achieved in the laboratory. The possible effects of the virus in this form are given in Table 10, Annex 3. The disease might be introduced by mosquito vectors and/or by infected monkeys. Successful introduction would depend upon the establishment of foci of infection in a few or many areas within a short space of time. The presence of the disease in even one locality would require extraordinary protective measures to be taken, including mass vaccination of the population and extensive and persistent mosquito control. Health resources in south-east Asia are extremely limited and would undoubtedly be unable to deal with multiple foci of infection and the resulting epidemics, which would entail anything from tens of thousands to millions of cases and deaths. There would also be severe disruption of community life and services and a constant threat of spread of the disease to uninfected areas. Long-term effects would include the permanent establishment of uneradicable enzootic reservoirs in monkeys and perhaps other wildlife. Periodic prophylactic vaccination of large population groups and mosquito control for an indefinite duration would be needed.

(ii) *Tick-borne encephalitis*

This disease occurs as two sub-types—Far Eastern and central European—in the USSR, parts of central and western Europe and in the Scandinavian countries. It is usually transmitted by the bites of infected ticks. With the central European sub-type, milk-borne transmission (milk of goats and probably also of sheep and cattle) frequently occurs, over 600 persons having been infected in a milk-borne epidemic in Czechoslovakia in 1951. The natural cycle of infection involves reservoirs in wild rodents, hedgehogs and birds, with transmission by *Ixodes* ticks among themselves and to man and domestic animals. The virus can be grown in tissue culture and is quite stable in milk or milk products, relatively high temperatures being required for its inactivation. It is one of the most

dangerous to work with in the laboratory because of its high infectivity by contact or by air-borne droplets.

The Far Eastern sub-type of the disease in man has an incubation period of 1-2 weeks. The initial phase of the disease may be mild, with headache, respiratory symptoms, and general malaise. Severe headache, fever, nausea and vomiting then occur, followed in severe cases by stiffness of the neck, somnolence, delirium or coma, convulsions, partial or complete paralysis and, usually, death within a week. In non-fatal cases, severe illness may last only a week but convalescence may take months, and residual paralysis of the arms and shoulder girdle is common. The case fatality rate is 20-30%, and often higher in children. The Central European sub-type of the disease is more benign, with a case fatality rate of 0-5% in different outbreaks. Treatment is symptomatic and hospitalization is required for all seriously ill individuals. Available vaccines give only moderate protection.

Use as a biological agent

People are almost universally susceptible. The ease with which the Far Eastern virus can be grown in the laboratory and its high infectivity and lethality by the aerosol route would make it likely that a case fatality rate of 25% would be achieved. The introduction of a Central European sub-type of the virus into milk after pasteurization could affect large numbers of people, especially children, but this would be difficult to accomplish in modern milk sterilization or pasteurization plants. These do not exist, however, in many parts of the world and where raw or insufficiently heated milk is consumed, widespread infection could be produced. Secondary effects would include the establishment of enzootic reservoirs in suitable wild animal hosts; the ticks that transmit the disease are common in many areas.

(iii) *Japanese encephalitis*

This disease is epidemic in Japan, Taiwan, mainland China, Eastern Siberia, Korea and some of the western Pacific islands, and endemic in the Malay peninsula, Thailand and India. Periodic epidemics can be severe, such as the one in Korea in 1958 in which there were 5 700 reported cases and a 20% case fatality rate. The ratio of clinically apparent to inapparent infections is 1 : 500 to 1000. Epizootics occur in horses and pigs, causing abortion and foetal abnormalities in the latter. The natural cycle of infection involves culicine mosquitos, which feed on lower animals (pigs, birds, horses and perhaps bats) and then transmit the disease to susceptible hosts, including man. The virus can easily be reproduced in tissue culture and has apparently been used in aerosol form in laboratory experiments (Wedum, 1961).

Symptoms in man include severe headache, very high fever, stiff neck and encephalitic signs such as stupor, confusion and delirium, or somnolence progressing to coma and death in about 10 days. Non-fatal cases may have a prolonged convalescence, with weakness, incoordination, and partial paralysis. Serious sequelae, commonly seen in children under 10 and in adults over 60 years of age, include mental impairment and behavioural changes. The case fatality rate is 20-30%. Good hospital care is required to keep mortality as low as possible. Available vaccines confer some, but not a high degree of, protection.

Use as a biological agent

Populations outside endemic areas are universally susceptible. Since aerosol infection of animals has apparently been achieved in the laboratory, it is reasonable to assume that Japanese encephalitis can be disseminated by aerosols with effects similar to those described above for Far Eastern tick-borne encephalitis. Secondary effects would include infection of susceptible domestic animals and wildlife and the establishment of enzootic reservoirs.

(iv) *Dengue*

This is an acute febrile illness caused by several different types of the dengue virus, transmitted from man to man by mosquitos of the *Aedes* group. In the last 50 years some very large epidemics, involving from ½ to 2 million people, have occurred in Australia, Greece, Japan and the USA. The disease is endemic in many countries of the western Pacific, south-east Asia, Africa and the Caribbean area.

Dengue virus can be readily grown in the laboratory and vector mosquitos can be infected with it.

The disease generally has an incubation period of 5-7 days. The onset is sudden, with fever, severe headache and backache, accompanied by equally severe pains in the muscles and joints. It is usually self-limiting, but highly incapacitating during the acute phase.

In some instances the disease may develop into a more serious haemorrhagic form which has a case fatality rate of about 5%. This form is considered by some to be a result of sensitization caused by previous infections with strains of dengue virus.

Use as a biological agent

A widespread incapacitating effect could be expected from aerosol use of dengue virus on susceptible populations. The serious haemorrhagic form might occur in certain population groups, resulting in a large number of deaths. Theoretically, the introduction of dengue into a carefully

chosen area by infected vector mosquitos is possible but would be difficult and unpredictable in its effects. If infection were introduced in such a way, small local epidemics would first result and would gradually build up to an explosive epidemic as succeeding groups of humans and mosquitos became infected.

(v) *Venezuelan equine encephalitis* (VEE)

Epidemics of this disease have occurred periodically in man and equines in Venezuela (where it was first reported in 1938), Colombia and Panama, and in equines in Ecuador and Argentina. Multiplication of the virus is easily produced in tissue culture. Numerous laboratory infections have been reported in man through contact or by air-borne droplets. In nature, transmission occurs through mosquitos that have fed on infected lower animals (rodents, birds, equines). In the laboratory, aerosolized virus has infected monkeys at relatively low concentrations—1 000 or more guinea-pig ID₅₀ values (50% guinea-pig infective doses) (Kuehne et al., 1962).

The disease is sudden in onset and characterized by severe headache, chills and fever, nausea and vomiting, muscle and bone pains, and encephalitis (5% of cases in man). The case fatality rate may reach 0.5%, but usually recovery is rapid after one week, although residual weakness may occur for up to three weeks. Treatment is symptomatic. Protection by vaccination is still experimental.

Use as a biological agent

Since the virus can be produced easily in large amounts in the laboratory and air-borne infection has readily occurred, concentrated aerosols could be expected to incapacitate at least half the population exposed and to kill some of them (Table 10, Annex 3 ; also see Introduction). Most populations are completely susceptible. Severe incapacitation would last for about a week, with a return to fairly normal activity within three weeks after exposure. Hospital facilities would be required for the cases resulting in encephalitis. The equine population would be similarly affected, and enzootic reservoirs might be established for future epidemics.

(vi) *Chikungunya*

Large epidemics of this disease, affecting up to 40% of the population, have occurred since the early 1950's in Tanzania and in Thailand. It has also been reported in Southern Rhodesia, Congo (Brazzaville), the Democratic Republic of the Congo, Cambodia and India. A wide variety of mosquito species in various areas have been shown to harbour the virus, and non-human primates and perhaps other lower animals are thought

to act as natural reservoirs and amplifiers. The virus grows well in tissue culture.

The incubation period is 3-12 days and the onset very sudden. Severe joint pains in the limbs and spine incapacitate within hours. The patient doubles up and remains immobile with a high fever, which lasts up to 6 days. After a remission of a few days another less intense bout of fever occurs, accompanied by an irritating rash on the trunk and limbs. The second stage lasts for about a week, although joint pains can recur for up to 4 months and may cripple the patient. There is no treatment except analgesics, and preventive vaccines are not available.

Use as a biological agent

Susceptibility is almost universal in temperate climates. Aerosol delivery and entry of large amounts of virus through the lungs might be expected to produce severe incapacitating effects within one or two days and some deaths. Where suitable lower animal hosts and mosquitos are present, enzootic reservoirs might be established.

(vii) *O'nyong-nyong*

The virus of this disease is closely related to the chikungunya virus. A very large epidemic started in 1959 in Uganda and spread into neighbouring countries, where by 1962 over two million people were infected, the attack rate being over 70%. The vectors are anopheline mosquitos.

The symptoms resemble those of chikungunya with sudden onset, chills, severe pains in the back and joints, headache, rash, and neck lymphadenitis. Recovery without sequelae occurs in about a week.

Use as a biological agent

Similar to chikungunya.

(viii) *Rift Valley fever*

At present restricted to parts of central, eastern and southern Africa, this is an important disease of sheep, cows and goats, causing abortion and high mortality in young lambs and calves. A great epidemic and epizootic occurred in South Africa in 1950-51, during which an estimated 20 000 people became infected and 100 000 sheep and cattle died. The virus can easily be cultivated in chicken embryos and tissue culture. Infection in man by inhalation or through handling infected animals is very common. The virus is stable in aerosols (Miller et al., 1963). Transmission in nature occurs through infected mosquitos, with wild animals, possibly rodents, acting as reservoirs.

In man the disease is severe but usually not fatal. After an incubation period of 4-6 days there is sudden fever, malaise, nausea and vomiting, severe headache, muscular pains and dizziness. After 2-3 days of fever, there is a 1-2 day period of remission, followed by another 2-3 days of fever. Recovery is uneventful, but malaise and weakness may persist. There are rare ocular complications.

Use as a biological agent

Similar to chikungunya.

2. Other viral infections

(i) *Influenza*

Pandemics of influenza occur when a shift in the composition of the influenza virus results in a new strain with an unusual infecting capacity. Advances in virology have enabled research workers to examine closely the strains isolated since 1933, including the current (1968-69) Hong Kong strain. Although the occurrence of certain changes in the protein coat of the virus has been established, the factors responsible for infectivity and rapidity and universality of spread remain unidentified. Thus it is not known why the 1918 pandemic (which resulted in the death of about 20 million people) or previous and subsequent pandemics occurred. Equally, it is still impossible to anticipate the change that will give rise to the next natural pandemic.

A large number of influenza virus strains closely related to the human strains that have caused pandemics are circulating freely in the lower animal kingdom throughout the world, affecting wild and domestic birds, swine and equines. Experimental recombinations of these strains among themselves and with human strains are easily achieved in the laboratory. It is now being postulated by some workers that such recombinations occur periodically in nature, or individual virus strains may mutate and then emerge as a new human pandemic strain. It is therefore possible that with the present rapid progress in fundamental research on the influenza virus, sooner or later a recombinant influenza virus may be produced in the laboratory that would be capable of causing a pandemic, against which a suitable vaccine could be prepared to protect the population and military forces of the attacker. Human trials of such strains may be feasible under strictly isolated conditions.

Influenza is an airborne infection, and aerosol dissemination, as well as aerosol immunization, is easily possible. The virus grows easily in large quantities in embryonated chicken eggs, and can be dried or frozen for storage.

Influenza in man is characterized in its benign form by fever, general malaise, respiratory distress; headache, myalgia and prostration lasting several days. One or two weeks of convalescence are required for full activity to be resumed. The disease most affects the very old, pre-existing cardiovascular or respiratory difficulties increasing the mortality. The large number of deaths occurring in young males (but not young females) during the 1918 pandemic was completely at variance with the previously known character of influenza as an epidemic disease; they may have been associated with host rather than viral factors. Influenza complications such as pneumonia can now to some extent be controlled by antibiotics. Present vaccines are effective (about 50-70%) against current strains of virus, but against a new strain it would take 3-4 months in technically advanced countries to prepare sufficient vaccine to protect populations.

Use as a biological agent

With a hypothetical new strain, very limited aerosol dissemination in a few crowded urban areas in temperate climates might spark off an epidemic or pandemic. If the factor or factors responsible for pandemic spread were to be identified and incorporated into the new strain, the rapidity of dissemination throughout the world would be great, probably within a matter of a few months with modern means of travel, and in much less time within the confines of a country attacked. Large-scale aerosol dispersion over a populated area could incapacitate the population of the area within the 1-3 days incubation period and kill a number of people (Table 10, Annex 3). The mortality from current strains is low (about 0-2%). A high mortality, perhaps causing millions of deaths, could occur if the 1918 experience was repeated.

(ii) *Smallpox*

One of the oldest known communicable diseases of man, smallpox remains endemic in parts of South America, Africa and Asia. While extensive and systematic vaccination is carried out in many parts of the world, some degree of susceptibility to the disease is still found in many areas, e.g. 40-70% in Europe, the Eastern Mediterranean area and the USA.

The causative agent is the variola virus. This can be easily produced in large quantities in the laboratory in embryonated eggs and tissue cultures. The virus can be freeze-dried and its virulence thus preserved for months or years.

The sites of entry of the virus are the upper respiratory tract and the skin, where the virus multiplies during the usual incubation period of 9-12 days. A short period of viraemia then follows, characterized by fever, malaise, headache and backache, abdominal pain and prostration. The

virus is localized in the skin, mucous membranes and other tissues where a rash shortly appears.

The eruption is usually most profuse on the face. The initial macular rash quickly becomes papular, then vesicular, and finally pustular. The pustules in turn form crusts which are shed, leaving indelible scars of varying size and severity. The sites of focal eruptions are extremely rich in infective particles, and early erosion of the mucous membranes ensures heavy contamination by the saliva and other mucous secretions. The majority of deaths occur in the pustular stage and the case fatality rate of classical smallpox in unvaccinated people is of the order of 30% ; the milder form of the disease (alastrim) causes mortality in less than 1%.

Unvaccinated human beings are extremely susceptible to variola virus. Fortunately, smallpox vaccine is one of the most effective known in medical practice, and may still give some protection if applied shortly after exposure. Chemoprophylaxis with methisazone has been successful.

Use as a biological agent

Because of the effectiveness of the vaccine and the relative ease with which it can be produced and administered, it is unlikely that smallpox virus would be used as an agent for a large-scale biological attack against countries systematically practising periodic vaccination.

The variola virus, however, can easily be employed for acts of sabotage. Such acts, at selected points within a country, could have serious socio-economic effects unless efficiently dealt with by the public service. Although variola major may cause severe illness and a high mortality in the unvaccinated, the disease spreads comparatively slowly, infecting only one third of the susceptibles who are in very close contact with the patient. Once detected, outbreaks can be rapidly contained through isolation of patients and vaccination of close contacts. However, if public health measures are not efficiently applied, the disease may become widely disseminated and extensive programmes of vaccination may be required.

B. RICKETTSIAL INFECTIONS

1. Typhus, epidemic

The great epidemics of typhus that have plagued man since ancient times ceased shortly after the Second World War. Pockets of the disease still exist in a number of countries, and in conditions such as occurred in the First and Second World Wars major epidemics might again arise. The disease is caused by *Rickettsia prowazeki* and is transmitted from man to man by lice. The rickettsial organism can readily be grown in chicken

embryos, and aerosol infection of man and experimental animals can be produced.

The disease in man is usually very severe and prolonged. The usual incubation period of 10-14 days may be shortened by heavy exposure. The first symptoms are sudden—chills, aches and pains, headache and weakness. Fever remains until recovery or death. During the first week a rash appears. The symptoms grow progressively more severe, with the critical period in the second or third week. Stupor and coma may be interrupted by attacks of delirium. The case fatality rate increases with age, being about 3% in infants, 30% in the 40-50 age group and 50% in old people. Vaccines and antibiotics are effective in prophylaxis and treatment respectively.

Use as a biological agent

Most populations are completely susceptible to typhus, and therefore a surprise large-scale attack with an aerosol form of this agent could cause death, illness and social disruption over a wide area, especially where there is a shortage of antibiotics (Table 10, Annex 3).

