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DELAYED TOXIC EFFECTS OF CHEMICAL WARFARE AGENTS

A SIPRI MONOGRAPH

SIPRI

Stockholm International Peace Research Institute

Delayed Toxic Effects of Chemical Warfare Agents

SIPRI

Stockholm International
Peace Research Institute

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PREFACE

The acute effects of exposure to chemical warfare agents are fairly well known. On the other hand, little is known in general by the public about the variety and extent of the delayed effects of such substances.

This book reviews the present state of knowledge about the delayed effects of militarily important chemicals and appraises the clinical experience gained in World Wars I and II and the Viet-Nam War insofar as the data have been openly published. It was written by Professor Dr Karlheinz Lohs, member of the Academy of Sciences of the GDR and Director of the Institute of Chemical Toxicology of the Academy of Sciences of the GDR, while working at SIPRI during 1974.

June 1975 *Frank Barnaby*
Director

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FIGURES AND TABLES

Chapter 1. Introduction

Square-bracketed references, thus [1], refer to the list of references on page 48.

Only very few specialists today know a great deal about the variety and extent of delayed lesions caused by chemical warfare (CW) agents and other militarily important chemicals. The military experts among them, and the representatives of industries manufacturing these poisons, have shown little interest in disseminating the findings on delayed lesions. Nevertheless, some of this information has managed to reach the public, which has been deeply aroused by the use of CW agents by the USA in Viet-Nam.

This publication aims at the following:

1. to inform the public about the present state of knowledge about delayed lesions inflicted by militarily important poisons;
2. to evaluate the clinical experience gained up to now in connection with the production, storage and use of CW agents, particularly on the basis of data from World Wars I and II and the Viet-Nam War;
3. to propose various ways of reliably informing the public about the dangers of delayed lesions caused by military poisons, with a view to promoting present-day efforts at attaining a ban on chemical weapons and making a substantial contribution towards general disarmament; and
4. to stimulate research in biochemistry and toxicology for elucidating the problems of delayed lesions in general, and the mode of action of CW agents in particular.

In the following discussion, the term *delayed lesion* is defined to mean a lesion—caused by acute or subacute poisoning by CW agents—noticed either as a residual injury or by the unexpected onset of related symptoms after a protracted period of months or years, and being essentially irreversible. It must be emphasized that a lesion of this kind is not the same as one caused by chronic poisoning. By *chronic poisoning* is meant protracted—continuous or intermittent—exposure to a small quantity of poisonous substance. A delayed lesion results, however, from a single dose or brief exposure—the onset of symptoms months or years later requiring no further intake of substance in the meantime.

The discussion below deals primarily with present-day organophosphorus CW agents, as well as with various irritants and vesicants belonging to the group of so-called mustard gases. The conclusions drawn from a study of these compounds ought to be viewed in the light of the overall problem of delayed lesions caused by them and by other militarily important poisons.

Where non-CW agents are discussed below, they belong to the group of chemicals closely related to CW agents both in their chemistry and in their effects. In some cases such chemicals have been described in the literature as “models” for CW agents since no publications are available on the CW agents proper because of reasons of secrecy.

Chapter 2. Delayed lesions—an historical résumé

The history of CW agents and other militarily important chemicals has been dealt with at great length in *The Problem of Chemical and Biological Warfare* published by SIPRI [1]. There is therefore no need to take up here the discovery, production and application of CW agents and other chemicals. It is necessary, however, to deal with various aspects of the observable effects of these poisons on man, since the SIPRI study, for obvious reasons, treats this topic only in a general way. Such data are rarely found even in the majority of other publications on CW agents or chemical weapons, and then only in association with medical literature. The effects of CW agents—if dealt with at all—are described almost invariably in terms of their immediately perceptible effects—that is, *acute poisoning*. This has helped to focus public attention on the immediate hazards of CW agents to the exclusion of their delayed effects.

Already after World War I, concrete data were published in medical literature on wartime victims of exposure to CW agents, who had subsequently recovered from the effects of poisoning—that is, they were regarded as cured of the symptoms of acute poisoning. Such publications were not, however, accorded any great interest as cases of this kind were considered exceptional. Moreover, no comprehensive, scientific, medical investigations were made at that time into these cases, and it is likely that the cause-and-effect relationship between exposure to CW agents and the ensuing signs was largely missed.

A few noteworthy publications on this subject which appeared after World War I will be, dealt with separately.

The growing importance of occupational medicine in the 1920s and 1930s in the developed industrialized countries thrust the problems of occupational diseases—including the delayed effects of acute and subacute poisoning—into the foreground. Increasing attention was also paid to the effects of chronic poisoning. It is not known whether the findings were applied in the sector of military medicine. This state of affairs persisted even after World War II.

As a result of the spectacular developments in the field of nuclear weapons in the years immediately following World War II, the question of CW agents receded into the background, giving rise to the mistaken public view that chemical weapons had become outdated. Only a handful of specialists knew that enormous quantities of known and new CW agents had been produced before and during World War II, and that they were stockpiled ready for use.

When in the course of the Nuremberg trials against the Nazi war criminals, the first details of CW agents—the manner and extent of their use, and their development, production and stockpiling—became known, public interest was focused exclusively on the extremely high toxicity of these new CW agents.

Further details of new CW agents which became known in succeeding years—notably organophosphorus chemicals such as DFP, tabun, sarin and soman

—referred almost entirely to their acute poisonous effects. This is understandable since these poisons constituted a biochemically and toxicologically novel class of compounds, which—apart from their military importance—opened up the way for interesting discoveries in the field of nerve-cell transmission.

In the early 1950s, these and other CW agents were generally held to be obsolete from the military point of view. Three reasons then largely played a part in the reassessment of this view at the end of the 1950s, and shed new light on the problems of delayed lesions caused by CW agents.

1. The first reason was the resumption of production of CW agents after World War II and the extension of production to include organophosphorus chemicals such as tabun, sarin and soman. The intensified production of CW agents was accompanied by increased research activity. The latter, in its turn, was governed by such stringent secrecy regulations that the comparatively free publication of scientific results on CW research in the early 1950s was later classified or almost completely rescinded.

2. The second reason, which centred on the problem of delayed lesions, related to litigation on insurance rights. These problems had arisen after a number of people—mostly former CW production and storage workers in the Wehrmacht, now living in FR Germany—had advanced legal claims concerning their state of health. In 1951–53, A. Weiss was the first to raise the medical aspects of the question. These cases were then taken up by U. Spiegelberg [2].

3. The third reason for the practical and scientific reassessment of the problems of delayed lesions lay in the enormous expansion of pesticide production in many industrialized countries and in the worldwide use of pesticides. Since many pesticides are closely related to CW agents in chemical structure and biological effect (see table 5.1), a comparison between the symptoms engendered by civil and military applications is justified. The conclusions to be drawn from such a comparison will be dealt with in the following chapters.

Some 10 years ago, the military attempted to make a clear-cut distinction between civilian and military research in the field of biologically active compounds. It was seen, however, particularly from the final stages of the Viet-Nam War, that this was no longer practicable. Poisons which had been used solely for civilian purposes up to that time were thenceforth also used for military purposes. The effects of these poisons on man and his environment turned out to be incalculable—a situation not envisaged by the military when they initially used these substances.