2. Rocky Mountain spotted fever

This disease has been reported only in the Western Hemisphere—in Brazil, Canada, Colombia, Mexico, Panama and almost all of the continental USA, particularly the Rocky Mountain area. It is transmitted by ixodid ticks from a variety of infected lower animal species (field mice, rabbits, hares, squirrels, chipmunks, dogs). The causative organism, *Rickettsia rickettsi*, can be cultured in large quantities in embryonated eggs. Aerosol experiments in the laboratory have shown that monkeys die after inhaling only 4-6 times the dose used to infect eggs (Saslaw & Carlisle, 1966). The disease in monkeys very closely resembles that observed in man.

The incubation period in man is 3-12 days (5-7 days in aerosol-infected monkeys). The onset is abrupt, with severe headache, chills, fever, muscle and joint pains, and prostration, and the symptoms continue for 2-3 weeks. A rash begins to appear on about the fourth day and gradually involves most of the body. In fatal cases death occurs during the second week from toxæmia, shock, blood vessel alterations and renal failure. Before antibiotic therapy the case fatality rate in some areas reached 80% for unvaccinated adults, and about 37% in children; the overall case fatality rate was 20%, but in adults over 40 years of age about 50% died. Antibiotic therapy and intensive medical care in the hospital can reduce mortality to 3-7%. Vaccinal prophylaxis gives a varying degree of protection.

Use as a biological agent

Susceptibility is world-wide. Aerosol infection has been proved possible, and the extent of illness and death it would cause would depend on the

quantities of micro-organisms that could be disseminated, the availability of hospital care and antibiotic therapy, and vaccinal prophylaxis prior to attack. The estimated effects are given in Table 10, Annex 3. Enzootic reservoirs of infection would probably be established in rural areas of the world where suitable animal reservoirs and ticks exist.

3. Q fever

Q fever, caused by *Coxiella burnetii*, occurs in most parts of the world. It is a zoonosis, the organism residing naturally in an extensive range of lower animal hosts, including all kinds of domesticated livestock and poultry, dogs, rodents, baboons and wild birds. Natural infection occurs also in some 40 different species of ixodid and argasid ticks, mites and parasitic flies, which play a principal role in maintaining the disease in nature. Transmission to man occurs primarily by the airborne route via inhaled droplets or dust that also may contaminate the skin and conjunctivae, or by ingestion through insufficiently heated milk or milk products. Low temperature vat pasteurization is insufficient to kill the organism. The Q fever organism is relatively resistant to environmental influences such as temperature changes and humidity, and is extremely infectious to man. Experimental studies indicate that even one micro-organism is sufficient to infect man (Tigertt et al., 1961). It is easy to produce very large amounts in embryonated chicken eggs (20 billion organisms per ml).

The incubation period in man is 18-21 days, but falls to 10 days when large doses of the organism are inhaled. The onset is sudden, with chills, fever, headache, loss of appetite, muscle and chest pains, and general malaise. In severe cases these progress to stiffness of the neck and back, confusion and disorientation, and pneumonia. The fatality rate is usually less than 1%, but somewhat higher among Africans. In patients who recover complications are not common but weakness and fatigue may last for months, accompanied by weight loss. In persons over 40, fever may continue for a month or more. Antibiotics are effective in treatment only if given early, and can abort infection if administered late in the incubation period. Prophylactic vaccines are not very successful and often cause undesirable reactions.

Use as a biological agent

It is clear from this description that a Q fever aerosol could produce an incapacitating effect on a large segment of the population of an area attacked and cause some deaths (see Table 10, Annex 3). The infective agent could persist in the environment for many months and infect the animal life, creating permanent reservoirs of infection. Food products could be contaminated and, since ingestion of the organism is known to cause disease, would have to be cooked thoroughly before consumption.

C. BACTERIAL INFECTIONS

1. Plague

Plague, the Black Death of history, rarely causes serious epidemics at present. It is endemic, however, in many countries of Africa, the Americas and Asia, with many species of rodents acting as reservoirs. The usual form of the disease, bubonic plague, is spread to man by fleas from infected rodents. The much more virulent pneumonic form is transmitted directly from man to man by droplet infection.

Pasteurella pestis, the causative organism of plague, can easily be prepared in large quantities and, if properly stored, retains its virulence for many years. It is resistant to environmental conditions, at least one hour of exposure to sunlight being needed to kill the organism when contained in small droplets. While desiccation is harmful to *P. pestis*, when protected by mucous or other substances it can resist drying for many days. It can survive a wide variety of temperatures (-2°C to $+45^{\circ}\text{C}$) and would therefore be relatively unaffected by hot or cold weather. Freeze-drying procedures can preserve the organism for long periods.

Pneumonic plague can be produced by means of aerosols containing *P. pestis*, the size of the droplet nuclei that penetrate the alveoli and cause pneumonic plague being between 1μ and 5μ in diameter. Animal experiments have shown that particles of 1μ diameter containing single cells can cause typical pneumonic plague. In experimental pulmonary plague in monkeys about 100 organisms administered intratracheally were sufficient to cause fatal pneumonic infection (Meyer, 1965). Inhalation of about 20 000 cells induced a chronic pneumonic process in some *Macaca mulatta* monkeys from which virulent bacilli were recoverable for up to 40 days (Ransom & Krueger, 1954). Organisms in droplets that would not reach the alveoli but be deposited in the nose or conjunctiva could also cause bacteraemia.

The incubation period in man is 2-6 days in bubonic plague and 3-4 days in pneumonic plague. Bubonic plague is characterized by high fever, shock, mental confusion, acute and painful swelling of the lymph nodes draining the site of entry of the micro-organism, prostration, delirium and coma. Pneumonic plague results in primary pneumonia. Untreated bubonic plague has a case fatality rate of 25-50%, while pneumonic plague is usually fatal. Antibiotics are effective if used early in the disease. Preventive vaccination is moderately effective against bubonic but not against pneumonic plague. With killed vaccine, protection is relatively short-lived (3-12 months) and periodic revaccination is necessary. Massive infection can overcome vaccine-conferred immunity.

Use as a biological agent

Plague is a suitable potential weapon of biological warfare. The micro-organism is resistant to environmental conditions and highly infective,

most populations are completely susceptible, and the disease is severe with a high fatality rate.

A large quantity of organisms could easily be grown and kept ready for use. The delivery of droplet nuclei of the desired size is not a major problem; the addition of various stabilizers would increase the viability of the plague bacilli in the nuclei.

If an initial infection with pneumonic plague were to involve about 50% of a population, it is likely that, unless precautions had been taken, up to about 90% of the rest of the population would be infected in 20-30 days, with a case fatality rate of 60-70%.

Infection would also be transmitted to urban and field rodents. Those animals that did not die very soon of pulmonary plague would develop bubonic plague, and either die or survive and transmit the infection to the next generation of rodents. Thus a natural focus of plague would be created which would constitute a permanent danger for the geographical areas affected.

If for some reason primary infection was not too widespread and fewer people contracted pneumonic plague, an epidemic starting with a limited number of primary human cases might produce secondary cases and gradually gather speed in a population migrating and living under war conditions. The effect on rodents would also be slower but would gradually increase, resulting in widespread bubonic plague among rodents and consequently among men.

2. Anthrax

This is a world-wide acute septicaemic disease of domesticated animals caused by *Bacillus anthracis*, which produces highly resistant spores that persist in the environment for decades. Man becomes infected by contact with animals or contaminated animal products, or by inhalation of infected dust from hides, wool and similar substances. The organism and its spores can be produced in almost unlimited amounts in the laboratory, and much experimental work has been done on the aerosol dispersion of the spores. Virulent antibiotic-resistant strains have been produced in the laboratory through selection procedures. Lethal aerosol infections of monkeys have been readily produced, and the spores can persist in the lungs of surviving animals for many months. Over a period of 5 days, 1 000-5 000 spores were sufficient to kill 25% of monkeys exposed to a naturally contaminated environment (Brachman et al., 1966). In cynomolgus monkeys exposed to aerosols of anthrax the ID₅₀ was slightly more than 4 000 spores (Glassman, 1966).

Natural infection in man occurs principally through the skin, although inhalation and ingestion of the organism can cause small-scale epidemics. Infection through the skin starts as a malignant pustule and progresses to

septicaemia and death in about 20% of diagnosed cases if not treated with antibiotics. Inhalation anthrax has a fulminating course, with death following toxæmia and septicaemia in over 80% of cases. Ingestion anthrax appears to be equally fatal. Incubation periods range from a few days to 1-2 weeks, depending on the magnitude of the exposure. Antibiotics are moderately effective if the disease is recognized sufficiently early and treatment is prolonged. Recently developed vaccines seem to confer good protection on man in the small exposures encountered in industrial establishments, but their value is not known where heavy exposures are concerned.

Use as a biological agent

Heavy concentrations of anthrax spores in aerosols are feasible. This could result in up to 70-80% fatalities in untreated cases (Table 10, Annex 3) and in domesticated livestock, with less infection and a lower fatality rate in areas where aerosol dilution occurs. Antibiotic treatment would have to be prolonged for weeks, since it has been shown that monkeys exposed to aerosols die if antibiotic therapy is discontinued after 10 days (Henderson et al., 1956). Vaccines available at present might not protect efficiently against heavy aerosol exposure. Food contamination would require prolonged sterilization to make all animal and food products safe. The environment would be contaminated indefinitely, and restocking with livestock and all aspects of food production would be rendered difficult for a long period. Air carriage of spores could be expected to contaminate localities far distant from the area of immediate attack.

3. Tularaemia

In the natural cycle of infection, tularaemia is primarily a disease of a wide variety of wild mammals and birds and is transmitted by arthropods (different species of ticks, fleas and flies). The disease is world-wide in distribution. Man and domesticated animals enter accidentally into this cycle through contact with infected animals (rabbits, hares, etc.) or arthropods, ingestion of contaminated food or water, or inhalation of contaminated dust. Tularaemia is easily transmitted by aerosol and the infective dose for man is as low as 25 bacterial cells (McCrum, 1961). The organism, *Pasteurella tularensis*, which can be produced on a large scale, easily resists environmental influences; it can be stored for years in dried form, and virulent and antibiotic-resistant strains have been produced in the laboratory.

The incubation period varies from 1 to 10 days, averaging 3 days. Its length of time depends upon the portal of entry, the skin and conjunctiva giving the longest and the respiratory and alimentary systems the shortest incubation periods. Infection through the skin or conjunctiva is characterized by swelling of the lymph glands draining the area, malaise and fever.

Ingestion tularaemia resembles typhoid fever, and infection from inhalation causes pneumonia in about half the cases (Overholt et al., 1961). Pleuro-pulmonary tularaemia has a high case fatality rate (40-60%) if untreated (McCrumb, 1961). Septicaemia, which results from the disease, causes necrotic lesions in many organs. Streptomycin is highly effective if administered early (one hour) after exposure to the disease, and works well even if started within 48 hours. However, it would not be effective against streptomycin-resistant strains of the micro-organism. Other antibiotics (tetracyclines, chloramphenicol) are also effective, but antibiotic therapy must be prolonged (about 10 days) to prevent relapses. Aerosol immunization has been successfully achieved, but the immunity can be broken by as little as 1 000 human infective doses (approximately 25 000 organisms) (McCrumb, 1961).

Use as a biological agent

The high infectivity of the tularaemia organism by various routes makes it a particularly suitable agent for biological warfare. Aerosol delivery (Hedén, 1967; Jacksén et al., 1968) could be expected to cause infection in at least half the people exposed, and probably much more in those receiving high doses of the organism. A case fatality rate of approximately 25% could be expected if a virulent strain were used (Table 10, Annex 3 and Annex 5). If an antibiotic-sensitive strain of relatively low virulence was used, with the aim of incapacitating, as opposed to killing, deaths would be considerably reduced but still be appreciable in number. Illness in survivors would last several weeks and relapses could occur over a period of months. Water and food would be contaminated and have to be subjected to heat treatment before consumption. Enzootic reservoirs of infection would be established in wild mammals and serve as future sources of disease. Preventive vaccination would probably only marginally modify the effects of exposure to concentrated aerosols.

4. Brucellosis

Brucellosis is an acute or chronic infection in man and domesticated animals and is caused by any one of three species of *Brucella*, namely, *abortus*, *suis* and *melitensis*. The disease is world-wide in distribution and is characterized by abortion in infected animals. *Br. abortus* particularly affects cattle, *Br. suis* swine and *Br. melitensis* sheep and goats, although all these species as well as man are susceptible to all three types. In man the *melitensis* and *suis* types produce the severest disease. Infection of man easily occurs by contact (small abrasions in the skin or mucosa), ingestion or inhalation. The organism can be produced in unlimited amounts by continuous culture in fermenters, and in its dried form retains its virulence for years. In its moist form it can persist in the environment

for weeks. About 1 000 organisms are considered necessary to produce infection in man. Some 50% of individuals subjected to heavy natural exposure show frank disease, although up to 80% can be infected to the extent that sensitivity and the possibility of subsequent chronic infection result.

The ID₅₀ of *Br. melitensis* in cynomolgus monkeys inoculated intradermally was less than 100 bacterial cells (Elberg & Faunce, 1962), and the ID₅₀ of *Br. suis* administered as an aerosol to guinea-pigs was 36 cells (Elberg & Henderson, 1948).

The incubation period varies between 1 and 4 weeks, with shorter periods after severe exposure. The symptoms, highly variable and taking many forms, consist principally of chills and undulating fever, headache, loss of appetite, mental depression, extreme exhaustion, aching joints and sweating. They last for 2-4 weeks but may continue for months. Spontaneous recovery may occur but periodic relapses with a return of symptoms often occur. The cycle may continue for months or years and result in invalidism accompanied by liver and bone complications. Even prolonged treatment with antibiotics is only moderately effective, and vaccines protect to only a limited extent. Superinfection can occur after severe exposure because previous natural protection or protection by vaccination confers only a moderate level of immunity. All age groups are susceptible, although children resist light exposures more easily than adults. The overall mortality rate is less than 2%.

Use as a biological agent

The high infectivity of *Brucella*, its relative resistance to environmental influences and its proved infectivity in aerosol form suggest that 50% of people could readily be infected by aerosol attack (Table 10, Annex 3). Incapacitation of the affected population would be achieved for at least 2-3 weeks despite antibiotic therapy, and could be prolonged for several weeks with relapses continuing for months or years. With a high enough exposure abortion could be expected to occur epidemically in cattle, sheep, goats and swine despite vaccination, which protects only against moderate exposure. High exposure would also overcome the limited protection obtainable in man with the vaccines available at present. The usual low case fatality rate might well be markedly increased through exposure to aerosols.

5. Typhoid fever

This disease is endemic in most parts of the world where low levels of sanitation exist. It occurs only rarely in economically developed countries. The classical epidemics were often the result of contaminated community water supplies.

The typhoid organism, *Salmonella typhi*, grows very rapidly on simple media and can be prepared in large quantities with little equipment and skill. It is a hardy micro-organism that withstands normal environmental conditions well. Normal water treatment procedures, including chlorination, are sufficient to kill the small number of bacteria that may be present.

Infection usually occurs through the gastro-intestinal tract, but aerosol infection can also be produced with far fewer bacilli than are necessary for the alimentary route of infection. The ingestion of 10^7 or 10^5 organisms is sufficient to produce infection in 50% or 25% respectively of immunized people (Hornick & Woodward, 1966), while 10^9 organisms can infect nearly all exposed persons and overcome protection by vaccination against the disease (see Annex 5). Vaccination therefore produces only a relative immunity that may last for a few years. Of the people infected, 3-5% remain carriers and sources of infection for long periods, even for life.

The incubation period in man is 1-2 weeks. The onset of the disease is gradual, with malaise, headache and fever. It then progresses to prostration, abdominal distress, rash and a high fever often resulting in delirium. Without treatment the case fatality rate is about 10%. The antibiotic chloramphenicol is effective in treatment, reducing the case fatality rate to less than 1%, but hospitalization and isolation are required for 2-3 weeks to prevent the spread of the disease and to ensure adequate treatment of complications.