The unpredictability of the lesions caused by such chemicals and the inability to appraise them properly are considerations which particularly call for the prohibition of the use of CW agents.

In the meantime, however, the results of environmental research have aroused further world interest in the delayed effects of chemical compounds. There is an ever-growing awareness among all sections of society about the carelessness in handling chemicals which has precipitated a precarious environmental situation. In coming decades this may lead to a general ecological

crisis and pose a serious threat to the continued existence of the human race—perhaps the gravest in its history.

CW agents and other militarily important poisons are today capable of bringing about the self-annihilation of man via their acute effects and, particularly, via their delayed effects on human health and the environment. Neither can we continue to enjoy the cold comfort for the belief that CW agents will not be unleashed by the military save in some grave "emergency". It is quite likely that serious repercussions have already been caused by accidents in CW production plants or by technical defects in field tests and other trial runs. The report on the Skull Valley, Utah, accident—when accidental release of VX nerve gas from the Dugway Proving Grounds of the US Army led to the death of some 6 000 sheep—brings home even to laymen the consequences of such tests that miscarry [3].

Since World War I there have been a number of such accidents in field tests on CW agents or in production plants for military and related poisons. The fact that the effects of such accidents remained localized, depended—apart from luck—mostly on the relatively low toxicity of the substances in question, compared with present-day CW agents. The mind shrinks from the spectre of the 1928 Hamburg phosgene disaster, repeated today with VX or other modern CW agents in a similarly densely populated area.

So long as a comprehensive ban on CW agents is not attained, CW agents still more dangerous than the super poisons of today will doubtless appear. Even civilian toxicological research can give rise to new classes of compounds of unprecedented toxicity; in addition to the problem of the acute effects of such compounds, this also poses the problem of delayed effects.

In view of these prevailing hazards, research work is being carried out in many countries in an endeavour to clarify the problems of the delayed effects of civilian and military poisons. These problems will be discussed in the following chapters.

Chapter 3. Delayed lesions caused by “classic” CW agents

I. *Preliminary considerations*

The mode of action of important CW agents was widely discussed in the literature on military medicine published between the two World Wars. Clinical and experimental data were compiled in many monographs—the accounts by Gilchrist, Gillert, Flury and Zernik, and Muntsch may be mentioned as examples [4–7]. There is, however, not much concrete information to be found on the subject of delayed lesions; moreover, there are many contradictions in the data published at that time. In this connection it is interesting to note that delayed lesions caused by exposure to CW agents have been dealt with to a much smaller extent in German literature (several authors rule out the possibility of delayed lesions) than in Anglo-American, or particularly, French literature, where the problems of delayed lesions figure to a much greater extent.

Based on the most important CW agents of World War I, a survey is given below of those publications which deal with delayed lesions and of the results discussed in current military literature.

II. *Delayed lesions caused by lung poisons*

General evaluation

Phosgene and the other poison gases used in World War I are CW agents producing an immediate effect—that is, acute poisoning. Massive exposure of the human organism to these lung poisons leads to death.

In present-day military literature there is general agreement to the effect that phosgene—and also diphosgene, triphosgene and chloropicrin—no longer have any importance as CW agents. Nevertheless, the high toxicity of phosgene, its harmfulness and its ease of availability in all countries having a chemical industry are factors which by no means rule out the possibility, that—contrary to general opinion—it may again play a role in, say, localized conflicts in the Third World. The discussion on phosgene still continues in practically all monographs on military chemistry and in related literature. The 1970 WHO report *Health Aspects of Chemical and Biological Weapons* likewise discusses this compound [8].

In addition to the fact that phosgene is itself a potential CW agent, this highly toxic substance is formed as a decomposition product in many industrial processes—for example in the pyrolysis of certain varieties of plastics or of other synthetic compounds.

Specific toxicological evaluation

Apart from bis(2-chloroethyl) sulphide (mustard gas), there is hardly any other CW agent that has been so intensively studied since World War I from a medical angle as phosgene. The clinical picture of phosgene poisoning typifies that of lung-damaging CW agents. Phosgene acts immediately on the lungs, and all other symptoms that manifest themselves in other organs are secondary effects caused by the primary lung damage.

Henschler has rightly pointed out the fact that lung edema, although characterized by a uniform pathological picture, is really a polyetiological syndrome [9].

Although this book deals primarily with the problems of delayed lesions, a description from the monograph by Muntsch—a military expert in CW diseases—of the last stages of acute phosgene poisoning may be included [7]:

> . . . cyanosis and dyspnea reach their height, the groaning victims struggling and gasping for breath. At this moment the patient looks a pitiable picture of wretchedness. One sees him drowning, as it were, in the fluid that has gushed into his lungs . . . . Since . . . World War [I], many an utterance has been heard on the humaneness of a gas war: he who has ever seen a victim of gas poisoning in the above-described state of pulmonary edema at its peak would do well—if he has any spark of humanity in him—to remain silent . . . .

The above description of the acute stage of pulmonary edema could equally well apply to those who have survived phosgene poisoning, but have had to suffer for years from bronchial asthma and are doomed to die of pulmonary emphysema.

Nowadays it is taken as a generally accepted—although biochemically not fully proven fact, that lung poisons cause a general intoxication of the organism rather than "chemical corrosion" of the lungs. Although the primary effects of phosgene and related poisons appear at the surface of the respiratory tract, the fact should not be overlooked that hypoxia and carbon dioxide retention are important for the mechanism underlying toxic pulmonary edema and the delayed effects [9–10]. Moreover, according to the results of US investigations, the increased hemorrhagic tendency of the phosgene-damaged lung is attributable to the reactivity of phosgene with thrombokinase present in rich supply in lung [R. W. Gerard, quoted in ref. 10]. On inactivation or destruction of thrombokinase, other vital metabolic processes in lung tissue are also blocked, thus creating the basis for the development of delayed lesions.

A literature survey showed that although comparatively many experimental (including pathologicoanatomical) studies of lung poisoning have been made, the scanty casuistic and clinical reports offer little scope for generalization.

Special note should be made of the publications by Galdston and co-workers in regard to the particular emphasis laid on psychopathological and neurological problems [11]. They report that three out of six persons suffering from acute phosgene lesions developed psychopathological symptoms, producing neur-

asthenic, depressive and hypochondriac manifestations. (These authors are of the opinion that mentally retarded persons are much better adapted to overcoming traumatic experiences resulting from such poison-gas injuries.) Reference should also be made to the paper by Veil and Sturm, who observed the development of peptic ulcers in former victims of phosgene poisoning [12]. A general study of pulmonary irritants—including the question of delayed lesions—was published by Kehoe [13].

In a comprehensive study made by Achard [quoted in ref. 2] on the delayed effects of lung poisons (based on more than 3 500 cases of illness but, unfortunately, not differentiating between the various poisons employed) delayed lung symptoms are rated foremost in significance for the overall clinical picture. Next, as effects of secondary importance, are rated diseases of the nervous system, damage to the cardiovascular system, gastrointestinal disorders, eye and skin damage, and laryngeal diseases.