Use as a biological agent

Aerosol dispersion of the organism and infection of community water supplies are both feasible. Quantitative estimates of effects following intentional contamination of a community water supply are given in Annex 5. Aerosol dispersion would contaminate exposed food and water supplies, which would consequently require disinfection and sterilization. Chemoprophylaxis and immunoprophylaxis would not be effective against very large doses of the organisms. The usual bacteriological detection procedures would not give any forewarning of deliberate introduction of infection into a water supply over a period of hours or even days.

D. FUNGAL INFECTIONS

1. Coccidioidomycosis

This is a dust-borne disease caused by the fungus *Coccidioides immitis*. The organism occurs in the soil, mainly in arid and semi-arid countries. It is diphasic, with a hyphal or so-called "saprophytic" form and an arthrosporic form that is resistant to environmental influences. The fungus is endemic in south-western USA, northern Mexico and Venezuela. It has also been reported in the USSR.

Infection usually takes place through the respiratory tract by breathing in dust containing infective arthrospores. Subclinical infections are common.

The organism can easily be grown in laboratories and yields a large number of resistant arthrospores that could be widely disseminated by aerosol.

After an incubation period of 10-20 days, there is an influenza-like illness with fever, chills, cough, pleural pain, headache and backache. About one-fifth of all clinically recognized cases develop erythema nodosum.

The primary infection may resolve without any detectable sequelae, or it may result in lung lesions (fibrosis and calcification) detectable by X-rays. In rare cases extrapulmonary dissemination occurs, with abscesses and involvement of bones and the central nervous system. Before the use of amphotericin B the disseminated form had a mortality rate of 50%. The drug is relatively toxic, and relapses may occur when treatment stops. There is no satisfactory preventive immunization procedure applicable on a large scale (Smith et al., 1961).

Use as a biological agent

Concentrated aerosols, which are technically feasible, could no doubt cause widespread infection, but it would be extremely difficult to make any predictions as to their effect. Used as a biological weapon, the organism might succeed in causing general disruption because of the lack of effective methods of prophylaxis or chemotherapy.

E. THE PREDICTABILITY OF EPIDEMICS

1. Epidemiological considerations

The extent to which contagious diseases spread through, and their manifestations in, human populations are highly variable. In a developed country a few hundred cases of smallpox or plague may produce anxiety or even mild panic, but the outbreak can usually be controlled by routine public health measures. Such an epidemic is not a threat to the survival of the community. In developing countries diseases may be much more widespread and have a regular endemic character ; but massive spread to the whole community is limited by a high degree of naturally acquired immunity and public health measures will help. On the other hand, diseases like influenza or measles may attack a large proportion of a community, especially if it has acquired little immunity from previous exposure or by immunization. That some diseases (e.g., influenza, measles, plague, and smallpox) are in fact capable of affecting a large part of a population in a highly disastrous fashion is a matter of historical fact.

A major question is whether epidemics are rare accidents or whether they could be started deliberately. It is possible that, by a deliberate selection of mutants or through recombinants, highly virulent and spreading strains could be obtained. However, it is very difficult to say whether strains with such properties have in fact been selected or produced without prior testing in man. A clearer picture of some of the quantitative elements involved can be built up by certain theoretical mathematical considerations.

2. Mathematical considerations

In order to gain insight into the quantitative factors determining the occurrence and size of epidemics, it is useful to construct a simple mathematical model. It is assumed that there is a large population at risk, of size N , and that all members of this population have the same chance of meeting each other.¹

The chance that a susceptible person will meet an infectious person is assumed to be proportional to the number S of susceptibles and the number I of infectious persons. It is also assumed that the chance of infection resulting from such a meeting is constant. The rate of occurrence of new infections will then be ASI where A is assumed to be a constant. The value of A will depend both on the nature of the community and on the epidemiological features of the disease.

Isolation, physical disability, and death will remove infected persons from contact with the general population at a rate proportional to I , so that the total rate of removal will be BI , where B is assumed to be a constant which will again be dependent on the nature of the community and on the epidemiological features of the disease.

A disease will spread if the rate of appearance of new infections in the ambulatory population is greater than the rate of removal of infected persons from circulation, that is, if the ratio of ASI to BI is greater than unity and, hence, if AS/B is greater than unity.

If $S = N$ before an epidemic gets under way, which is likely to be the case, the condition that an epidemic shall start is that AN/B should be greater than unity. It is usual to put $AN/B = C$. It will be clear that if C is less than unity, this means that infected persons are being removed faster than new infections are occurring, so that no epidemic can occur. But if C is greater than unity, the disease will spread by contact faster than it is being removed. Moreover, at least to begin with, the rate increases as time goes by. For example, in a population where $N = 1000$ and $I = 1$ initially, the rate of new infections is $ANI = 1000A$ to start with. But if at a later stage there are, say, 10 circulating cases and 5 removals, then $S = 985$ and

¹ This will not be strictly true, but as long as the chance of two people meeting does not depend on whether one is infectious and the other is susceptible to infection, the average value of the chance of meeting is all that needs to be specified.

$I = 10$. The rate of new infections is now $9850A$, nearly ten times as great. Eventually a point is reached when the spread begins to slow down again.

In relation to biological warfare, the main interest is in the total number of cases occurring during the whole course of the epidemic. This can be shown to depend primarily on the value of C , and Table 3 shows what might be expected to happen on the basis of this simple model when C has various values.

TABLE 3. RELATIONSHIP BETWEEN THE PERCENTAGE OF THE POPULATION INFECTED AND C

C	Percentage of population eventually infected
1.00	0
1.03	5
1.05	10
1.12	20
1.19	30
1.28	40
1.39	50
1.53	60
1.72	70
2.01	80
2.56	90
3.15	95

In interpreting this Table, it is important to remember that $C = AN/B$, and that both A and B are dependent on social factors as well as on the properties of the infecting organism. Thus, any organized response to an epidemic that reduces A and increases B by social measures will reduce C . The chance that this will happen during an epidemic will depend very much on the nature of the community.

It should be clear that if organisms that possess a high infectivity were to be selected for biological warfare purposes, the value of A would be high, other things being equal. Also, the value of B would remain close to zero for the major part of the incubation period, since there would be nothing to trigger off a social response until clearly diagnosed cases appeared in appreciable numbers. The value of C could therefore remain very high over a period of time, which would be of the same order as the incubation period. Consequently, in a biological warfare attack, in which the fraction of the population primarily infected might be expected to be very much greater than it is likely to be in any natural epidemic, it seems very unlikely that any constructive response to the first appearance of signs of the disease could have any effect on the size of the epidemic.

3. Danger of epidemic warfare as a tactical weapon

The use of epidemic warfare on a strategic scale might therefore seem to be impracticable, since—if it works at all—it might affect a very high

proportion of the population attacked and, even if the attacking country were protected in some way (e.g., by immunization), changes to more virulent forms of the organism employed might overcome the protection or the massive doses involved might overwhelm ordinary levels of immunity. This might lead to its alternative use as a tactical, as opposed to a strategic, biological weapon. It could be employed tactically to achieve the simultaneous infection of key groups of people, including military units. If they were

TABLE 4. SOME POTENTIAL BIOLOGICAL WEAPONS AGAINST MAN

	Protection by vaccination against currently known strains	Effectiveness of serotherapy or chemotherapy
A. Viruses	\pm^a	$—^a$
Adenoviruses (some strains)		
Arthropod-borne viruses (eastern, western and Venezuelan equine encephalitis; Japanese B; Russian spring-summer group; dengue; yellow fever; etc.)	+ to —	—
B virus and related herpesviruses	—	—
Enteroviruses (some members)	—	—
Influenza	\pm	—
Marburg virus (vervet monkey disease)	—	—
Sandfly (phlebotomus) fever	—	—
Smallpox	+	\pm
B. Rickettsiae and bedsoniae		
Psittacosis (ornithosis)	—	+
Q fever	?	+
Rickettsialpox	—	+
Rocky Mountain spotted fever	\pm	+
Scrub typhus (tsutsugamushi fever)	—	+
Typhus (epidemic)	+	+
C. Bacteria		
Anthrax	\pm	\pm
Brucellosis	\pm	\pm
Cholera	\pm	+
Glanders	—	?
Melioidosis	—	?
Plague	\pm	+
Shigellosis	?	+
Tularaemia	\pm	+
Typhoid fever	\pm	+
D. Fungi		
Coccidioidomycosis	—	?
E. Protozoa		
Schistosomiasis (bilharziasis)	—	\pm
Toxoplasmosis	—	\pm

^a + = suitable or good
 \pm = moderately effective
 — = unsuitable or poor
 ? = marginal or of questionable value, either because of the nature of the agent or because of insufficient knowledge.

simultaneously attacked by sufficiently virulent plague or influenza organisms, the military consequences might easily prove great. If the level of virulence were chosen so that the coefficient C was well below the critical value of unity, then the incipient population epidemic could be easily contained by the usual public health measures. No special action would be required by the enemy, and he would have to take only the minimal steps to protect his own troops or civilian population.

Biological warfare of this kind as a tactical weapon could easily be widely adopted. The danger would be that, though apparently relatively safe in the sense that only limited outbreaks of disease would be planned, there would always be a possibility of a virulent and spreading mutant appearing unexpectedly and producing an uncontrollable epidemic on a large scale. Mutants might also be deliberately sought in the laboratory, with the ever-present danger of their escape from the laboratory itself.

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ANNEX 3

BASES OF QUANTITATIVE ESTIMATES

A. HYPOTHESES CONCERNING DELIVERY, DISPERSION AND CONCENTRATION OF AGENTS

1. Delivery

Chemical and biological weapons have been developed that are suitable for delivery by most of the systems now used for conventional weapons. Thus means already exist for spreading chemical and biological agents by missile warheads, spray-tanks mounted on manned or unmanned aircraft, and aircraft bombs, bomblet clusters, or bomblet dispensers. Chemical agents can also be spread by tube or rocket artillery, mortars, land-mines, grenades, and portable dispensers.

In this report, attention is focused on the effects that could be produced by weapons dropped from one or a very few aircraft and generating an aerosol cloud extending across the direction of the wind along a continuous line 2 km in length.

2. Specification of dosage

The chance that a particular dose will be received by a person when the air around him contains a toxic substance will be proportional to its concentration in the air and to the time for which he is exposed to this concentration. This function of concentration and time is referred to as the Ct.

Generally, when the concentration changes with time, the total dosage received will be proportional to the area under the concentration/time curve and the Ct will be equal to this area. Where the concentration is constant, the Ct is the product of the concentration and the time of exposure.

If concentration is expressed in mg/m^3 and time is in minutes, then the Ct is expressed in $\text{mg}\cdot\text{min}/\text{m}^3$. For example, if a man goes into a chamber in which the air contains $10 \text{ mg}/\text{m}^3$ of an agent and stays there for 10 minutes the Ct will be $100 \text{ mg}\cdot\text{min}/\text{m}^3$. Next suppose that the agent is absorbed solely through the lungs. If the man is at rest he is likely to have breathed in 100 litres ($= 0.1 \text{ m}^3$) in the 10 minutes and he will have taken in 1 mg of the agent, but he is not likely to have absorbed all of it. However, if the concentration had been twice as great or the exposure time twice as long and everything else had been equal, the man would have received

twice the dose. Thus, the Ct is a measure of the *intensity of exposure*, and not of the dose that actually penetrates into the body, and the concept applies as much to pathogens as to chemical agents.

3. Specification of toxicity and infectivity

The LD₅₀ (lethal dose₅₀) of a drug or a microbe is the dose that will kill 50% of the subjects receiving it. It may also be defined as the dose that has a 50% probability of killing any particular individual. Correspondingly, and more generally, one can specify an ED₅₀ (effective dose₅₀) as the dose that has a 50% probability of producing any precisely definable effect, for infective agents the term ID₅₀ (infective dose₅₀) is used for the dose that has a 50% probability of producing a specified response to infection, considered in this report as symptoms or signs of disease or death.

Correspondingly, the ED₅ indicates the dose likely to cause an effect in 5% of those exposed and the ED₉₅ is the dose likely to affect 95% of exposed persons.

Neither the LD₅₀ nor the ED₅₀ gives sufficient information in itself to form a guide to the relation between dose and effect. The additional information needed is provided by the "slope of the probit line", which can always be calculated from the data required for the accurate determination of an ED₅₀ (Finney, 1952, 1968). This figure is dimensionless, so that its meaning is independent of the units of dosage.

The steepness of the slope indicates the factor by which the ED₅₀ must be multiplied to give any other specified probability of producing a response to the drug. The steeper the slope, the more rapidly the probability of an effect increases with increase in dose (see Table 5).

TABLE 5. INFLUENCE OF PROBIT SLOPE ON AGENT INFECTIVENESS¹

Slope of the probit line	Ratio of ED ₉₅ to ED ₅	Ratio of ED ₉₅ to ED ₅₀ ^a
0.5	3.80×10^5	1.95×10^3
0.6	3.04×10^5	5.51×10^2
0.7	5.01×10^4	2.24×10^2
0.8	1.30×10^4	1.14×10^2
0.9	4.53×10^3	6.73×10
1.0	1.95×10^3	4.41×10
1.5	1.56×10^2	1.25×10
2.0	4.41×10	6.65
5.0	4.55	2.13
10.0	2.13	1.46
20.0	1.46	1.21

^a This is equal to the ratio of the ED₅₀ to the ED₅.

¹ N.B. At low probit slopes, the probability of effect changes so slowly with dose, even in the neighbourhood of the LD₅₀, that it is not possible to specify the LD₅₀ with any great exactitude, even when large numbers of animals are used for its estimation.

This table shows that for slopes appreciably less than unity, there is a very slow change of effectiveness of dosage, whereas for slopes of 20 or over the change of effectiveness is so abrupt that doses just detectably smaller than the ED₅₀ are almost harmless and doses just detectably greater are almost 100% effective. This has a bearing on the comparison of toxicities. Quite small differences between the ED₅₀ values of two compounds will imply real differences in toxicity if both slopes are large, but very large differences in the ED₅₀ may have no practical significance if both slopes are small.

In the intermediate range of values of the slope, it is essential to consider the slope of the probit line and the ED₅₀ together when making comparisons between effectiveness of toxic substances, especially if interest centres on probabilities of effectiveness well removed from 50%.

Consider, for example, two potential incapacitating agents, A and B. Agent A has an ED₅₀ of 1 mg-min/m³ and a probit slope of 1. Agent B has an ED₅₀ of 5 mg-min/m³ and a probit slope of 5.

On the basis of ED₅₀ values, agent A appears to be 5 times as effective as B. But reference to Table 5 will show that the ED₉₅ of A is 44 mg-min/m³, whilst the ED₉₅ of B is less than 11 mg-min/m³. Thus, when a high probability of effect is required, B can be 4 times as effective as A. When the probit slopes are lower (e.g., 0.5 and 1.0) larger ratios of ED₅₀ values can be misleading.

Whereas very highly toxic chemical agents can have probit slopes (5-10) many biological agents have slopes less than or near to unity. This means that a biological agent cloud may travel a considerable distance downwind before its dosage drops from an LCt₅₀ to an LCt₅, but that exceedingly high concentrations are needed to give an ED₉₅. Table 6 shows experimental probit slope values for different pathogen/host-species combinations.

TABLE 6. PROBIT SLOPES FOR INFECTION BY SELECTED PATHOGENS

Agent	Host	Route of administration	Probit slope
<i>Coxiella burnetii</i>	guinea-pigs	aerosol	1.7 (Tigertt et al., 1961)
VEE α virus	guinea-pigs	aerosol	0.8 (Ehrlich & Miller, 1968)
<i>Bacillus anthracis</i> (spores)	cynomolgus monkeys	aerosol	0.7 (Glassman, 1966)
<i>Pasteurella (Francisella) tularensis</i>	mice	aerosol	0.9 (Lincoln & DeArmon, 1959)
<i>Salmonella typhi</i>	man	oral	0.7 (Hornick & Woodward, 1966)

^a Venezuelan equine encephalomyelitis.

4. Local meteorological factors

Winds are nearly always inconstant in force and direction and every irregularity in or on the surface of the ground contributes to the irregularities of their motion. Much work has been done on the effect of these irregularities of motion on the distribution of pollution through the atmosphere, and it is important to determine what can be learnt about the probable distribution of chemical and biological agents from this work.