Minkowski also reported similar observations on CW lung poisons, such as chlorine and phosgene [14]. However, the reservations made by him and by several contemporary authors about the dependence of toxic effect upon "blood uptake" are no longer accepted as fully valid at the present time. The observation by Ricker, that the lung poisons phosgene, disphosgene and chloropicrin lead to anatomic changes in the white matter of the brain (purplish extravasation of blood), is important [15]. Its significance lies in its explanation of psychic disorders, as the clinically observable symptoms—such as mental confusion, stupor, speech disorders, loss of memory, mania, hallucinations and delirium—accompanying discernible structural changes in the brain need not necessarily be primarily traceable to toxic effects, but may also result from psychic shock sustained in gas warfare.

It is to the credit of Petri and, more recently, of Pentschew, and Rothlin, that they collected data from World War I on the pathologicoanatomical effects of CW agents and made them available in comprehensive reports [16–20]. According to these findings, lesions of the central nervous system are anatomically discernible, especially in phosgene poisoning. The authors trace back lesions of the intimal vascular system to the acute toxic effect of the "poison taken up by the circulatory system" or regard them, in a more general way, as being caused by anoxemia.[1]

Flury and Zernik—the foremost experts of their day—also dealt with the problems of delayed lesions in persons afflicted by CW agents during World War I, and attached special importance to residual lesions of the respiratory tract caused by lung poisons, such as phosgene [6]. They rightly pointed out that exposure to such CW agents inevitably lowers the resistance and efficiency of the victim, thus making it extremely difficult—or well-nigh impossible—to arrive at a clear-cut distinction between organic disease and functional or psychogenic disorder.

[1] See also ref. [21] for the pulmonary and extrapulmonary effects of phosgene.

Without intervening in the medical/biochemical dispute on whether phosgene and other lung poisons exert a direct or indirect toxic effect, it can be stated that leading international experts have indisputably proved that this category of CW agents are liable to cause delayed lesions of the respiratory tract—particularly bronchial asthma and pulmonary emphysema—neuropathological symptoms, cardiovascular damage and, in individual cases, injury to the stomach, intestines, skin and eyes. Neither should it be overlooked that a typical feature of survivors of phosgene lesions is the inevitably lowered resistance to infection as a result of severe damage to the ciliated epithelium lining the respiratory tract. Even asthmatic conditions and allergic reactions can be traced back to the loss of ciliated epithelium—and to its replacement by the alien, laminated variety—and to the resultant functional disorders in self-cleansing of the respiratory tract and, thus, in its ability to ward off infection.

III. *Delayed lesions caused by organoarsenic CW agents*

General evaluation

In military literature, organoarsenic CW agents are divided into two groups—*sternutators* (sneeze gases or vomiting gases), primarily causing nose and throat irritation, and *vesicants* (blister gases), attacking any part of the body with which the liquid or vapour comes in contact, especially moist parts.

Organoarsenic compounds are regarded as the most important military sternutators so far. The main representatives of this group are the CW agents, Clark I (diphenylchloroarsine), Clark II (diphenylcyanoarsine) and adamsite (diphenylaminechlorarsine).

The above-mentioned organoarsenic sternutators—as well as organoarsenic vesicants such as lewisite (chlorovinyl dichloroarsine) and the phenyl-, methyl-, and ethylchloroarsines—are now, however, considered obsolete from the military viewpoint, and it is very doubtful that they will ever again play a part as war gases. This does not eliminate the possibility, however, that those working in stores where residual stockpiles of such CW agents are still being kept—or at places where sunken or buried deposits from World War I or II someday come to light—run long-term health risks; not to mention the ecological consequences of arsenical poisoning of the environment [22]. The great stability of arsenic compounds in soil and water points to the continued imminence of an arsenical hazard to health even in coming decades [23–24].

Specific toxicological evaluation

As most organoarsenicals have attained great practical importance outside the military sphere of interest (the militarily interesting arsenic compounds were really “by-products” of civilian research) there are a great many publications on acute and chronic injuries caused by them. Publications on the toxicology

of organoarsenic CW agents draw heavily upon the results of civilian research programmes [6, 17, 25].

Unlike the case of many other groups of biologically active compounds, the biochemical facts here are unequivocal—arsenic, in virtually any form, is poisonous to the human organism.

A comprehensive report on the enzymatic effects of organoarsenic CW agents—and therewith the biochemical basis of delayed lesions—was published by Dixon and Needham in 1946, as the result of studies carried out during the wartime years of 1940–45 [26].

It is now generally accepted that arsenicals owe their toxicity to their ability to combine with thiol groups—which form part of the active centres of a number of widely different enzymes [27–28].

Studies on the biochemical mechanism of arsenical action have been in progress since World War II. We thus know that the enzymes susceptible to inhibition by arsenic compounds include pyruvic dehydrogenase, carboxylase, α-ketoglutaric dehydrogenase, malate dehydrogenase and ATPase. Interference with the breakdown of pyruvic acid is also known to have an important bearing on the clinical picture of arsenical poisoning [29]. It is thus clear, that in view of the manifold derangements of normal enzymic metabolic action caused by organoarsenicals, their classification as “simple irritants” belies the true extent of their toxic action.

Flury and Zernik had already in the 1930s pointedly drawn attention to the fact that—apart from having an irritant effect—organoarsenic CW agents also have nerve-damaging effects [6]. Mention ought also to be made of the carcinogenic effects of arsenic compounds [30], and of their mutagenic activity [31a–31d].

In view of the diverse noxious effects of arsenic on the human organism—and of the fact that compounds containing arsenic in the trivalent state are particularly poisonous (all known organoarsenic CW agents fall into this category)—the causative link with the psychopathological-neurological, gastrointestinal, hepatotoxic, nephrotoxic and hematotoxic delayed effects is considered fully proven. The use of organoarsenicals by the US Army in Viet-Nam therefore makes it all the more urgent to attain an unconditional ban on the production, stockpiling and use of CW agents.

IV. *Delayed lesions caused by vesicants of the mustard-gas type*

General evaluation

For decades, bis(2-chloroethyl) sulphide (mustard gas, sulphur mustard, yperite) was regarded as the “King of Chemical Warfare Agents”. Despite the availability of highly toxic organophosphorus CW agents, this compound can not be omitted from any present-day appraisal of CW agents.

Though mustard gas and other similarly acting vesicants have been discontinued in US arsenals and in those of other countries, the use of these extremely effective substances in future localized conflicts—in the Third World, say—is a possibility that cannot be ignored. The reason is that there are not many CW agents which unite such a large number of "favourable" properties for military application as mustard gas. Even an army equipped with modern CW defences would find itself in considerable difficulty if attacked with mustard gas. This CW agent or its analogues must therefore necessarily figure in any consideration of a possible resort to chemical warfare.

The use of mustard gas in World War I and its production until the mid-1950s was reflected in numerous publications in the field of military medicine, where the question of delayed lesions was also taken up in varying detail [32–37]. It thus became clear—as had already been perceived during World War I—that systemic absorption is a factor strongly underlying the clinical picture of toxication by this substance. With a few exceptions, which will be mentioned later, mustard gas may be regarded as the prototype of all militarily important vesicants.

Another factor to be reckoned with in the complex of problems relating to mustard gases is that—for many years to come—workers and soldiers who came in contact with mustard gas during its production, storage or destruction will have to be given health checks and enabled to make legal insurance claims for injury or disablement benefit and rehabilitation. In FR Germany alone, some 300–400 persons were still on record in 1970 as having suffered health damage during 1933–45 through exposure to CW agents—particularly sulphur and nitrogen mustards—and placed under continual medical observation [38]. Even allowing for any automation in CW production plants, a world total of many thousands of persons engaged in the production, storage or stockpiling of CW agents are today risking their health.

Specific toxicological evaluation

In virtue of its large penetrative capacity, high fat-solubility, relatively good hydrolytic stability and extensive biochemical activity, mustard gas is transmitted rapidly by skin absorption or inhalation to distant organs, where it proceeds to exert its effects. It affects the liver, kidneys, stomach and intestinal tract, as well as the central nervous system and the metabolic pathways in general.[2]

Exposure of the skin to either the liquid or its vapour results in erythema or blisters which are extremely slow and painful in healing and may become sources of secondary infection. Mustard gas is insidious in its action, producing no pain at the time of exposure. The damage to the body does not occur until several hours later. A large number of general symptoms also appear in addi-

[2] For a fuller account of the pharmacology and toxicology of mustard gas, see ref. [39, 40a].

tion to these vesicant effects, leading to general malaise, apathy and deep depression. The general symptoms are, to some extent, even more insufferable than the vesicant effects proper. Advances in modern medicine have so far been able to do little to help.

Literature data on the chronic and delayed lesions of mustard-gas poisoning are, however, not as plentiful as might be expected [5, 14, 16, 41–42]. This may be a result of the fact that victims of mustard-gas poisoning—if they survive the acute effects—suffer from any of the several secondary effects, or even die of them. Eye lesions and the problem of blindness resulting from war injuries are matters which have received greater publicity than those relating to lesions and disabilities of other kinds [43–48]. More detailed research on chronic and delayed lesions was undertaken after World War I [18–20, 49].

The clinical cases of workers employed at mustard-gas production sites and stores before and during World War II afforded the opportunity for far more systematic studies to be carried out on chronic and delayed lesions [2, 38, 50–52]. In 1958, A. Weiss said the following in this connection [53]:

> Long known as permanent injuries [of mustard-gas poisoning] are: primarily injuries of the respiratory tract—from asthma-like conditions to very severe emphesematous bronchitis, recurrent pneumonia and bronchiectasis with brain abscesses, and so on—besides disorders of the autonomic regulation of the heart, circulation and breathing which may or may not be linked to chronic infection of the injured region. Chronic conjunctivitis often persists in addition to the results of severe eye damage . . . Let me now append a list of new findings from our investigations:
> 1. The inevitable development—as a result of lowered resistance to infection—of periodontosis with catastrophic speed, leading to tooth decay.
> 2. Anybody who has observed a number of former mustard-gas workers cannot possibly regard the progressive bodily deterioration and the premature aging as chance symptoms. It is often not possible to tell the victim of severe mustard-gas injury—even if maintained on a satisfactory diet—from the dystrophic patient.
> 3. Osteoporosis is frequent. Here there must obviously be disorders of cell metabolism—primarily anabolism. Loss or premature decline in libido and potency frequently occurs.
> . . . Further findings . . . include:
> 4. Changes in the mucous membrane in the form of swelling and polyp formation in the paranasal sinuses, with relatively rare incidence of severe empyema.
> 5. High incidence of achylia and hypoacidity, with no increase in peptic ulcer morbidity.
> 6. Incidence of perigastric overgrowth of the liver, with relatively rare incidence of permanent liver injury, and—last but not least—
> 7. Injuries of the central nervous system . . . . Where the delayed effects of mustard gas are concerned, there are no differences between those resulting from chronic exposure and those resulting from acute injury. It has been shown that slight or severe delayed effects may result in either case. Seemingly good resistance to acute poisoning or to the chronic subtoxic effect does not protect from the delayed effects. Men whom I myself at that time pronounced as practically immune to the effects of work with mustard gases—and who were even drafted for military service at the end of the war-have, meanwhile, already died through the extremely late, but typical, delayed effects of mustard gas. The individual reaction—also evident in the case of other poisons—is of greater significance for the delayed effects of CW agents.

Information and data have also been collected over the past 10 years from patients treated in cancer clinics with derivatives of mustard gas (mainly N-mustard) [54–55].

It is known that mustard gas and its derivatives are highly effective alkylating agents [28, 56–59, 61–62].

Nearly all the effects of these substances can be explained in terms of chemistry and toxicology. The alkylating properties of chemical compounds will be dealt with more fully in the chapter on organophosphorus agents. Attention is drawn, however, to the fact that the effects of the mustard gases include lesions which are functionally and morphologically similar to those produced by X-rays. The analogous mutagenic effects of X-rays and N-mustard derivatives led Dustin—as far back as 1947—to coin the term *radiomimetica* for these chemicals and to speak of the *radiomimetic effect* of synthetic poisons [63].

The large number of experimental studies on radiomimetica will not be discussed here as comprehensive reviews have already been published [38, 64–67]. The question of mutagenic effects underlies all these studies. Mutagenic effects have often been demonstrated in bacterial and cell cultures and also in experimental animals. Much reservation must be exercised in extrapolating these results to human beings. Since similar experiments cannot be performed on man, the only alternative is to study the mutagenic effects of the mustards and related synthetic poisons on former workers in CW production works now making up the bulk of the patients.

W. Hellmann of FR Germany, acting upon a lead from H. Spiegelberg, was the first to conduct clinical and genetic examinations on the families of persons afflicted with lesions caused by the N- and S-mustards [38]. Basing his studies on the descendants of 134 former workers in CW production plants, he detected dominant, sex-linked, lethal mutations in connection with a significant increase in the sex ratio among the offspring of fathers who had been exposed to CW agents (mainly mustard gases). These studies revealed not only the occurrence of sperm damage but also the impairment of various stages of spermatogenesis.

Figure 3.1. Alkylating mechanism of mustards

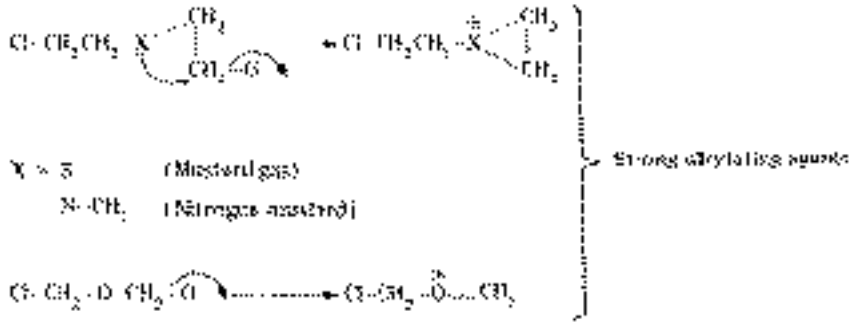
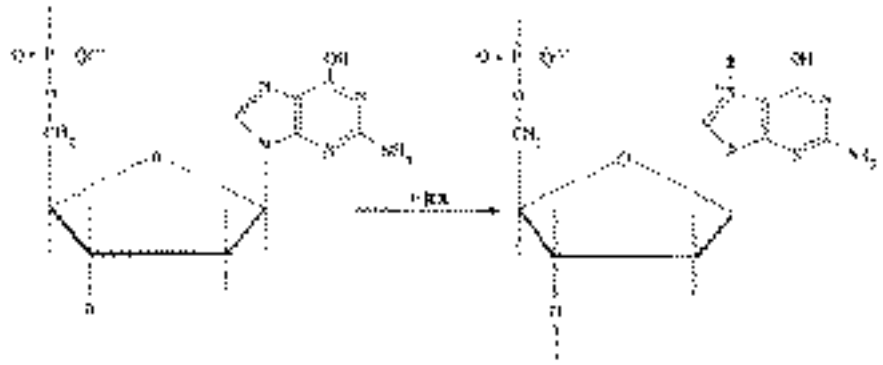


Figure 3.2. Possible mechanism of alkylation of DNA



Weakened potency has also been reported as a result of handling CW agents and related compounds [2, 52, 68–69]. The results obtained by Hellmann imply extraordinarily far-reaching consequences and prompt the need for carrying out such studies in other industries, or of making public the results obtained in analogous studies.