Pasquill (1962) has devised categories of atmospheric turbulence that are generally accepted for making rough estimates of the spread of atmospheric pollutants. Of these, category A is the most turbulent, and it is rare in the only regions for which frequency of occurrence is well known. Category F is the most stable atmospheric state for which realistic predictions can be made. Examination of long-term meteorological records for the United Kingdom have shown that, in most places, states E, F and those of greater stability than F (which can be considered for present purposes as similar) are likely to occur at around midnight on about half the nights throughout the year. The longer the nights, the longer will be the period in which these degrees of stability will be observed; in mid-winter, it may extend from 6 p.m. to 6 a.m. (from 18.00 to 06.00 hours). For the purposes of this discussion, maintenance of this degree of stability for two hours would suffice; in the United Kingdom this degree of stability occurs during different times at all periods of the year.

Most of the information about the dissemination of pollutants in the atmosphere under different conditions of atmospheric stability has been derived from studies in open country. It is usual to predict the likely atmospheric stability from the wind speed, the state of the sky, and the time of the day. Over cities, the atmospheric turbulence may be expected to be augmented by the extra surface roughness and by heating from industrial, commercial and domestic processes. Pasquill (1962) provided estimates of the vertical spread of a pollutant released at ground level after it had travelled different distances over open country. A study carried out by the US National Air Pollution Control Administration in the city of St Louis (McElroy & Pooler, 1968) provides the only published evidence of the extent of the additional vertical spread that is to be expected over urban areas.

It is unfortunate that the best data are available for one of the world's most labile climates, namely that of the United Kingdom. Much more meteorological information from many more locations needs to be collected and analysed before the estimates made here can be considered to have more than illustrative value.

5. Influence of local meteorological factors on the effectiveness of an attack with chemical weapons

In the model used here by way of illustration, it is supposed that 4 tons of sarin are dropped at ground level along a 2-km line at right angles to the mean wind direction, and that there is negligible cross-wind dispersion of the aerosol cloud as a result of variations in wind direction about the mean, so that it passes downwind as a 2-km wide band to the point at which the Ct becomes too low to give a significant probability of a lethal effect.

It is assumed that the initial cloud extends from ground level to a height of 10 metres. Since the concentration in this cloud will be inversely proportional to its downwind spread and since its time of passage downwind past any point will be directly proportional to this spread, the Ct is independent of the spread. When the wind speed is 2.5 m/sec the initial Ct of the postulated pattern of attack with sarin will be 1330 mg-min/m³.

It appears that the probit lines of very toxic agents have high slopes. It is legitimate therefore to take the critical distance as that at which the Ct corresponds to an LD₅₀. This Ct is referred to as the LCt₅₀. The probability of death will amount almost to certainty for an agent of high probit slope (5-10) when the Ct is only a little larger than the LCt₅₀, and the probability of survival will be equally high when the Ct is only a little smaller than the LCt₅₀.

When considering the factors that determine the distance that the cloud can travel downwind before the Ct falls below the LCt₅₀, it is assumed that the particles of aerosol are so fine that they do not settle out at all on the ground or impact on vertical surfaces. This does not correspond with chemical warfare practice, but it enables one factor to be examined at a time.

Suppose that the atmospheric stability category is F in open country and that the wind speed is 2.5 m/sec. It can then be calculated from Pasquill's curves that the cloud will have to have spread vertically to such an extent that the concentration at 200 m altitude is 10% of that at ground level in order that the initial Ct of 1330 mg-min/m³ at ground level shall fall to 100 mg-min/m³, which is estimated to be the LCt₅₀ of sarin for man. Vertical spread of this extent is achievable with the degree of atmospheric stability assumed, but Pasquill has calculated that even after making reasonable allowance for the more rapid spread expected in an urban area it will not be achieved until the cloud has travelled 4-6 km.

Thus, in this state of atmospheric stability, dilution of the agent as the result of atmospheric turbulence will play a trivial role in mitigating the effect of sarin on an urban area.

On the other hand, if the stability state of the atmosphere falls into category D in open country, it is estimated that the distance downwind at which the ground level Ct of sarin would fall below the critical value would be only about 1.5 km. Even at midnight there is a substantial chance of

this happening, and there is an appreciable chance of still more unstable states making their appearance in the late hours of the night and the early hours of the morning.

With an agent that is 10 or more times as toxic as sarin (and this category includes VX and botulinal toxin) it is estimated that the reduction of Ct below the effective value within 1.5 km would require an atmosphere considerably more unstable than category B. In the United Kingdom, such a degree of instability occurs rather infrequently and usually only near the middle of the day.

6. Fall-out as a factor influencing the incidence of attack

The agents instanced as more toxic than sarin are VX, which is a non-volatile liquid, and botulinal toxin, which is a solid that is soluble in water and may therefore be expected to form droplets in most conditions of humidity. Droplets in an aerosol are always likely to encounter one another in the course of their random motions, and when they meet there will be a strong tendency for them to coalesce. The downward gravitational pull on a drop is proportional to the cube of its radius, while the frictional forces braking its fall under gravity are proportional to the square of its radius; therefore, as drops grow they precipitate more rapidly out of the air.

What will happen to the drops or droplets produced by a chemical weapon will depend on the spectrum of drop sizes produced.

It appears that aerosols of chemical agents generated by bombs or by spray-tanks are usually very coarse, consisting mostly of particles of more than $100\ \mu$ in diameter. It is only when the particle size is less than $10\ \mu$ in diameter that fall-out is slow.

Published data for such aerosols show an initial high rate of fall-out and a subsequent decrease in the rate as they pass downwind. For present purposes, it is assumed that the amount of material remaining in aerial suspension falls by a factor of 9 in the first km of travel and by a factor of 3 for each km thereafter. This gives the general rule that the amount remaining suspended at a distance of K km from the source has been reduced by a factor of $3(K + 1)$.

What will actually happen in practice will depend on the precise droplet spectrum produced by the weapon, but for moderate distances the empirical rule suggested here is not likely to be very inaccurate. This rule gives a direct measure of the fall in the relative Ct of the agent at different distances downwind from the line of release, but it can only be applied directly to an area of smooth ground. Relatively large droplets will impact on the vertical surfaces as the air carrying them flows around obstructions.

For the model attack with 4 tons of sarin spread along 2 km, it has been stated in section 5 that if the cloud is initially distributed uniformly between

the ground and a height of 10 m the initial Ct will be 1330 mg-min/m³, so that the distance at which this would fall to 100 mg-min/m³ (the LCt₅₀ of sarin) is about 1.3 km. Thus, in travel through a built-up area in any meteorological conditions which could cause any degree of vertical dispersion of the residual aerosol cloud, it is unlikely that the cloud could travel more than 1 km before the Ct fell below the LCt₅₀ of the agent.

For the more toxic agent VX (LCt₅₀ = 10 mg-min/m³) the same density of attack would result in the extension of the lethal zone (the area in which Ct > LCt₅₀) for a further 2 km, i.e., to 3 km downwind.

Among the poisons still more toxic than VX that might conceivably be used as chemical agents is botulinum toxin, whose LCt₅₀ in man is estimated to be around 0.02 mg-min/m³, and whose probit slope is steep. Assuming that this agent is sufficiently stable to be disseminated by the types of weapon considered here and to remain undetoxified in the aerosol state (conditions that might be fulfilled through the use of suitable stabilizers, if not already attainable with the untreated agent), the cloud would then travel about 6 km downwind before its ground-level dosage fell below the LCt₅₀.

It is instructive to speculate on the effects of these kinds of attack if weapons were used that were capable of disseminating the agent in a monodisperse aerosol, rather than the broad spectrum of droplets or particles produced by the weapons considered above. It has been calculated that only about 13% of a monodisperse, 5 μ diameter aerosol would be deposited on the ground during 20 km of downwind travel, under moderately stable atmospheric conditions with a wind speed of 2.5 m/sec (Johnstone et al., 1949). If this dosage-reducing factor is combined with the reduction due to eddy diffusion under open-terrain conditions with atmospheric stability F, the ground-level dosage after 20 km of travel can be calculated to be about 1% of that at the source line. This means that the ground-level dosage produced 20 km downwind by a source-strength equal to those considered above would be about 13 mg-min/m³, which corresponds to slightly more than the LCt₅₀ of VX.

In summary, 4 tons of sarin delivered along a 2-km line (open-terrain atmospheric stability = category F, wind speed = 2.5 m/sec) would deliver a Ct in excess of the LCt₅₀ over about 2 km², while the corresponding areas with VX and botulinum toxin would be 6 km² and 12 km² respectively. With a monodisperse 5 μ diameter aerosol of VX, the area would be slightly greater than 40 km² (Table 9).

It seems likely that an attacker would load on to an aircraft the maximum permitted weight of weapons, even if this involved some possibility of loss of efficiency by overhitting. It is therefore to be expected that the aircraft, whatever their size, would attempt to lay down line sources containing about 2 tons per km length, and that the effect would be to create lethal zones of approximately 0.5-3 km² per ton of agent, or about 0.1-0.75 km² per ton of weapons, depending on whether sarin, VX, or botulinum toxin

were used. For the hypothetical weapon disseminating the monodisperse 5μ diameter VX aerosol, the figures would be about 10 km^2 per ton of VX, or 2.5 km^2 per ton of weapons. It seems likely, however, that the VX-disseminating equipment needed to generate a monodisperse aerosol of this small droplet size would account for considerably more than 75% of the weight of the weapon, so that the lethal zone for VX might be considerably less than 2.5 km^2 per ton of weapons.

7. Influence of the volatility of the agent

Where the vapour pressure of the agent is low, as with VX, or negligible, as with a bacterial toxin, fall-out during travel does not represent any appreciable additional hazard, and the area coverage would be correspondingly reduced. Where the vapour pressure is high, however, as with sarin, material that has been deposited on roads, roofs, walls, soil, and vegetation may evaporate into the air and reinforce the hazard in the areas downwind of the point of fall-out. It is not possible to estimate the magnitude of this contribution to the effects of attack. It will be limited by two factors: (1) some of the agent that falls out will not be able to evaporate because it has dissolved in water films on various surfaces, because it has become bound by adsorptive forces on the surfaces of solids, because it has penetrated into crevices or pores in solids, or because it has reacted chemically with organic matter, living or dead; (2) in circumstances in which the atmosphere is stable, surface temperatures will generally be too low to permit appreciable evaporation.

All that it is possible to say with any confidence is that re-entry of deposited agent into the air in the form of vapour is not likely, in the case of sarin, to come anywhere near to compensating for the fact that the LCt_{50} of sarin is 10 times that of VX, i.e., if the high-risk area for VX extends downwind for 3 km, the high-risk area for sarin will extend downwind for a substantially shorter distance.

8. Possibility of more efficient means of attack

It will have been noted that although VX has 10 times the LCt_{50} of sarin (and is assumed to have a similar probit slope) it is by no means 10 times as effective when delivered in the pattern of attack considered here. If one tenth as much VX as sarin were delivered per km the effects of the two attacks would be similar, so that there would be considerable over-hitting with VX in the pattern of attack adopted.

Four tons of sarin or VX seems to be more than could be put on to a single bomber in a sufficient number of small bombs to create a continuous source over a length of 2 km because of the weight of weapons hardware required. But half this load of sarin would create a lethal zone of only a

little less than 1 km in depth downwind. An aircraft much smaller than a heavy bomber, carrying a multiplicity of very small VX bombs with a total payload of only 0.2 tons of VX (which might mean 1-1.5 tons of weapons) could cover the same area.

No consideration has been given to random attack with individual bombs scattered over the target area, since this type of attack is much more difficult to achieve than creating a line source and is bound to be less effective.

An alternative mode of attack that could produce a line source is dispersal by means of an airborne spray-tank. Here the crucial factor is the height of the release. By the time the aerosol, in its travel downwind, has reached ground level, its droplets will be spread through a vertical height greater than the height of release, and the ground area over which the Ct will exceed the LCt_{50} is bound to be less than if the same weight of attack had been released at ground level. Spray-tank delivery at ground level, as is done with insecticides, would have the same disadvantages as indicated above for small bomblets, and the effects would be similar.

It would appear from what has been said that the model of attack considered would have the order of effectiveness that could and would be achieved by a skilled aggressor furnished with the types of agent and weapons mentioned.

9. Conclusions on the feasibility of an attack with chemical weapons on urban areas

Even though it has been assumed that meteorological conditions would be favorable and although an attempt has been made not to weight the scales against the probable success of an attack, it is concluded that no agent less toxic than the nerve gases is worth taking into consideration as a means of making a surprise attack with present agents with a small aircraft. A ton of small weapons of 20% payload dropped by such an aircraft to form a 1-km line source would have very little effect outside the area of drop if the toxicity of the agent equalled or were less than that of sarin.

The factor limiting the effectiveness of the agents considered here is the large droplet size produced by the weapons. If very small droplets could be generated at ground-level by means that did not reduce the payload by a large factor, the effectiveness could be considerably increased.

It is therefore concluded that the large range of agents described in Annex 1 would be unlikely to be considered by a potential aggressor for use against an urban target. If indeed one of these agents was considered for any use at all, it would only be against some small specific target having features that would prevent its rapid dissipation, or with the intention of producing effects only in the immediate vicinity of the burst.

This conclusion is consistent with the fact that serious concern about the chemical warfare threat did not appear until agents of the order of toxicity of VX had been developed to the point where they might be used in practice. It can be anticipated that military authorities will now seek improvements in weapons delivery systems rather than more toxic agents.

10. Implications for protection

With a wind speed of 2.5 m/sec the cloud of agent would travel 150 m per min. It appears unlikely that, over the 3 km or so a VX cloud would travel before becoming effectively non-lethal (when the source strength is 2 tons/km), its spread along wind could have increased to as much as 1.5 km. If so, the time of passage of the cloud past any element of the target would not be likely to exceed 10-15 minutes. Consequently, the hazard would not persist for much longer than the duration of the attack. In order to maintain the hazard for an appreciably longer period than that due to fallout on the ground it would be necessary to maintain the attack over a similar period, which would necessitate an overall weight of attack of the same order as that needed when conventional weapons are used. Prolonged attack with relays of weapons therefore seems unlikely to prove attractive.

Thus, protective measures capable of mitigating the effects of very short-lived gross contamination of the target by fine aerosols might be a useful disincentive to potential users of chemical weapons against urban areas. Spray and other methods of delivery resulting in large droplets that would contaminate surfaces would require effective decontamination measures as well.

B. HYPOTHESES CONCERNING BIOLOGICAL AGENTS

An exponential decay has been assumed for the biological agents as follows: $V_t/V_0 = e^{-kt}$, where V_t and V_0 = the viabilities at the time t and time zero respectively, and k is a constant.

May et al., (1969)¹ have shown that organisms vary widely in their k factor when exposed in open air at night (0-20°C, relative humidity above 65%). Under such conditions k for bacteria usually falls in the range 0.03-0.1 decay per minute (where 1 = 100%). Indoors, the decay rate is much lower. Certain viruses are reported to have higher decay rates. Spores are much more resistant and probably become stable within a few hours, so that they persist for very long periods. Viruses containing lipids (arboviruses, influenza) are more resistant than lipid-free viruses. When biological agents are used in the form of aerosols, viability can be markedly increased by incorporating special stabilizers and other substances in order to provide

¹ For further references see Benbough, J. E. (1969) *J. gen. Virol.*, **4**, 473-477.

particles with diameters in the range of about 1-7 μ (suitable for deep penetration into the lungs) and to ensure protection against adverse environmental influences (e.g., solar radiation, variability in humidity). In assigning the *k* values listed in Table 7, it has therefore been assumed that such aerosol stabilizers would be used. In addition, it has been assumed that immediately after aerosolization (following bomblet explosion or spray delivery) 95% of the organisms would be rendered ineffective by heat, rapid initial decay, clumping, and sedimentation.

It is hoped that the use of high estimates of the early and progressive losses of infectivity will have minimized the chances of over-estimating potential casualty rates through assigning wrong values to such important factors as infective doses for man and the effective payload of weapons.