The link between mutagenicity and carcinogenicity is another factor which should confer the highest priority on such studies. As is known, N-mustard gas has been used for years as a cytostatic in cancer therapy [30, 70–72]. The close relationship between mutagenic and cytostatic phenomena is indicated in a study made by Conen and Lansky, who detected distinct chromosomal mutations in the form of deletions and fusions in cases of bronchial carcinoma treated with mustard gas [73]. The studies of Beebe and of Case and Lea on World War I soldiers who had survived gas poisoning show that this group exhibited a higher rate of lung cancer than “normal” persons [74–75]. In 1955, Case published a study on the possible relations between mustard-gas poisoning in the case of World War I soldiers and the subsequent development of lung cancers. This study yields the first evidence of a statistically significant, excessive liability to lung cancer noted in non-fatally gassed British ex-servicemen. Beebe obtained similar results in 1960 from an analysis of the cases of gas poisoning [74].

In 1958, A. Weiss of FR Germany reported on about 40 cases of death out of 261 former CW workers; 40 per cent of the deaths had occurred as a result of malignant neoplasms, indicating a causative link with work with mustard gas [53]. A. Weiss and B. Weiss later showed that these results were highly significant [52]. Yamada reported from Japan that an increased incidence of cancerous diseases had been observed in persons who had suffered non-fatal poisoning by CW agents [76–77].

Hueper of the USA—a leading expert in occupational cancerous diseases—pointed to the steady increase in lung cancer resulting from exposure to CW

agents [78]. According to him, all known respiratory carcinogens—in addition to producing cancers in different parts of the respiratory system in man—elicit a complex of symptoms which is partly characteristic of the carcinogen in question and which reflects its toxic action on the respiratory mucosa and other tissues. For mustard gas he lists: chronic dermatitis, chronic rhinitis, laryngitis, pneumonitis, emphysema and bronchiectasis in addition to cancer of the lung, larynx and nasal sinuses. These etiology-specific symptom complexes—serving partly as exposure stigmata—do not necessarily occur in all individuals afflicted with occupational cancers; besides, they may precede the manifestation of cancer by many years.

In 1968, Wada published a study on 495 persons who had been in direct contact with mustard gas over the period 1929–45 [79]. Of this number, 361 had meanwhile died—49 of the deaths being due to carcinoma of the respiratory tract.

The studies carried out by U. Hellmann show that the carcinogenic effect of N-mustard may be regarded as proven [51]. Since 1958, 43 of 157 former German CW workers have died—20 of them of carcinoma. The average period of exposure to N-mustard gas of the workers who died of carcinoma was 4.6 years. The average interval between the first contact with mustard gas and death from cancer was 18.5 years. By comparison with other population groups in FR Germany, Hellmann calculated an error probability of $p<0.001$—that is, the cancer mortality of these workers showed a highly significant increase.

Spiegelberg's publication on the psychopathological-neurological lesions in workers employed in German production plants for World War II CW agents has been fundamental to the evaluation of the problems of delayed lesions caused by mustard gas [2]. This publication arose as a result of the observations made by A. Weiss in 1951–53. Spiegelberg was the first to make a thorough appraisal of the material published in previous years and to support it with the results of his own investigations. It would be beyond the scope of this book to do justice to his numerous studies. All further studies of the problem of delayed lesions caused by CW agents will inevitably have to take account of Spiegelberg's results as his findings are probably the most important to have appeared in this field since World War II. Meanwhile, U. Hellmann and W. Hellmann—two of Spiegelberg's co-workers—have proceeded with studies in this field. In 1970, in a catamnestic study on the psychopathological-neurological lesions produced by CW agents, U. Hellmann reported in a highly significant statistical manner on increased symptoms in the CW workers previously examined in 1958–60 by Spiegelberg—debility, impaired concentration, loss of vitality, sensory hypersensitivity, diminished libido, weakened potency, neuralgiform complaints, epigastric complaints and heart senastions [51]. The author writes: "It is interesting that not only is there a distinct worsening of certain disorders of the peripheral or central nervous system but that bodily disorders are also accentuated."

To summarize the health aspects—mustard CW agents are capable of pro-

ducing a wide range of mutagenic, carcinogenic, hepatotoxic and neurotoxic effects. It is important to note that even in the case of exposure to very slight amounts which do not necessarily bring on acute symptoms, toxic reactions may set in. How far this may lead to nerve-cell, hematopoietic or parenchymatous lesions depends largely on the state of health of the individual (for example, previous injury to any particular organ), duration of exposure or intervals between exposures and, last but not least, on individual "detoxification capacity" (enzymic polymorphism, genetic disposition, and so on).

We shall meet with similar problems again in connection with organophosphate esters.

Chapter 4. Delayed lesions caused by other militarily important poisons

I. *Lacrimators*

Lacrimators, or tear gases, are among the oldest chemical weapons known. It is a matter of controversy in some circles whether they should be classified as CW agents in the strict sense of the term—and hence included in any proposed ban on the chemical means of mass annihilation—or simply regarded as a lawful means to be invoked by the police in times of crisis [80].

Past experience in the use of lacrimators has shown that, depending upon the manner and extent of their use, the harm they inflict on human health can be either negligible or grave and permanent [43, 45–46].

Apart from accidents (such as those which occasionally occur when using lacrimators in testing out the fit of gas masks), these substances are likely to cause health damage only under extreme circumstances. Such a situation would be one, for example, where a person is exposed without protection to high lacrimator concentrations and remains trapped for a long time as a result of being wounded or of being buried alive or forcibly held. Another example of an extreme situation of this type would be where the firing of tear-gas shells at a person results in a high local concentration of lacrimator, which—coupled with some traumatic injury—leads to serious health damage [45].[1]

Many cases are known from World War I and the Viet-Nam War, as well as from police actions against demonstrators, where the use of lacrimators has led to severe and lasting eye damage and also to serious lung damage comparable to that caused by phosgene [7].

There are good grounds, however, for fearing that exposure to lacrimators can have still more serious effects. Thus Neilands, referring to results obtained by Barry, has reported the carcinogenic activity of 2-chlorobenzylidene malononitrile (CS) [24]. The biological activity of substituted malononitriles in point of their neoplastic effect is very variable and has not yet been definitely elucidated [82–84].

It ought to be pointed out that the toxicological hazards of CS have often been underestimated [85]. Attention should also be paid to the allergenic properties of CS and other riot control agents because of their obvious significance particularly for workers and military personnel employed in production works and stores [86].

[1] In 1958, Martinius reported an entirely different kind of "delayed lesion": some fishermen sustained acute injuries in the Baltic from previously sunken deposits of xylyl bromide which, having meanwhile become resinous on the surface, had remained in a state of preservation [81]. Account will have to be taken in coming decades of such kinds of belatedly discovered agents sunk in the sea or buried in the earth. This topic however lies outside the scope of this book.

The suspected carcinogenic effect of dichloromethyl ether—used in World War I as an eye and lung irritant [87], and nowadays of some importance as an intermediate product in the chemical industry—was confirmed a few years ago by studies carried out in the USA and FR Germany [88].

Exposure to lacrimators can, at times, also cause considerable psychic disturbance such as anxiety hysteria and psychic shock. People exposed unpreparedly—without an adequate realization of the range of effects or the actual extent of danger associated with these substances—are liable to panic, and may thus incur psychosomatic lesions as secondary effects. What Haber, the German chemist, Nobel Prize winner and CW expert, said 50 years ago on the subject of the psychic factor in battle is equally true today [89]:

> The battles deciding the outcome of a war are won not by physical annihilation of the enemy but by psychic imponderables. At a critical moment these factors fail to sustain the [men's] power of resistance and allow the image of defeat to form in the mind. These imponderables turn soldiers from a military force in the hands of a leader into a crowd of dispirited men. Artillery is the most effective means in military strategy for inflicting a psychic shock of this kind. But its effects have been limited as the sensation accompanying the impact of shells on the target has remained essentially the same—namely, one of stupefaction. A shell may be twice or four times as big as another—it may accordingly penetrate more deeply and burst more frighteningly; but in the end a shell is still a shell, and a fairly small variation in distance from the point of impact can offset any quantitative difference in detonation and shrapnel effects. Having to live in a dugout where one can either suffer a direct hit or be buried alive makes terrible demands on the nerves, but war experience has shown that the strain becomes tolerable since the repeated action of like stimuli progressively dulls the senses. The situation is different in the case of CW agents. The important thing about them is that their physiological effect on man and the sensations produced by them may change in a thousand ways. Every change in impression perceived by the nose or mouth affects the psychic balanced and produces the fear of an unknown effect, thus imposing a fresh strain on the soldier's moral power of resistance at a moment when the task of battle calls for his undivided psychic strength . . .

Modern man appears to be extremely susceptible to stress situations, particularly those of chemical stress, which deviates somewhat from the normal run of stressors acting upon him.

The question of the delayed lesions caused by lacrimators needs to be examined afresh. The psychogenic constituent of lacrimator effect should also be given due consideration. The fact remains that lacrimators may cause permanent eye lesions, even blindness. It would be irresponsible to belittle their effects [90].

II. *Psychochemicals*

A discussion of psychochemicals in connection with the delayed lesions caused by CW agents and related compounds with military applications presents many problems. Apart from piperidyl benzylates such as 3-quinuclidinyl benzylate (BZ), it is not sufficiently clear which psychochemicals warrant true

military importance. Up to now, speculation has gone far beyond the realm of reality. Moreover, a great deal of experimental evidence on permanent lesions—notably teratogenic and mutagenic—has been provided by the psychopoisons used as military test chemicals: for example, LSD, cannabinol derivatives, DMT and psilocybin. Clinical observations on delayed-effect or permanent lesions are already available to some extent [91-95]. Some scientific workers doubt that psychochemicals lead to delayed lesions [96-98].

Although numerous psychochemicals have been synthesized [99-100], only very few have been the subject of any detailed toxicological research programme.

The following basic assessment of the situation can be made from a military and toxicological standpoint. Psychopoisons of the LSD type are substances which are effective even in minute quantities (microgram range). Under combat conditions it may be possible to use chemicals with an analogous effect in concentrations that do not cause permanent lesions in the human organism in a single dose, unless the psychic response of the persons concerned is extremely sensitive for reasons such as those outlined in connection with lacrimators. Delayed lesions may, of course, result from, say, terror or sabotage attacks on the civilian population, if large doses—or small doses over a long period—are administered.

It is obvious that delayed-effect and permanent lesions will also be met with where psychochemicals are repeatedly used in the requisite doses for the purpose of harassing people (brainwashing, extortion of confessions, and so on).

Although intensive research has been conducted for many years now on the mechanism of action of psychochemicals, and has resulted in remarkable findings, the latest publications in this field still provide too little new information on the metabolic pathways of such compounds [101].

In this discussion we are primarily concerned with the detrimental effects of psychochemicals on human health. Experience has shown that although animal experiments are indispensable in toxicology, the results obtained in man often differ radically from those in animals. In the field of pharmacology, the example of thalidomide demonstrated this difference impressively—and tragically—to a wide public: a preparation which had apparently been rigorously tested in animal experiments in line with the pharmacological knowledge of the day, caused teratogenic effects, leading to the birth of severely deformed children. This clearly illustrates the dangers of attempting to establish the innocuousness of biologically active compounds solely on the basis of results from animal experiments.

Because of the many problems surrounding the subject of delayed-effect and permanent lesions caused by CW agents, a great deal of incorrect information has reached the public, especially by way of exaggerated reports by journalists. The latter have generalized uncritically and arbitrarily on animal experiments, employed macabre epithets like “Dew of Death”, and painted a picture of mankind held in dire terror by psychochemicals. Such descriptions—sometimes

given with the best of intentions as earnestly felt warnings on the dangers of CW agents—are liable to misrepresent the already proven harmful effects. Factual information on the real dangers, based on known CW agents, should rightfully be used to promote a comprehensive ban on chemical weapons, and is therefore much too valuable to be made incredible by science-fiction descriptions, which thrust it into the realm of the lurid and the grotesque.

Summarizing the above brief discussion on psychochemicals, it may be said that, on the one hand, there is a great dearth of data on substances with military psychochemical potential, and that, on the other, the experience hitherto gained with model chemicals has plainly shown the great dangers of permanent and delayed lesions [92]. If, contrary to the findings of scientific research, the advocates of psychochemical warfare persist in taking the line that this type of warfare is the most humane, they are simply misleading public opinion.

III. *Antiplant agents*

The use of herbicides by the US Army in Viet-Nam and Cambodia has shown that even antiplant agents, when used in an "environmental war", must properly be classified as CW agents or chemical weapons.

Detailed reports have been published in both East and West on the use of these antiplant agents by the US Army in Viet-Nam and Cambodia, and on their effect on the soil and, in turn, on the plant and animal life in these heavily afflicted countries [60, 102]. While dwelling upon the ecological implications, such reports have ignored or, at any rate, attached secondary importance to the fact that these substances have caused a great variety of severe lesions among the civilian population and soldiers in combat areas in these countries. The Viet-Namese side drew attention to the severe injuries caused by the use of poisonous chemicals by the US Army. Only recently, however, has the full extent of injury become clear through the appearance of delayed effects, giving rise to grave concern.

It was but a few years ago, during the escalation of the Viet-Nam War, that the USA had categorically denied the possibility of delayed lesions being caused by the use of antiplant chemicals. But, at the same time, the results of scientific investigations were even available in the USA proving that, in addition to severe lesions, permanent and delayed neuropathological damage could also be caused to people by herbicides of the 2,4-dichlorophenoxyacetic acid (2,4-D) type [103].