Vaccine production laboratories can produce dry powder preparations of *Brucella* containing more than 1.3×10^{11} organisms per gram. It thus seems reasonable to postulate that in an attack with this agent some 50 kg of powder containing at least 6×10^{15} organisms might be disseminated along a 2-km line. Assuming an initial 95% loss of infectivity, this would leave about 3×10^{14} infective organisms. If the infective cloud extended initially for 10 m above ground and if the wind speed was 2.5 m/sec, the initial Ct would be 10^8 organism-min/m³, which means that a man over whom the cloud passed would take in at least 10^8 organisms (inhalation at 10 litres per minute).

The ratio of payload (dry powder) to disseminating equipment and medium may be as low as 1 : 40 for ground-functioning weapons so that the weight of weapons required for delivery of 50 kg of dry powder could

TABLE 7. ASSUMED HUMAN INFECTIVE DOSES AND AEROSOL DECAY RATES FOR BIOLOGICAL AGENTS

Disease caused by agent	Assumed 50% human infective dose (ID ₅₀) ^a	<i>k</i> factor (decay per minute) assigned for aerosol (<i>k</i> × 100 = %)
Venezuelan equine encephalitis	10 000 × guinea-pig ID ₅₀	0.3
Tick-borne encephalitis	10 000 × TCID ₅₀ ^b	0.3
Yellow fever	10 000 × EID ₅₀ ^c	0.3
Influenza	10 000 × EID ₅₀ ^c	0.3
Epidemic typhus	5 000 × EID ₅₀ ^c	0.1
Rocky Mountain spotted fever	5 000 × EID ₅₀ ^c	0.1
Q fever	100 organisms	0.1
Brucellosis	10 000 organisms	0.02
Plague	10 000 organisms	0.02
Tularemia	250 organisms	0.02
Anthrax	100 000 spores	0.001

^a ID₅₀ = the dose that would cause overt disease in 50% of exposed individuals

^b TCID = tissue culture infective dose

^c EID = egg infective dose

be as much as 2 tons, easily carried by one bomber. Proportionately higher payloads would be possible with spray delivery.

The same general input as given for *Brucella* to give an initial Ct of 10^8 organism-min/m³ (or, for viruses, 10^8 infective dose-min/m³) has been assumed for all the remaining agents in Tables 7 and 10. For some but not all of these agents production in the form of powders that would retain high infectivity over adequate periods of time would require the use of advanced technological procedures. Such procedures are well within the competence of several countries, and can ultimately be achieved by many more.

Table 7 also shows the assumptions made for each of the biological agents for which calculations have been made in Table 10. The estimates given in Table 10 take into account case fatality and morbidity rates and the probable effects of therapy (see Annex 2 for details of individual diseases).

Where the probit slopes of biological agents are known they are low. This means that as the concentration of agent in the aerosol decreases during its passage downwind there is a progressive fall in effectiveness; this is in contrast to what happens with a chemical agent of high probit slope, where there is only a small area of gradually decreasing effectiveness between the upwind area of very high toxicity and the downwind area of very low toxicity. Casualty estimates for biological attacks have therefore been based on the assumption that within the area covered the overall probability of a primary effect on an unprotected person would be 50%.

This may be a slightly conservative estimate. But as a very massive attack would be needed to raise the mean probability over the target area of causing incapacitating or lethal disease to 95% and, as such a massive attack would have unpredictable consequences for a very large distance downwind of the target, it is doubtful whether the 50% assumption would be in substantial error when applied to the kind of attack under discussion.

C. ESTIMATES OF NUMBERS OF CASUALTIES

There are two important factors that influence the estimates of the number of persons at risk.

The first is the probable degree of exposure of the population to the drifting clouds of pollutant. If it is assumed that the population lacks any kind of defensive equipment or training against an attack with chemical or biological weapons, protection would be furnished only by the buildings that people inhabit and by the shielding of occupied open areas by tall buildings and other obstacles to the travel of the clouds. In many instances, people inside buildings may not be much better off than people outside. Although the concentration of pollutant inside a building will rise more slowly than that outside, and to a lower peak, it will also fall more slowly, and the Ct dosages experienced inside and outside the building may be

TABLE 8. NUMBERS OF PERSONS AT RISK FROM AN ATTACK WITH CHEMICAL OR BIOLOGICAL WEAPONS ON THE MOST DENSELY POPULATED AREAS OF TYPICAL URBAN TARGETS

Population of town	Industrially developed country			Industrially developing country		
	Type of area ^a			Type of area ^a		
	I	II	III	I	II	III
500 000	50 000	75 000	120 000	180 000	200 000	250 000
1 000 000	60 000	100 000	180 000	100 000	160 000	250 000
5 000 000	150 000	300 000	500 000	60 000	150 000	250 000

^a The types of area selected are the most densely populated areas of the sizes specified below in the different kinds and sizes of town:

Area I extends from an attack line 1 km upwind of the town centre to 2 km downwind of the town centre, and is 2 km wide

Area II extends from 1 km upwind of the town centre to 9 km downwind of the town centre, and is 2 km wide

Area III extends from an attack line 10 km upwind of the town centre to 10 km downwind of the town centre and is 2 km wide

See Section D for explanation of population density.

very similar. The higher the ventilation rate of the building, the higher will be the peak concentration of the agent inside. Protection of the occupants may none the less be possible if the ventilation rate can be reduced as soon as there is warning of the attack or if the ventilation input can be filtered to some extent.

TABLE 9. EFFECTS OF AN ATTACK ALONG A 2-KM LINE USING UP TO 4 TONS OF CHEMICAL AGENT REQUIRING 15-20 TONS OF WEAPONS

Chemical agent	Area affected ^c
Sarin ^a	2 km ² in Area I
VX	Area I (= 6 km ²)
Botulinal toxin (if adequately stabilized) ^b	Intermediate between Areas I and II (approx. 12 km ²)
VX, dispersed as a monodisperse 5 μ diameter aerosol (if technically feasible) ^b	Area III (approx. 40 km ²)

^a Agents less toxic than sarin would produce effects only in the immediate vicinity of the explosion of a weapon

^b A larger weight of weapons, perhaps 2-3 times as great, might be required to deliver the botulinal toxin or to produce the fine VX aerosol because of the greater amount of hardware required for such purposes

^c See Table 8 for definitions of areas I, II and III.

Another factor that has to be taken into account is the distribution of dosages over the area covered by the cloud. An even distribution would be improbable, because the weapons used would be unlikely to set up a cloud of uniform density, and also because surface irregularities in the path of the cloud would undoubtedly alter the Ct dosages experienced at particular points. If the cloud had to rise over an obstruction due to tall buildings, the open area downwind of this would be equivalent to a poorly ventilated enclosure in which the concentration of agent would not reach that in the general cloud.

In view of these uncertainties, the casualty estimates for chemical warfare are presented in Tables 8 and 9 as populations at risk of death from primary infection in the most densely populated areas of urban targets. It is thought that non-lethal casualties would be much smaller in number than lethal casualties. In an attack with biological agents, the probability of infection of an exposed man may be much less than unity, even in a concentrated attack, and the proportion of fatal infections can vary greatly according to the infecting agent. In order to display the consequences of this sort of variation, the estimates of casualties from biological warfare have been set out in Table 10 as estimates of the deaths and the non-fatal infections that would ensue if the populations at risk received no warning and had no protection of any kind.

D. POPULATION MODELS

To illustrate the public health implications, 6 hypothetical cities have been taken, 3 typifying economically developed communities (e.g., in Europe or North America), and 3 typifying developing areas (e.g., in South-East Asia, the Eastern Mediterranean, or South America). The 3 cities in each of these groups have 500 000, 1 000 000 and 5 000 000 inhabitants, respectively.

These hypothetical cities have been made to conform to the Clark (1951, 1957) model of urban population distribution, in which it is assumed that the greatest density of population is in a small area surrounding the centre of the city and that population density falls off exponentially with increasing distance from this area. By integration of population density over areas of the sizes shown in the legend to Table 8, those areas of each size that have the greatest population density can be found for each kind of city.

The two parameters of the model, the maximum central population density and the coefficient of exponential decay, change with changes in the total population, but not in the same way in developed and developing countries. As a consequence, the maximum population at risk in attacks of the kind postulated here varies with city size in different ways in the two kinds of city.

TABLE 10. ESTIMATED POSSIBLE PRIMARY EFFECTS OF LIMITED (SINGLE BOMBER)

Disease caused by agent ^a	Pattern of attack (type of area) ^b	Downwind carriage of lethal or incapacitating concentrations ^c		Number of					
		Ap-proxi-mate extent	Ap-proxi-mate time	Population					
				1		2		3	
				D	I	D	I	D	I
Venezuelan equine encephalitis (similar effects can be expected from Rift Valley fever, chikungunya and Q'nyong-nyong)	I	1 km	5-7 min	100	10 000	100	12 000	300	30 000
Tick-borne (far Eastern) encephalitis (similar effects can be expected from Japanese encephalitis and yellow fever)	I	1 km	5-7 min	2 500	10 000	3 000	12 000	7 500	30 000
Influenza, antigenically modified, non-virulent strain	I	1 km	5-7 min	50	10 000	50	12 000	50	30 000
Epidemic typhus	II	5 km	30 min	2 500	30 000	3 000	37 000	8 000	125 000
Rocky Mountain spotted fever	II	5 km	30 min	2 000	30 000	2 500	37 000	7 500	125 000
Brucellosis	II	10 km	1 h	150	27 000	200	50 000	600	150 000
Plague	II	10 km	1 h	6 500	27 000	12 000	50 000	36 000	150 000
Q fever	III	>20 km	>2 h	50	60 000	100	90 000	250	250 000
Tularaemia	III	>20 km	>2 h	4 500	60 000	7 000	90 000	19 000	250 000
Anthrax	III	>>20 km	>>2 h	24 000	60 000	36 000	90 000	100 000	250 000

* Approximately 50 kg of dried powder containing 6×10^{15} organisms are assumed to have been aerosolized to form a band 2 km long at right angles to the wind direction under type F meteorological conditions.

^a For detailed descriptions, see Annex 2.

^b See Table 8 for definitions of attack patterns (areas) I to III.

^c For assumptions on which calculations are based, see pp. 88-91 and 93-95.

^d The figures are rounded estimates, based on the number of individuals at risk and taking into account such factors as an assumed attack rate of 50%, the case fatality rates, and for some of the agents the use of antibiotics as described under "Remarks" and in Annexes 2 and 3.

D = deaths

I = incapacitated, including deaths

BIOLOGICAL WARFARE ATTACK ON UNPROTECTED CIVILIAN POPULATION GROUPS *

casualties ^d						Remarks
group ^e						
4		5		6		
D	I	D	I	D	I	
400	35 000	200	20 000	100	10 000	
9 500	35 000	6 000	20 000	3 000	10 000	
100	35 000	100	20 000	50	10 000	
19 000	85 000	15 000	65 000	14 000	60 000	Use of antibiotic therapy considered to cause reduction of mortality by 70 % and 10 % for economically developed and developing communities, respectively.
11 500	85 000	9 000	65 000	7 500	60 000	Same as above for epidemic typhus.
500	100 000	400	80 000	350	75 000	
55 000	100 000	44 000	80 000	41 000	75 000	Same as above for epidemic typhus.
150	125 000	150	125 000	150	125 000	No calculations made for after two hours ; part of infective cloud would persist downwind.
30 000	125 000	30 000	125 000	30 000	125 000	Same as above for epidemic typhus. No calculations made for after two hours ; part of infective cloud would persist downwind.
95 000	125 000	95 000	125 000	95 000	125 000	No calculations made for after two hours ; part of infective cloud would persist far downwind. Use of antibiotic therapy considered to cause reduction of mortality by 50 % and 5 % for economically developed and developing countries, respectively.

^e The population groups are defined as follows :

1. Urban population of approximately 500 000 in economically developed country
2. Urban population of approximately 1 000 000 in economically developed country
3. Urban population of approximately 5 000 000 in economically developed country
4. Urban population of approximately 500 000 in developing country
5. Urban population of approximately 1 000 000 in developing country
6. Urban population of approximately 5 000 000 in developing country

For further explanations of the population model, see p. 97.

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ANNEX 4

MEDICAL AND PUBLIC HEALTH EFFECTS OF ATTACK WITH CHEMICAL OR BIOLOGICAL WEAPONS

INTRODUCTION

It is stressed that the following attempt to consider some of the potential medical and public health problems that would be produced by an attack on a major city with chemical or biological weapons deals only with the minimal attack model described in Annex 3 (a few bombers for chemical agents, and one bomber for biological agents). A maximal attack, or an attack with chemical and biological combined with nuclear weapons or even with conventional explosives or incendiaries, would produce problems quantitatively and qualitatively different from those discussed here, as would repeated attacks with chemical or biological weapons. A brief general discussion of the problems will be followed by an attempt to illustrate some of them more explicitly by descriptions of hypothetical attacks with :

- (1) a lethal and incapacitating antibiotic-sensitive biological weapon *without* secondary cases (tularaemia) ;
- (2) a lethal and incapacitating antibiotic-sensitive biological weapon *with* secondary cases (pneumonic plague) ; and
- (3) a lethal chemical agent (VX).

These descriptions will sketch the possible consequences of attacks on cities with a population of half a million and of 5 million in an economically advanced country and in a developing country.

Because the effects of the widespread use of such weapons have, fortunately, never been tested, the principles described and the hypothetical attacks are extrapolations from limited information. Extrapolations from naturally occurring epidemics can, however, provide limited clues to the effects of induced epidemics.

GENERAL PRINCIPLES

(1) Problems in preparing for defence against an attack

Medical and public health preparations for meeting a chemical attack on a city would include :

- (a) the stockpiling of drugs to counter the effects of the agents that might be used (e.g., atropine and the oximes for the nerve gases);
- (b) the preparation of additional hospital beds to handle a sudden influx of casualties;
- (c) the training of additional health personnel to treat the casualties;
- (d) the supply to each person of protective equipment (e.g., gas masks) or antidotes (e.g., syringes loaded with atropine for self-injection); and
- (e) preparation for decontamination.

Preparations for defence against a biological attack would include :

- (a) the immunization of the population against agents which might be used;
- (b) the stockpiling of antibiotics and other drugs;
- (c) the preparation of additional hospital beds and training of manpower;
- (d) the strengthening of diagnostic stations; and
- (e) preparation for decontamination.

Preparing against an attack would introduce other types of problem. Stockpiling of vaccines and drugs is very difficult and expensive, because they lose their potency with time and must be continually replaced. Preparation of additional beds and personnel diverts resources from other medical and public health purposes. While self-injecting syringes may be feasible in a highly trained and disciplined group, such as a body of troops, they would be unlikely to be effective and might be highly dangerous in the general population. Immunization of the population against a large number of potential agents is likely to induce considerable morbidity and some deaths due to the immunization procedure itself; it is also unlikely to be effective because an enemy could use an agent against which no immunization had been given or increase the dose of the agent sufficiently to overwhelm existing immunity. Finally, many of these methods would cause anxiety in the population and might lead to maladaptive responses (see Annex 6 on psychosocial effects).

(2) Immediate problems in the event of an attack

The response by medical and public health authorities would depend on the nature of the attack, the amount of warning given, the period of time that elapsed between the attack itself and identification of the agent, the nature of the population and the environment in which the weapons were used, and the resources available. Placing large masses of people in quarantine, of doubtful value in any case, would be impossible in most instances.

In almost all cases difficult priority decisions would have to be made. For example, if antibiotics were in limited quantity, who would be first to receive them? If hospital beds were limited, would those occupying them be discharged to make way for the casualties? If health manpower was limited, from what tasks would it be diverted?

(3) Problems after the attack

After the primary problems of the attack had been dealt with, there would be a number of secondary and residual problems. Certain agents, such as the nerve gases, cause anoxia which can produce cerebral damage, leaving neurological sequelae even though the person's life is saved. Biological agents spread from person to person can give rise to secondary attack waves which, in diseases like plague, may continue for months or years after the event. Massive attacks may alter the ecological relationship between man and lower animal vectors of disease and the human microbial flora, thereby initiating outbreaks of diseases previously latent. Decontamination would be required for persistent chemical and biological agents.

EXAMPLES BASED ON HYPOTHETICAL SITUATIONS

The following analysis of the medical and public health effects of hypothetical attacks will illustrate some of the problems more explicitly. The attacks are postulated as being on cities with a population of half a million and 5 million in economically developed and developing countries. The population dispersal would be according to the model used in Annex 3 (Table 8 and p. 97).

Assumptions on availability of health resources

(A) A city of 5 million in an economically developed country could be assumed to contain:

- (1) doctors: approximately 1 per 500 population, i.e., approximately 10 000;
- (2) nursing personnel including auxiliaries: approximately 60 000;

(3) hospital beds : approximately 10 per 1 000 population (50 000 beds) in the city and approximately 5 per 1 000 population (15 000 beds) in the immediately surrounding conurbation (assuming 3 million people in the surrounding area). Of these beds, 10% would be vacant at the time of the attack and an additional 30% could be made available in a few hours by discharging selectively ; thus 25 000 beds could be quickly available. In addition, 25 000 more beds could be mobilized in other institutions.

(B) A city of 5 million in a developing country could be assumed to contain :

(1) doctors : approximately 7 000 (doctors are much more numerous in large cities than in surrounding areas) ;

(2) nursing personnel including auxiliaries : approximately 7 000 ;

(3) hospital beds : approximately 2 per 1 000 population (10 000 beds) in the city and approximately 0.5 per 1 000 population (2 000 beds) in the surrounding conurbation (assuming 4 million people in the surrounding areas). Of these essentially none would be vacant at the time of the attack and only 5% could be made available in a short time : thus only 600 beds could be quickly available. Perhaps 5 000 more beds could be mobilized.

(C) A city of 500 000 in an economically developed country could be assumed to contain :

(1) doctors : approximately 1 000 ;

(2) nursing personnel including auxiliaries : approximately 6 000 ;

(3) hospital beds : in the city, 8 per 1 000 (4 000 beds) ; in the surrounding area 4 per 1 000 (800 beds) ; total, approximately 5 000 beds. If 40% were made available, there would thus be 2 000 beds. In addition, 2 000 more beds could perhaps be mobilized.

(D) A city of 500 000 in a developing country could be assumed to contain :

(1) doctors : approximately 250 ;

(2) nursing personnel including auxiliaries : approximately 200 ;

(3) hospital beds : in the city, 1 per 1 000 (500 beds) ; in the surrounding area 0.5 per 1 000 (150 beds)—a total of approximately 650 beds. If 5% were available, there would thus be 30 beds. Perhaps 1 000 beds could be mobilized in other institutions.

A. TULARAEMIA

1. *Assumptions about infectivity, virulence and antibiotic sensitivity of strain used*

There is now a variety of tularaemia strains that could be used for biological warfare, including antibiotic-resistant strains and strains with a reduced lethality. It is assumed that the strain used would have the following effects and characteristics :

(a) Illness would occur in 50% of untreated persons inhaling 25 or more tularaemia organisms (Table 10, Annex 3) ; ordinarily, hospitalization would be required for about half of these people (with pleuropneumonia and other complications).

(b) A 25% case fatality rate would occur in untreated persons who developed the clinical disease.

(c) The strain would be sensitive to antibiotics.

2. *Effect on a city of 5 million in an economically developed country*

Exposure

Taking the reduction factor variables into account, if approximately 500 000 people were exposed to 50% infective doses (ID_{50}), at least 250 000 clinical cases could be expected. Many more would probably occur because of the very large number of doses to which most of the population would be exposed.

Flight from the city

It is estimated that about a third of the entire population would flee from the city over the first 48 hours. The remaining population, whether actively exposed or not, would demand antibiotics over the first 48 hours.

Preventive treatment

About 1 million people in all would need preventive chemotherapy for 10 days.

About 50 000 exposed people, for one reason or another, would not start treatment within 48 hours even if it were available.

Morbidity and mortality

Of the 250 000 clinical cases that could be expected and would receive antibiotics within 48 hours, 10% (25 000) would need hospitalization and about 1% (2 500) would die.

Of the 50 000 for whom antibiotic therapy would not start within 48 hours, 50% (25 000) would need hospitalization and about 7-10% (2 000)

would die. In all, about 60 000 would need hospitalization and about 4 500 would die.

Burial problems

Assuming 4 500 deaths spread over 10 days, the authorities of such a city should be capable of coping with the situation.

Hospitalization problems

The 60 000 who would require hospitalization would not require it all at once and it appears that the 50 000 beds that might be mobilized could probably accommodate them, although not without displacing a considerable number of less acutely ill patients.

Manpower needs

(a) For the hospitalized patients, 2 doctors, 4 nurses, and 10 other personnel would be needed per 100 beds. For 50 000 beds, 1 000 doctors, 2 000 nurses, and 5 000 other personnel would be needed.

(b) The overall requirements would be for about 2 000 doctors, 3 000 nurses and 10 000 other personnel. In a modern industrial city with a population of 5 million, there would be about 10 000 doctors and 60 000 nurses and other health personnel. Assuming that the health personnel fled in about the same proportion as the rest of the population (one-third) and that the health personnel received antibiotics early so there was little morbidity or mortality among them, the city would be left with 7 000 doctors and 40 000 nurses and other personnel. This should be sufficient to meet the needs of the victims and to maintain a reasonable level of care in the rest of the population. In addition, personnel could be brought in from other cities. Of course, if panic broke out and social disorganization developed, it might prove impossible to bring the medical resources and the people who needed them together effectively.

3. Effect on a city of 5 million in a developing country

Exposure

Of 250 000 people exposed to the attack, approximately 125 000 would develop the disease.

Flight from the city

It may be assumed that about half the population would make their way out of the city within 48 hours after the attack had become known.

Chemotherapy

Much smaller quantities of antibiotics would be available than in the economically advanced city. Assuming that there were only enough

antibiotics to treat 10% of the clinical cases and partially treat an additional 40%, there would be no treatment for 50% of the people exposed. The resultant mortality would involve about 30 000 people over a period of about 10 days. Hospitalization would be required for about 60 000 severely ill cases.

Burial problems

3 000 deaths per day would unquestionably cause severe body disposal problems in such a city.

Hospitalization problems

The problem of hospitalizing those suffering from the attack would be completely unmanageable.

4. *Effect on a city of 500 000 in an economically developed country*

There would be a proportionally higher exposure rate in the smaller city than in the metropolis (Table 10, Annex 3). In economically developed countries the medical care resources in a city of half a million inhabitants are roughly proportional to those in a city of 5 million. The treatment of a proportionally greater number of casualties with proportionally the same resources would increase the problems. Possibly manageable in the larger city, they would be much more difficult to manage in the smaller city. On the other hand, evacuation would be easier and it would be simpler to bring in health personnel from the outside.

5. *Effect on a city of 500 000 in a developing country*

The casualties would be proportionally higher than in the city of 5 million, but the difference would not be as great as in economically advanced countries. Medical resources are proportionally very much more scarce in smaller cities in developing countries. The combination of a proportionally somewhat higher number of casualties with very much lower resources would make the situation even more difficult than that in the larger city.

B. PNEUMONIC PLAGUE

1. *Assumptions about infectivity, virulence and antibiotic sensitivity of strain used*

(a) Clinical infection would be produced in an unprotected person inhaling 1 000 organisms or more with an attack rate of 50%.

(b) Of those developing clinical disease, about three-fourths would ordinarily require hospitalization and death would occur in about 80% of untreated persons.

(c) If an antibiotic-sensitive strain were used, reasonably prompt treatment with antibiotics would reduce the need for hospitalization to about 50% of clinical cases and the case fatality rate by 70% and 10% respectively in developed and developing countries (Table 10, Annex 3).

(d) Person-to-person inhalation spread would occur, but could be prevented with reasonable effectiveness by the use of antibiotic prophylaxis and isolation of cases and contacts.

(e) Hospitalization would last about two weeks in non-fatal cases.

(f) In non-fatal cases there would be no residual ill effects.

2. *Level of preparedness against an attack*

Two different levels of preparedness are assumed :

(a) Antibiotics are stockpiled and contingency plans for their rapid administration have been prepared.

(b) No special stockpiles of antibiotics or other preparations have been made.

3. *Effect on a city of 5 million in an economically advanced country with antibiotics available*

Flight from the city

It is likely that about a third of the population would attempt to flee, even though chemotherapy was promptly offered to those exposed and antibiotic prophylaxis to the rest of the population. The authorities might attempt to block extension of the disease to other cities by trying to stop this flight, but would probably be largely unsuccessful, even in an advanced country.

Treatment

Immediate treatment of exposed persons and all the other inhabitants of the city with tetracycline or chloramphenicol would be attempted. Since these drugs can be taken orally, few medical personnel would be needed ; distribution centres would be required, as well as some means of identifying those who had already been given the drug.

Morbidity and mortality

With prompt treatment of the 150 000 clinical cases (Annex 3, Table 10) there would be about 36 000 deaths, but hospitalization and isolation would be required for 80 000-100 000 people. Secondary cases would occur amongst the rest of the population and the proportion might be as high as 10% despite prophylactic tetracycline, thus possibly affecting as many as

500 000 additional people. In all some 500 000 people might require hospitalization and over 100 000 people might die. These hospitalizations and deaths would, however, be spread over many weeks in successive waves. Despite the blockade, some patients with plague would reach other cities: the secondary outbreaks of plague developing in the cities should be fairly easy to contain in an advanced country.

Burial problems

Burial facilities would be taxed and some difficulties could be expected.

Hospitalization problems

The hospitalized cases would be spread over a long period, but each patient would have to spend at least 2-3 weeks in hospital. Consequently, hospital beds would be unlikely to be able to accommodate in the early stages more than a third of those who might normally warrant hospitalization and probably no more than a half in the secondary wave.

Manpower problems

The city should be able to deal with manpower problems, although severe social disruption could be expected.

4. *Effect on a city of 5 million in a developing country with a small supply of antibiotics*

Flight from the city

It is likely that over 50% of the population would attempt to flee, and it would probably be harder for the authorities to stop their flight than in the economically advanced countries.

Treatment

Even though a limited supply of drugs was available, distribution and persuasion problems would be much greater in a developing country than in an advanced country.

Morbidity and mortality

Both morbidity and mortality would be much higher, with many more secondary cases. An overall case fatality of 50-70% could be expected. With successive epidemic waves occurring, 250 000 deaths might result.

Hospitalization problems

Facilities and manpower resources would be totally inadequate.

C. NERVE GAS—VX

1. *Assumptions about the extent of morbidity and mortality (Annex 1 and Annex 3)*

(a) Of those who inhaled a dose of 10 mg-min/m³ or who received 2-10 mg of liquid VX on the skin, 50% would die unless intensive medical therapy and decontamination were carried out within seconds or minutes after exposure. An additional 25% would die unless intensive medical care and decontamination were instituted within minutes to hours after the exposure; the remaining 25% would survive with decontamination and supportive care.

(b) the most critical period is seconds to minutes after exposure. After this there is little that can be done for most of those exposed to doses in or greater than the range mentioned.

(c) A persistent agent such as VX presents a grave danger to those attempting to reach the casualties and to others entering the area of contamination without appropriate protective equipment. Contaminated medical facilities would be useless for a long period after the attack.

(d) Atropine and oximes may be stockpiled, but would be almost useless unless immediately available and unless training in self-administration had been given and large numbers of health personnel had been instructed in their use.

2. *Effect on a city of 5 million in an economically advanced country (Annex 3, Tables 8 and 9)*

Casualties

In such a city, if 150 000 people were exposed to a lethal concentration of VX, 80 000 could be assumed to die before any help arrived, 35 000 could perhaps be saved with prompt administration of atropine and oximes and heroic supportive care, and the remaining 35 000 might be saved by drugs and general supportive care.

Morbidity and mortality

It is extremely unlikely that in such an attack many of the 70 000 not immediately killed would be saved. There would probably be about 120 000 deaths and about 10 000 hospitalizations. Many of the survivors would require extraordinary care if they were to be saved or preserved from residual damage due to anoxia.

Burial problems

Most of those who died would do so almost immediately, and the 120 000 deaths would therefore occur in the course of one or two days. It would probably take a city of this type about two weeks to cope with

this number of deaths, unless considerable outside help was brought in. The persistence of liquid VX in the area of densest concentration would make collection of the bodies and burial a hazardous undertaking without excellent protection for the personnel. The extent of putrefaction prior to burial would depend on the delay and the temperature.

Hospitalization problems

The city would barely be able to cope with the 10 000 patients requiring hospitalization. These individuals would require intensive care and large numbers of personnel.

In addition, many of the hospitals would be contaminated with VX and so be unusable. The precise proportion is impossible to predict, but as many as 25% of hospital beds might be affected, since these are concentrated near the centre of the city. Further complicating the problems is the fact that at least 10% of medical personnel (probably closer to 20%, since they too are more concentrated near the centre of the city) would themselves be casualties.

Rehabilitation problems

Some survivors would have residual effects. The number is indeterminate but might be of the order of 1 000 and it would severely test the rehabilitation facilities of the city.

3. *Effect on a city of 5 million in a developing country* (Annex 3, Tables 8 and 9)

Casualties

It could be assumed that 60 000 people would have been exposed to a lethal dose of VX. Since it is quite clear that very few of the victims would receive adequate medical care, it is likely that 50 000 or more of these victims would die. Most of the remainder would require hospitalization and intensive care.

Morbidity and mortality

Those who survived the initial period would require intensive medical and nursing care, with atropine and oximes, respirators, intravenous fluids and other therapy. Even if the drugs were available, it is extremely unlikely that the personnel or equipment would be available for the purpose.

Burial problems

Fifty thousand deaths at once would be unmanageable and burial of the bodies would take many weeks of effort. The burial problem would depend on the temperature and on the protection available for the personnel.

Hospitalization problems

Clearly most of those who required hospitalization could not receive the intensive care needed. Probably, only those requiring minimal care would reach the hospital alive.

Manpower problems

Despite the smaller number of survivors, medical personnel in the city would probably be incapable of dealing with them.

Rehabilitation problems

The low number of survivors likely suggests that the number of patients requiring rehabilitation would probably be much smaller than in a city of the same size in an economically advanced country. No rehabilitation facilities would be likely to be available in the city, and the victims would have to be sent to other countries for rehabilitation.

4. *Effect on a city of 500 000 in an economically advanced country (Annex 3, Tables 8 and 9)*

It is clear that the hospitals, the medical personnel and the rehabilitation facilities of the attacked city could not manage in any significant way to deal with the casualties or the burial of the approximately 40 000 bodies that would result from the attack.

5. *Effect on a city of 500 000 in a developing country (Annex 3, Tables 8 and 9)*

The medical resources available, already far less than in a larger city, would be further reduced by the attack, and it is conceivable that less than half of the already minimal manpower and facilities would be functioning. Most of those exposed (180 000) would simply have to be left to their own devices and the majority would probably die.

ANNEX 5

SABOTAGE OF WATER SUPPLIES

INTRODUCTION

Various methods of contaminating a public water supply, including aerial attack and sabotage on the ground, have been considered in constructing a model for quantitative assessment of possible use of chemical and biological weapons. These include the introduction of a biological or a chemical agent into (a) the water source at the intake or treatment works, (b) a raw-water or treated-water reservoir, and (c) a transmission main, by injection. It would appear that the third method of contamination would be potentially the most devastating in effect, difficult to prevent and to detect, and feasible in practice in many water systems. One other method, perhaps the most damaging of all, would be the subornation of water-works staff and injection of the agent within the treatment works, at the same time sabotaging the control and detection procedures. This possibility has not been taken into consideration in the following model because it would require very special preparations and arrangements on the part of the attacker, coupled with the unlikely convergence of a set of particularly favourable circumstances.

The introduction of a contaminating agent into an open reservoir, which would at first sight seem to be the simplest way of affecting a large number of consumers, would be unlikely to produce anything like the widespread devastation possible by controlled injection into a trunk main, and the effects would be far less predictable.