The pro-US Administration press, both domestic and foreign, has repeatedly taken the line that "herbicides"—as commercially available and used by every farmer—are neither potential CW agents nor can they conceivably be rated as a threat to man. These poisonous substances were accepted as legal and militarily necessary means of warfare in jungle areas, and the reservations and objections raised by US scientists and scholars in regard to the ecological

implications and the destruction of useful plants and crops were belittled by the US military and politicians as regrettable but inevitable peripheral problems of warfare.

The study entitled *The Effects of Herbicides in South Vietnam*, published by the US National Academy of Sciences, has made it clear that most of the statements made by US governmental and military representatives during the Viet-Nam War were false and misleading [102]. Even if allowance is made for the fact that those responsible for herbicide spray missions were unable to predict the biochemical effects of such poisons on man and his environment, and also that scientists were not fully aware of some of the possible effects (see below)—this in no way absolves those who gave the order to spray over 17 1/2 million gallons of biologically highly active chemicals over forests, arable lands and inhabited regions during the period 1965–71.

No attempt will be made here to touch upon the various properties peculiar to the individual antiplant chemicals used in the Viet-Nam War because, as already mentioned, a large number of publications, together with papers on specific scientific issues, are available. Detailed data can also be found in the US Armed Forces manuals [104].

Two important facts relating to the use of poisonous substances in the Viet-Nam War should be singled out as they illustrate the diversity of problems involved in the use of such poisons against man and his environment. These are the teratogenic dangers accenting the delayed lesions produced by these poisons [105], and the carcinogenic effect, several indications of which have also been found [106].

The first indications of teratogenic damage observable after the use of chlorinated phenoxycarboxylic acid herbicides—for example, 2,4-D and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid)—led to intensified investigation into the chemistry and toxicology of these compounds. As a result of these investigations, it was shown that during the chemical reactions of the corresponding chlorophenyl sodium salts a side reaction is triggered off (neglected in earlier studies), leading to one of the most poisonous synthetic products known up to now. It is the chemical compound 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin for short)—a very powerful vesicant with general injurious effects.

The following is an excerpt from the above-mentioned US publication *The Effects of Herbicides in South Vietnam* [102a]:

> Although available toxicological information had indicated that, within a considerable dosage range, the herbicidal compounds are relatively innocuous, no sizeable human population had previously been thus exposed. Moreover, at the time the program began, it was not known that preparations of the herbicide, 2,4,5-T, were contaminated with the extraordinarily toxic compound, TCDD (2,3,7,8-tetrachlorodibenzo-*para*-dioxin), about 200 to 300 pounds of which, mixed with about 50 million pounds of 2,4,5-T were dispensed over South Vietnam. That no serious sequelae have since been definitely discerned is fortunate indeed. However, the continued presence of possibly significant concentrations of this material in fish in inland rivers, taken as recently as 1973, is considered to be a matter that warrants further attention.

A closer scrutiny of the international literature and a more critical attitude towards the chemical agents employed in Viet-Nam would have brought home, much earlier, to scientists and Pentagon experts that these substances were more dangerous than a cursory investigation would appear to indicate.

Dermatologists have now for 75 years known of the clinical picture of the disease—first described by Herxheimer in 1899—known as *chloracne* (erroneously attributed to free chlorine, hence the name). This chronic skin eruption is characterized by persistent acne, follicular inflammation, hyperkeratosis, pustulosis and furunculosis. The external dermatological signs of its early stages are associated with pain and weakness in the lower limbs, mild paresthesia, heart complaints and psychovegetative disorders. These conditions may later be followed by severe hepatic degeneration (cirrhosis and necrosis), bronchitis, polyneuritis, encephalitis, renal and splenic damage, and multiform psychopathological-neurological delayed and permanent lesions.

In 1961, Bauer, Schulz and Spiegelberg made a comprehensive evaluation based upon a study of 100 chloracne cases [107]. They confirmed the suspicion that dioxin—produced as a by-product in the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene to 2,4,5-trichlorophenol—was the toxic compound proper that set off the diversified sequence of poisoning. Their publication did not, at that time, receive the attention it deserved; neither did the results published earlier in 1957 by Schulz receive due attention [108].

A case of industrial mass poisoning was described by Goldmann in 1972 [109]. Fifty-five persons were stricken with very severe, acute chloracne in 1953 as a result of a disaster in the works of Badische Anilin- & Soda-Fabrik AG in Ludwigshafen in FR Germany. In addition to exhibiting the typical skin eruption, 21 of these cases partly showed serious effects of systemic poisoning, manifested in damage to the parenchymatous organs (liver, spleen, kidneys), respiratory tract, myocardium, eyes and central nervous system. It is of interest that it was not until three years after the disaster that it was possible to pinpoint dioxin as the toxic causative; and animal experiments performed in 1961 at the site of the accident—as required by the circumstances of the case—still revealed the presence of the product in wall and plaster specimens. The unfeasibility of carrying out a 100 per cent decontamination led, in 1968, to the decision to demolish the building. Animal experiments carried out in this connection at the BASF medicobiological research laboratories showed that 10 *u*g/kg was a lethal dose for rabbits, and that even 3 *u*g/kg—while nonlethal—caused liver damage. Hexachloronaphthalene—alleged until then by many to be the causative agent of chloracne, hence the name *Perna Disease* from *per*chlorinated *na*phthalene—is of hardly any importance as compared with dioxin, the latter being 10 000 times more potent.

At present there appears to be a widespread, deep interest in dioxin. It is suspected that this belated interest derives more from the potential use of this extremely toxic poison as a CW agent than from purely scientific considerations [110–111].

Another fact has emerged in the past few years which has disclosed the incorrectness of all the calculations hitherto made on the actual and supposed proportion of dioxin in 2,4-D and 2,4,5-T preparations or in crop plantations and other regions treated with chlorophenol-containing agents. Buu-Hoi and co-workers found that not only is dioxin formed as a by-product in the alkaline hydrolysis of tetrachlorobenzene to 2,4,5-trichlorophenol—the industrial precursor of 2,4,5-T—but that it is also produced by the pyrolysis of 2,4,5-T [112]. In 1957, Sandermann and co-workers had already reported on the possibility of this chemical reaction but could not, at that time, assess its far-reaching implications. In his comprehensive report of 1974, Sandermann gives a striking account of the entire problem of polychlorinated aromatic compounds as environmental poisons [113]; this publication also refers to a preliminary report, according to which five out of 30 workers employed in applying chlorinated phenoxyacetic-acid weed killer to Swedish railway embankments died shortly after–four out of five of cancer [114a]; it was subsequently revealed, however, that the workers had also been exposed to the herbicide amitrole (3-amino-1,2,4-triazole)—a known but neglected carcinogen [114b]. Meantime, it has been indicated in the USA that the burning of brushwood treated with chlorophenol-containing herbicides may lead to the formation of dioxin [115].

Looking back on the use of herbicides by the US Army in Viet-Nam and recalling the fact that defoliated forests were then often burned down by means of napalm, one begins to surmise the true extent of the impact of dioxin on the territory and people of Viet-Nam. The grim results will, however, only be made plain in the years and decades to come in the form of a rising cancer rate and an increasingly large number of deformed children.