An attempt has been made to work out a pattern of drinking water consumption, and thence to forecast the numbers of people who would be affected by sabotage of this nature before preventive measures to counteract the contamination could be taken. The following assumptions have been made :

1. The contaminating agent belongs to one of the following three types :
 - (a) the typhoid bacillus, which produces no recognizable symptoms for about 1 week ;
 - (b) botulinal toxin, type A, which would produce no recognizable symptoms until 6 or 8 hours after ingestion and, in a stabilized form, would resist denaturation by the elements found in a normal water supply (see Annex 1) ;

(c) LSD, which produces recognizable symptoms within 2 hours after ingestion.

All these have the common factor of being virtually impossible to detect by conventional means available to the average waterworks. All can produce effects in low concentrations, and therefore require a relatively small bulk of initial contaminant to be introduced.

2. The sabotage has been prepared well in advance, the saboteur has a thorough knowledge of the water system, and the point of injection into the mains has been selected so as to reach the maximum number of people possible. This point of injection is after the water has left the treatment plant.

3. There is no chlorine residual in the mains (as is the case in many countries) to reduce the viability of the agent ; alternatively, the disinfecting property of this residual has been counteracted by the simultaneous application of a dechlorinating agent such as sodium thiosulfate.

4. The attack is without warning and no special precautions have been taken by the waterworks authority.

5. The size of the population to be attacked has been arbitrarily selected in accordance with what is felt to be within the capacity of a single act of sabotage.

In the case of contamination by the typhoid bacillus, the limiting condition has been taken as the quantity of culture to be injected. The assumption has been made that 1 kg of freeze-dried culture is introduced into the system of a large city (population one million or more) through a main feeding a sector of the distribution system.

For botulinal toxin and LSD, a town of 50 000, or a similar sized segment of a larger city, has been assumed. Scaling down to small populations may be taken as proportional, with a slight increase in the effectiveness of the attack ; scaling up by too large a factor could lead to the quantities required for injection becoming unmanageable.

6. With the typhoid bacillus used as the contaminating agent, no symptoms would become apparent during the incubation period of several days, hence there would be no warning to throw suspicion on the water quality.

With botulinal toxin or LSD, consumers would first experience symptoms 8 hours (botulism) or 2 hours (LSD) after drinking an effective dose. Assuming that the symptoms were recognized as such and the waterworks authorities were prepared for emergency action, this would enable them to take immediate action to warn people not to drink the water, to flush out and swab the mains, and to take other actions, such as superchlorination, which would soon put an end to the spreading of the agent.

7. Two types of consumption pattern have been postulated. One is for an industrialized community in a temperate climate, and the other for an arid tropical area with little industry. The patterns have been based upon known demand curves, modified by assumptions as to mixing, dilution, storage capacity, and drinking habits. In the first community, it is assumed that during the relevant period there will be 15% of people who will not drink mains water; in the second case it is assumed that practically the whole of the population will do so within 3 or 4 days. Only water drunk as taken from the tap has been considered, and no allowance has been made for water consumed in food or hot beverages.

CONTAMINATION BY THE TYPHOID BACILLUS

Basic data

It is assumed that 1 kg of freeze-dried typhoid culture, containing 8×10^{10} organisms in 0.6 g is used, i.e., 13.3×10^{13} organisms are injected during a period of 24 hours or more.

Because of die-off upon entering the mains, unequal distribution, dilution, and other factors, the effectiveness of the culture has been assumed to be reduced by 95%. Thus, of the 13.3×10^{13} organisms injected, 6.65×10^{12} will actually reach consumers' premises.

Table 11 shows the percentages of persons becoming infected after ingesting a specific dose: these figures are based on challenge trials in human volunteers (Hornick & Woodward, 1966).¹

TABLE 11. PROPORTION OF PERSONS INFECTED AFTER INGESTING TYPHOID BACILLI

Number of viable <i>S. typhosa</i>	Number of persons with typhoid	
	Number challenged	
		Persons infected (%)
10^9	40/42	95
10^8	8/9	89
10^7	16/32	50
10^5	32/116	28
10^3	0/20	0

Case 1. Large city, industrialized society, temperate climate. Water supply: 400 litres per person per day; amount drunk raw per person: 0.5 litre.

¹ Hornick, R. B. & Woodward, T. E. (1966) *Trans Amer. clin. climatol. Ass.*, 78, 70-76.

The total number of typhoid cases under these conditions would be about 35 000. Assuming a fatality rate of 0.6% (given early and adequate antibiotic treatment), some 200 of these would die.

Case 2. Large city, non-industrialized society, hot arid climate. Water supply : 100 litres per person per day ; amount drunk raw per person : 2.0 litres.

In this case, a much higher proportion of the water delivered is actually drunk—one fiftieth as compared with one eight-hundredth in Case 1. Injection of the same quantity of material would provide an average dosage of 10^5 organisms to 133 000 people, 95% of whom would drink infected water during the period.

If no facilities for mass treatment were available, the fatality rate would be expected to reach 10%, or 4 500 people.

CONTAMINATION BY BOTULINAL TOXIN, TYPE A

In making the following projection of the hypothetical use of botulinal toxin, it should be borne in mind that we have no information as to the possible inactivation of this toxin in the water during a period of 6-8 hours in the mains. Oxidation or other denaturing action could reduce very considerably the effects calculated. Further research might result in a stable toxin suitable for use in the manner described below, if such a toxin is not already available.

Basic data

The lethal dose per person (by ingestion) has been taken as $1\mu\text{g}$. The first symptoms have been assumed to appear within 6-8 hours of ingestion.

Case 1. Urban community of 50 000 people. Industrialized society, temperate climate. Water supply : 400 litres per person per day ; amount drunk raw per person : 0.5 litre.

The theoretical dose needed in 20 million litres, assuming perfect distribution and equal dilution, is 0.04 kg. Allowing a factor of $\times 6$ for unequal distribution, dilution, etc., the quantity required will be 0.24 kg.

Injection could be spread over 6 hours (midnight to 06.00 hours) but would cease before the first symptoms became apparent. The initial concentration on entering the mains would be 0.05 mg/litre, at which rate 20 g of water would carry a lethal dose.

At 17.30 hours, 10% of the population would have received a lethal dose 8 hours earlier ; if remedial measures were taken at that time, 60% of the consumers would already have received a lethal dose (30 000 people).

Recognition of symptoms one hour earlier, at 16.30 hours, when 1 200

people would be exhibiting symptoms, would reduce the number who had by that time ingested a lethal dose to about 28 000 people.

Case 2. Urban community of 50 000 people, non-industrialized society, hot arid climate. Water supply : 100 litres per person per day ; amount drunk raw per person : 2.0 litres.

The theoretical dose needed in 5 million litres, assuming perfect distribution, is 0.0025 kg. Allowing a factor of $\times 6$ for unequal distribution, etc., as in Case 1, the quantity required for injection will be 0.015 kg. Again assuming that the injection is spread over 6 hours, the initial concentration on entering the mains would be 0.012 mg/litre, at which rate 80 g of water would carry a lethal dose.

At 17.30 hours 10% of the population would have received a lethal dose 8 hours earlier ; if preventive measures were taken at that time, 55% (27 500 persons) would already be affected.

Recognition of symptoms one hour earlier at 16.30 hours, when 5% of the population were beginning to show symptoms, would reduce this proportion to 50% (25 000 people).

On the other hand, delay in recognition until 18.30 hours would mean that 65%, or 32 500 people, would already have consumed a lethal dose.

Note :

Case 1 and Case 2 describe the probable pattern in towns with populations of 50 000 but with different characteristics. Similar patterns would be expected in limited sectors of larger cities having comparable water consumption patterns.

CONTAMINATION WITH LSD

Basic data

The individual dose (by ingestion) needed to produce incapacity has been taken as 250 μg . The lethal dose has not yet been adequately determined, but it would seem certain that deaths would result from the consumption of concentrated doses in water withdrawn at short distances from the point of injection of the agent into the mains.

The first symptoms have been assumed to appear within 2 hours of ingestion.

*Case 1.*¹ Urban community of 50 000 people. Industrialized society, temperate climate. Water supply : 400 litres per person per day ; amount drunk raw per person : 0.5 litre.

The theoretical incapacitating dose needed in 20 million litres of water, assuming perfect distribution and equal dilution is 10 kg. Injection would

¹ See note above at end of section on contamination by botulinal toxin.

be over one hour, so that it would have been completed before the first symptoms became apparent.

Allowing a factor of $\times 8$ for unequal distribution, dilution, etc. (bearing in mind the short period over which injection must take place), the quantity required would be 80 kg.

The initial concentration would be 100 mg/litre, at which rate 2.5 g of water would carry an incapacitating dose.

At 11.15 hours 10% of the population would have drunk contaminated water 2 hours earlier, and of these some would have ingested a lethal dose. If symptoms were recognized and preventive measures taken immediately, 25% of the population would already have been affected (12 500 people).

Recognition of the symptoms by 10.30 hours, when 5% of the popula-

TABLE 12. POSSIBLE EFFECTS OF LIMITED SABOTAGE OF CITY COMMUNAL WATER SUPPLY *

Agent	Quantities of agent required ^a	Population at risk	Number of casualties			
			Deaths		Incapacitated (includes deaths)	
			Economically developed country ^b	Developing country ^c	Economically developed country ^b	Developing country ^c
Botulinal toxin (if in stable form)	0.24 kg	50 000	28 000 ^d 30 000 ^e 40 000 ^f			
	0.015 kg	50 000		25 000 ^d 28 000 ^e 48 000 ^f		
LSD	80 kg	50 000	Indeterminate number	Indeterminate number	10 000 ^d 13 000 ^e 40 000 ^f	
	5 kg	50 000				14 000 ^d 19 000 ^e 48 000 ^f
Typhoid bacillus	1 kg	400 000 to 500 000	200	1 500 to 4 500 ^g	35 000	45 000

* See text for descriptions of procedures.

^a The differences in the quantities required reflect differences in consumption of water in temperate and hot climates.

^b Temperate climate.

^c Hot climate.

^d If recognized when 5% of the population started showing symptoms and if remedial action started immediately.

^e If recognized when 10% of the population started showing symptoms and if remedial action started immediately.

^f If no remedial action were taken within 24 hours.

^g According to treatment facilities available.

tion had drunk the contaminated water 2 hours earlier, would reduce the proportion already affected to 20% or 10 000 people.

*Case 2.*¹ Urban community of 50 000, non-industrialized society, hot arid climate. Water supply : 100 litres per person per day ; amount drunk raw per person : 2.0 litres.

The theoretical dose needed in 5 million litres, assuming perfect distribution is 0.625 kg.

Allowing a factor $\times 8$ for unequal distribution, etc., the quantity required would be 5 kg injected over one hour.

The initial concentration on entering the mains would be 25 mg/litre, at which rate 10 g of water would carry an incapacitating dose.

At 11.30 hours, 10% of the population would have drunk contaminated water 2 hours earlier, and some of these would have ingested a lethal dose. If symptoms were recognized and preventive measures taken immediately, some 37% (18 500 people) would have already been affected.

Recognition of the symptoms at 10.30 hours, when 5% of the population had drunk contaminated water 2 hours earlier, would reduce this proportion to about 27% (13 500 people).

On the other hand, delay in recognition until 12.30 hours would mean that 40% (20 000 people) would be affected, some of them fatally.

If the symptoms remained unrecognized and no remedial action were taken within 24 hours, almost the entire population at risk would be affected (say, 47 500 persons).

PREVENTIVE MEASURES

Although no waterworks can be completely proof against attack by an enemy agent who has the necessary knowledge, time and resources, there are measures that can be taken to minimize the extent of the area affected and to increase the chances of early detection. The measures taken to protect against an act of "casual" sabotage by an individual, would in many cases be the same as those for protection against natural or accidental hazards. They include the following :

1. A thorough study of the entire system should be made to identify points at which a saboteur could do the maximum harm, i.e., places where the water is accessible and points where injection could introduce a contaminant into trunk or transmission mains.

2. The normal treatment processes of coagulation, sedimentation, filtration and chlorination will be effective to a greater or lesser extent against most contaminants, though they cannot be relied upon to be completely

¹ See note at end of section on contamination by botulinal toxin (page 117).

effective in every case. Chlorination is probably the most significant stage of treatment, and the disappearance of a chlorine residual that is normally maintained throughout the mains system can provide a rapid warning of organic contamination if regular tests at different points are made.

3. Service reservoirs or high-level distribution tanks should always be locked against casual access and regularly inspected for evidence of tampering.

4. Non-return valves should be fitted to services taken directly from trunk mains and, if possible, to all service connexions.

5. Valves or other means should be used to ensure that only one sector of the distribution system can be affected from a single injection point. The most vulnerable type of distribution system is one that provides water on an intermittent basis, with intervening periods of low or negative pressure; every endeavour should be made to maintain a positive pressure in all mains at all times.

6. Close liaison should be maintained between the authorities responsible for the water supplies and the health authorities so that any case of sickness or other circumstances that might throw the slightest suspicion upon the water supply as a vehicle for a contaminating agent would immediately be brought to the attention of the engineer in charge for appropriate action. Such action would include identification of the area involved; warning of the public against drinking the water; the flushing to waste of the content of all mains, followed by swabbing with polyurethane foam cylinders and superchlorination; and increase of chlorine residual throughout the whole system.

7. Activated carbon and/or ozone should be used in the treatment works—an expensive form of treatment but effective (in conjunction with chlorination) against nearly every contaminating agent. If this is impracticable for the whole supply, it may be considered worth while for key points, e.g., hospitals, or for mineral water or food factories where contamination might be continued in another form subsequent to its elimination from the mains.

ANNEX 6

PSYCHOSOCIAL CONSEQUENCES OF CHEMICAL AND BIOLOGICAL WEAPONS *

INTRODUCTION

Discussion of the public health or medical effects of chemical or biological weapons would be incomplete without consideration of the psychological and social effects of their development, stockpiling, or use. Analysis of these effects is extremely difficult and so far little has been published in this field.¹ A considerable amount of research has, however, been conducted on the psychosocial consequences of preparation for or actual engagement in nuclear warfare (Group for the Advancement of Psychiatry, 1964; Frank, 1967; Liederman & Mendelson, 1963), and many of the findings are relevant to the problems posed by chemical and biological weapons. This annex is limited to a brief consideration of some of the most relevant factors and suggests avenues for further study of the psychosocial consequences of chemical and biological warfare. Considerable research is needed; this should be carried out by a special study group that would collect and interpret existing information and gather additional data.

Although a decision to develop chemical and biological weapons may seem justifiable on the basis of apparently rational considerations of national security and national self-interest, a great deal of irrationality enters into it. However, an exploration of the irrationality is beyond the scope of this annex, which has been somewhat artificially divided into reactions to the threat of warfare with chemical and biological weapons and reactions to their actual use. Preparations for chemical and biological warfare may be viewed as representing in themselves a response to the threat of enemy attack. However, they serve equally to induce and intensify widespread fears and anxieties, with their accompanying psychological defences of

* This annex was prepared at WHO's request by an independent group of specialists co-ordinated by Dr Viola W. Bernard, Director, Division of Community and Social Psychiatry, Columbia University, New York, USA, and this group is solely responsible for the views expressed.

¹ An analysis entitled *Social and psychological aspects of CW* was prepared for the Stockholm International Peace Research Institute (SIPRI) in July 1968 by John Cohen, Department of Psychology, University of Manchester, England (unpublished document, available on request from SIPRI).

projection, denial and dehumanization. These reactions not only constitute psychosocial consequences of chemical and biological warfare but may also increase the risk of its occurrence through the mechanism of self-fulfilling prophecy. Reactions of this kind have already begun, so that appropriate systematic studies can and should be undertaken immediately.

The psychosocial consequences of the actual use of chemical and biological weapons are of necessity less amenable to direct study, but research designs and methodologies can be based on the already documented observations and studies of the psychosocial consequences of nuclear attack, attack by other weapon systems, and disasters involving large population groups.

POSSIBLE PSYCHOSOCIAL CONSEQUENCES OF THE THREAT OF CHEMICAL AND BIOLOGICAL WARFARE

1. Anxiety and fear¹

The implication of the decision to develop chemical and biological weapons is that they will ultimately be used, for reasons not now ascertainable, at a time now unknown, either on or by those preparing to use them. It is assumed in this discussion that these weapons do in fact pose an awesome threat to man's survival, and that therefore the possibility of their use engenders real feelings of danger in everyone. As in most dangerous and threatening situations, both anxiety and fear are mobilized.

Although within certain limits fear may fulfil an adaptive function by motivating an individual to avoid or to overcome impending danger, it can often be maladaptive, leading to short-sighted and/or unrealistic behaviour in the single-minded pursuit of an immediate sense of personal safety, no matter how illusory. Fear may lead to an inability to distinguish between the consequences of various types of weapons or of different modes of attack. Rational discussion of methods for prevention will then be

¹ *A psychiatric glossary* (Washington, American Psychiatric Association, 1964) defines anxiety and fear as follows:

Anxiety: Apprehension, tension or uneasiness which stems from the anticipation of danger, the source of which is largely unknown or unrecognized. Primarily of intrapsychic origin, in distinction to fear, which is the emotional response to a consciously recognized and usually external threat or danger. Anxiety and fear are accompanied by similar physiologic changes. May be regarded as pathologic when present to such extent as to interfere with effectiveness in living, achievement of desired goals or satisfactions, or reasonable emotional comfort (p. 13).

Fear: Normal emotional response to consciously recognized and external sources of danger, to be distinguished from anxiety (p. 32).

impossible. Fear may cause withdrawal, immobility, or functional paralysis; for example, several studies of stress phenomena have described the retreat into sleep of a threatened organism (Engel, 1962).

Conversely, fear may lead to impulsive or habitual reactions constituting an inappropriate response to the specific danger. For example, although the launching of a widespread immunization campaign against a specific organism may be a reasonable response to the danger posed by a naturally occurring epidemic, it may be completely unreasonable in a situation in which it is extremely likely that such an immunization programme would lead to an enemy's selecting a different organism for an attack. Moreover, even if an enemy chose to use the same organism, it is not at all certain that an immunization programme would be at all worth the very marginal protection that might be conferred in the face of the overwhelming doses of the agent that would be employed by an attacker: a more primitive and immediate mass reaction might be precipitate flight from a dangerous area, even though the danger was really over. Furthermore, the development of chemical or biological weapons, whatever the underlying national policies, can lead to a national and foreign policy that is actually based on the fears and self-defeating defences against them.

A powerful source of anxiety is lack of perceptual clarity in the face of apparent danger. Many chemical and all biological weapons are undetectable by the senses, so that there are no warning signs to enable the person attacked to protect himself. Additional uncertainties with biological weapons are the latent periods between infection and illness and the unpredictability of spread through the community. As a result, a person may fear that if he is exposed to these weapons he will not know for certain when he has been infected, how ill he will be, or when the danger has passed. A further confusing factor is that many of the symptoms of illness, especially those involving the gastrointestinal tract, are also symptoms of emotional stress. Thus, if a person develops nausea, vomiting and diarrhoea, he may still not be sure whether he has been infected or not.

Certain specific features of chemical and biological weapons, such as their invisibility and modes of action, are particularly likely to revive and intensify anxieties, fantasies and conflicts dating back to childhood which, although outgrown by many people, often remain buried in the irrational depths of the mind. Under certain types of stress external and internal threats may merge and the individual's overt behaviour become dominated or distorted by the irrationality that is linked to such anxieties and to the attempt to defend himself against them.

2. Defences against anxiety and fear

Several mechanisms of defence are prominent in man's reaction to the threats posed by chemical and biological warfare.

(i) *Projection and rationalization*

The fear of being attacked and destroyed can engender reactive urges to exterminate potential attackers by any possible means. Scruples against using chemical and biological weapons against other human beings can be overcome if this fear-engendered impulse to exterminate "the enemy" is projected on to him. For if it is "they" who are about to destroy "us" by such diabolic weapons, then "we", through rationalization, can feel justified in resorting to these weapons. "They" and "we" vary, of course, with the nationality of those who make use of these universal mental mechanisms. But whatever the population, such psychological defences increase rather than decrease the actual risk of what is feared, and hence are self-defeating.

Preparing for chemical and biological warfare increases the danger that stockpiled supplies of lethal materials may be disseminated accidentally or deliberately. Furthermore, such preparation in any one country stimulates preparation in other countries by giving credibility to the fears of those who also react to the fear of annihilation with a justification of chemical and biological warfare. Thus, reciprocal fears between nations, and the projection and rationalization to which they give rise in defence, contribute to the spiralling of a chemical and biological weapons race that imperils all mankind.

Also, as Dr Jerome B. Wiesner¹ has pointed out, the secrecy that a number of nations with large-scale resources impose on the means whereby they seek to buy security in the nuclear age (a goal Wiesner views as technically unachievable) requires each person "to guess what he is likely to face technologically and militarily a few years ahead. Our best guesses are based on what each of us is doing, because these give us the images which we project to the future. The consequence, particularly for the United States, is that we are running an arms race with ourselves, and very frequently the threats that we see five years ahead, for example, are the threats that we ourselves pose." (Wiesner, 1969).

(ii) *Denial*

This is a "term applied to the various degrees of non-perception, misperception, non-recognition, non-understanding, or non-acceptance of certain realities in order to cope with otherwise unacceptable intra-psychic conflicts, feelings, or memories" (Group for the Advancement of Psychiatry, 1964). People also resort unconsciously to denial as a reaction to threats that they feel unable to cope with. Such denial in turn detracts from and

¹ Provost of the Massachusetts Institute of Technology and former science adviser to Presidents Kennedy and Johnson.

inhibits their potential ability to resolve problems realistically. With respect to chemical and biological warfare, the difficulty of facing the massive and unprecedented nature of the threat may be so great that many people simply choose to ignore its existence. Or the threat may be so difficult to bear that it is met only by "it can't happen to me" or "it can't happen to us".

Another aspect, perhaps not strictly within the concept of denial, is failure to comprehend the consequences of an event that not only has never been personally experienced but is unimaginable because of its extraordinary magnitude. For example, although the epidemic of plague called the Black Death caused the death of half the population of certain parts of Europe in the 14th century, the concept of the death of half the population of a modern city is inconceivable in all its dimensions and consequences and thus may have no psychological meaning for most people.

(iii) *Dehumanization*

The term "dehumanization" has been used to cover two separate but related phenomena both employed as a psychological defence against various anxieties. These phenomena are (1) object-directed dehumanization and (2) self-directed dehumanization.

Object-directed dehumanization is "the tendency to view other individuals or groups as though they do not quite belong to the 'human race'". There are circumstances in which such dehumanization serves as a useful protective device enabling individuals to function effectively under stress, as in certain occupations and in rescue operations. Such a process of dehumanization, however, can often be extremely maladaptive and socially dangerous. In the case of chemical and biological warfare, for example, it may lead to preoccupation with the statistical aspects of morbidity and mortality caused by weapons, with relatively little concern for their consequences in human terms.

Self-directed dehumanization, which may also be increased by preparation for chemical and biological warfare, includes diminution of the sense of personal responsibility for one's own actions, as well as feelings of powerlessness and of inability to question or to affect the course of events.

As described in detail by Bernard et al. (1965) and summarized by the Committee on Social Issues of the Group for the Advancement of Psychiatry (1964) in its report on "Psychiatric aspects of the prevention of nuclear war", there is an increasing tendency towards dehumanization as a response to many facets of modern life. Certain features of the preparations for nuclear war are particularly conducive to this reaction. In turn, dehumanization may increase the risk of nuclear warfare by inhibiting some of the psychological deterrents to it. This tendency toward dehumanization is likely to be further accelerated by preparations for chemical and biological warfare because of the specific characteristics of this kind of warfare.

POSSIBLE PSYCHOSOCIAL CONSEQUENCES OF THE USE OF CHEMICAL AND BIOLOGICAL WEAPONS

1. Panic

Maladaptive reactions to the nuclear attacks on Hiroshima and Nagasaki have been described (Nagai, 1951). Panic after the use of chemical or biological weapons may be so great that those agents which might be useful in the control of certain consequences of the attack—such as atropine or antibiotics—will not be used effectively. Panic may also cause individuals to flee from the area of attack, even when there is no longer any danger of exposure, thus making it almost impossible either to bring personnel or material into the city to help cope with the casualties or to evacuate those affected.

2. Fear of those affected

From the attempt by the rest of the population to isolate the victims of the attack on Hiroshima and Nagasaki (Lifton, 1967), although there was no danger that the affected would injure the unaffected, it may be expected that in a biological attack the unaffected will view the affected as potential agents of the spread of the disease. Not only will the obviously sick be suspect but so also will those who might become sick or might be using health care resources for other reasons. Analogous instances to those in which people said they would shoot anyone who tried to force his way into a fall-out shelter (Sidel et al., 1963) may be found among those who might attack others attempting to gain access to scarce supplies of antibiotics or food.

3. Changes in social organization

The response to a chemical or biological attack may require mobilization of resources, evacuation, or immunization on such a scale that extraordinary means of social control will have to be introduced. Once this has been done, it may be very difficult to relax the control. Thus the introduction of chemical and biological weapons may lead to profound social changes out of proportion to the amount of death or disability caused by the agent directly. In addition, an attack on a city with chemical or biological weapons would probably cause a breakdown of communications, transport, sanitation, and food distribution, thus further endangering the lives of many not directly affected by the agents themselves.

4. Special consequences of specific agents

Many of the specific chemical and biological agents raise special problems. For example, in a report on tests of a hallucinogen on a group of soldiers, it was reported that "the 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 behaviour as eccentric ” (Rothschild, 1964) (see also Annex 1, p. 47). It is thus impossible to predict the effect of such irrational behaviour on a battle or on a war, particularly in situations involving the use of nuclear, chemical or biological weapons in which a rational opponent is being counted on not to escalate beyond given limits without provocation. Equally impossible to predict are the long-term effects of the presence of a potentially large group of people who have suffered irreversible brain damage as a result of use of one of the chemical agents (e.g., anoxia secondary to the use of nerve agents) or of one of the biological agents causing encephalitis.

CONCLUSION

This discussion briefly highlights some of the psychosocial risks and consequences of a decision to develop chemical and biological weapons. It is apparent that reciprocal fears between nations and the various defensive measures to which they give rise contribute to the intensification of the arms race—whether nuclear, chemical or biological. Although stockpiles of chemical and biological weapons may have been maintained only to “deter” the “enemy”, those in control of such weapons may use them in retaliation against an attack or to forestall what they have become convinced will be a certain and lethal attack.

Appropriate systematic studies of these and other related phenomena can and should be undertaken immediately so that there is greater awareness of and control over the irrational forces that interfere with and at times make impossible rational solutions to conflicts between peoples.

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ANNEX 7

RESOLUTION 2454 A (XXIII) OF THE
GENERAL ASSEMBLY
OF THE UNITED NATIONS

Question of General and Complete Disarmament

The General Assembly,

Reaffirming the recommendations contained in its resolution 2162 B (XXI) of 5 December 1966 calling for strict observance by all States of the principles and objectives of the Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare, signed at Geneva on 17 June 1925,¹ condemning all actions contrary to those objectives and inviting all States to accede to that Protocol,

Considering that the possibility of the use of chemical and bacteriological weapons constitutes a serious threat to mankind,

Believing that the people of the world should be made aware of the consequences of the use of chemical and bacteriological weapons,

Having considered the report of the Conference of the Eighteen-Nation Committee on Disarmament which recommended that the Secretary-General should appoint a group of experts to study the effects of the possible use of such weapons,²

Noting the interest in a report on various aspects of the problem of chemical, bacteriological and other biological weapons which has been expressed by many Governments and the welcome given to the recommendation of the Conference of the Eighteen-Nation Committee on Disarmament by the Secretary-General in the introduction to his annual report on

¹ League of Nations, *Treaty Series*, vol. XCIV (1929), No. 2138.

² See *Official Records of the Disarmament Commission, Supplement for 1967 and 1968*, document DC/231, para. 26.

the work of the Organization submitted to the General Assembly at its twenty-third session,¹

Believing that such a study would provide a valuable contribution to the consideration by the Conference of the Eighteen-Nation Committee on Disarmament of the problems connected with chemical and bacteriological weapons,

Recalling the value of the report of the Secretary-General on the effects of the possible use of nuclear weapons,²

1. REQUESTS the Secretary General to prepare a concise report in accordance with the proposal contained in paragraph 32 of the introduction to his annual report on the work of the Organization submitted to the General Assembly at its twenty-third session and in accordance with the recommendation of the Conference of the Eighteen-Nation Committee on Disarmament contained in paragraph 26 of its report ;
2. RECOMMENDS that the report should be based on accessible material and prepared with the assistance of qualified consultant experts appointed by the Secretary-General, taking into account the views expressed and the suggestions made during the discussion of this item at the twenty-third session of the General Assembly ;
3. CALLS UPON Governments, national and international scientific institutions and organizations to co-operate with the Secretary-General in the preparation of the report ;
4. REQUESTS that the report be transmitted to the Conference of the Eighteen-Nation Committee on Disarmament, the Security Council and the General Assembly at an early date, if possible by 1 July 1969, and to the Governments of Member States in time to permit its consideration at the twenty-fourth session of the General Assembly ;
5. RECOMMENDS that Governments should give the report wide distribution in their respective languages, through various media of communication, so as to acquaint public opinion with its contents ;
6. REITERATES its call for strict observance by all States of the principles and objectives of the Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare signed at Geneva on 17 June 1925, and invites all States to accede to that Protocol.

1750th plenary meeting, 20 December 1968.

¹ See *Official Records of the General Assembly, Twenty-third Session, Supplement No. 1A (A/7201/Add. 1)*, para. 32.

² *Effects of the Possible Use of Nuclear Weapons and the Security and Economic Implications for States of the Acquisition and Further Development of These Weapons* (United Nations publication, Sales No. : E.68.IX.1).

RESOLUTION WHA20.54 OF THE
TWENTIETH WORLD HEALTH ASSEMBLY

**Consideration of Resolution 2162 (XXI) of the General Assembly of the
United Nations : Question of General and Complete Disarmament**

The Twentieth World Health Assembly,

Having considered resolution 2162 (XXI) of the United Nations General Assembly which notes in particular that weapons of mass destruction constitute a danger to all mankind and that strict observance of the rules of international law on the conduct of warfare is in the interest of maintaining the accepted norms of civilization ; and which calls upon all States to accede to the Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare, signed at Geneva on 17 June 1925, and to observe strictly the principles and aims of the Protocol ;

Guided by the aims and principles of the Constitution of the World Health Organization, and proceeding from the humane nature of both the Organization and the medical profession in general ;

Referring to resolutions WHA11.31 and WHA15.51, in which the World Health Assembly already expressed its thorough interest in the consolidation of peace as an inalienable prerequisite for preservation and improvement of the health of all nations ; and

Deeply convinced that the scientific achievements, and particularly in the field of biology and medicine—that most humane science—should be used only for mankind's benefit, but never to do it any harm,

1. WELCOMES resolution 2162 (XXI) of the United Nations General Assembly ; and
2. CALLS UPON all Member States to exert every effort to implement the above-mentioned resolution.

Twelfth plenary meeting, 25 May 1967.
(Committee on Programme and Budget, ninth report.)

ANNEX 9

RESOLUTION WHA22.58 OF THE
TWENTY-SECOND WORLD HEALTH ASSEMBLY

Question of General and Complete Disarmament: Chemical and Bacteriological (Biological) Weapons and the Consequences of their Possible Use

The Twenty-second World Health Assembly,

Having considered the report of the Director-General on co-ordination with the United Nations, the specialized agencies and the International Atomic Energy Agency ;

Noting with satisfaction resolution 2454 A (XXIII) of the General Assembly of the United Nations ;

Recalling resolution WHA 20.54 of the Twentieth World Health Assembly ; and

Convinced of the necessity of achieving a rapid international agreement for the complete prohibition and disposal of all types of chemical and bacteriological (biological) weapons under an effective system of controls which will ensure full compliance by all parties,

1. THANKS the Director-General for his efforts in participating in the preparation of the report of the Secretary-General of the United Nations on the question of chemical and bacteriological (biological) weapons and the consequences of their possible use ; and

2. REQUESTS the Director-General to continue his co-operation with the Secretary-General of the United Nations in the further study of this question.

Fourteenth plenary meeting, 25 July 1969.
(Committee on Programme and Budget, seventh report.)