Chapter 5. Delayed lesions caused by organophosphorus CW agents

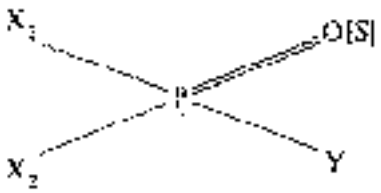
I. *General evaluation*

The sole examples of openly published, discrete studies on delayed lesions caused by organophosphorus CW agents are the investigations made by Spiegelberg [50], U. Hellmann [51] and W. Hellmann [38]. A number of other scientific investigations have, of course, been carried out meanwhile on widely different types of delayed lesions caused by industrially important organophosphorus compounds. In these publications—mainly concerned with organophosphorus pesticides, solvents and plasticizers—it is possible, however, to find the occasional reference to CW agents. Since all these organophosphorus compounds are structurally and functionally closely related to each other, the earlier findings on industrial compounds can—with justification—be essentially applied to their CW analogues.

The advent of binary weapons has, moreover, made it more difficult to decide whether certain chemical compounds are meant for civilian or military applications. The personnel engaged in the manufacture and storage of such compounds are themselves very often unaware of the nature of the civilian or military use for which the products are intended.

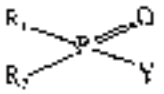
Depending upon the manner of production and application of these CW agents, the victims of attack are exposed to a wide mixture of organophosphorus compounds—a main component, incompletely reacted or partially decomposed components, and organophosphorus compounds formed in side reactions—a veritable cocktail of chemically and toxicologically diverse organophosphorus constituents. Shaffer and West have shown that inclusion of Tetram (a phosphoric ester related to the V-agents) as one of the components in binary phosphoric ester mixtures leads to a great increase in toxicity [116].

Where the term *organophosphorus compounds* is used without qualification in the following sections—as is frequently the case—it is intended to denote all those organic compounds of phosphorus which are closely related to each other in their chemical and toxicological properties, and which can be represented by the general formula first stated in 1937 by Gerhard Schrader of Germany, the pioneer investigator in the field of organic phosphorus insecticides:



According to Schrader, effective (that is, toxic) esters are obtained when the central phosphorus atom—in addition to being doubly bonded to an oxygen or sulphur atom—is bonded to two identical or different substituents and to an organic or inorganic acidic group [117]. Table 5.1 lists some important CW agents and civilian pesticides corresponding to the Schrader formula.

Table 5.1. Properties of some important phosphoric and phosphonic esters

	General formula: 			
	Substituents			Toxicity (LD_{50})
Trivial name	R_1	R_2	Y	mg/kg
HEPP	C_2H_5O–	C_2H_5O–	O–P(O)–$(OC_2H_5)_2$	1.5 p.o. (rats)
Paraoxon	C_2H_5O–	C_2H_5O–	O– 	3 p.o. (rats) 0.6–0.8 s.c. (mice)
DFP	i-C_3H_7O–	i-C_3H_7O–	F	~5 s.c. (mice)
Sarin	i-C_3H_7O–	CH_3–	F	0.1 s.c. (mice)
Soman		CH_3–	F	0.03 p.o.
Tabun	$(CH_3)_2N$–	C_2H_5O–	CN	0.4 s.c. (mice)
Tammelin esters	CH_3– C_2H_5O–	F CH_3–	O–CH_2CH_2–$N(CH_3)_2$ S–CH_2CH_2–$N(CH_3)_2$	0.1 i.p. (mice) 0.03 i.p. (mice)
Amiton	C_2H_5O–	C_2H_5O–	S–CH_2CH_2–$N(C_2H_5)_2$	0.4 i.p. (mice)
Metasystox	CH_3O–	CH_3O–	S–CH_2CH_2–S–C_2H_5	1.5 p.o. (rats)

Militarily, the organophosphorus V-agents—and, to some extent, the G-agents—play the most important role as CW agents. In this connection, binary weapon techniques are likely to constitute the most important system of application [118]. The advent of binary weapon technology might also lead to a reappraisal of other highly toxic organophosphorus compounds, which only a few years ago were dismissed as potential CW agents because of their unsuitable properties—for example, poor transport and storage stability.

II. *Specific toxicological evaluation*

Symptomatology of acute poisoning by organophosphorus compounds

In order to elucidate the subject of delayed lesions it is first necessary to give a brief account of the symptoms produced through acute poisoning by organophosphorus compounds. The reader is referred to monographs for a more detailed treatment [119–121].

Phosphoric and phosphoric esters may enter the human body by inhalation, ingestion or—a noteworthy feature—by skin contact. The entry of these virtually odourless and tasteless compounds into the system is not marked by any perceptible effects, being only manifested later by the onset of grave symptoms.

Symptoms of intoxication by organophosphorus compounds are usually classified as (1) muscarinic effects, (2) nicotinic effects, and (3) central nervous system toxication:

1. The muscarinic effects include miosis, accommodation spasm, bronchoconstriction, bronchospasm, bradycardia, nausea, vomiting, abdominal cramps, diarrhea, urinary and fecal incontinence, pallor, increased salivation, perspiration, lacrimation and increased blood pressure.
2. The nicotinic effects include tremor, myasthenia, cramps, and perhaps paralysis.
3. The effect on the central nervous system leads to giddiness, insufferable headache, feelings of anxiety, speech and balance disorders, depression of the respiratory centre, and finally coma and convulsions.

All these symptoms arise from the intense stimulation of the autonomic nervous system by the accumulation of acetylcholine at parasympathetic post-ganglionic fibres (muscarinic action), at synapses between preganglionic and post-ganglionic fibres of both sympathetic and parasympathetic neurones (nicotinic action), at the myoneural junctions of striated muscle (nicotinic action), and in the central nervous system.

The above symptoms of poisoning are reviewed in table 5.2.

Biochemical mechanism of poisoning by organophosphorus compounds

It would go beyond the scope of this brief account of delayed lesions to attempt to provide a survey of the numerous scientific papers published on the biochemical mechanism of poisoning. In this section we shall, therefore, confine ourselves to a consideration of important facts which are fundamental to an understanding of the problem as a whole. The reader is again referred to the many articles and monographs in this field [40b, 123–128].

The organophosphorus compounds which concern us here are powerful poisons having a specific inhibitory action on the enzyme cholinesterase. Facts concerning this anticholinesterase activity on the part of organic phosphate derivatives were already known to German biochemists and pharmacologists

Table 5.2. Survey of symptoms of poisoning with cholinesterase inhibitors

Bronchopulmonary symptoms	Sensation of constriction, possibly light pain in the thorax increased secretion with coughing and expectoration, possibly lung edema-like condition, dyspnea
Gastrointestinal symptoms	Anorexia, nausea, vomiting, tenesmus, diarrhea, involuntary discharge of feces
Urinary tract symptoms	Pollakiuria, possibly involuntary discharge of urine
Cardiovascular symptoms	Pallor, possibly initial tachycardia with increased blood pressure, subsequent bradycardia with decreased blood pressure, possibly shock, cyanosis
Glandular symptoms	Perspiration, salivation, epiphora
Ocular symptoms	Miosis, nebulous vision, headache (ciliary pain)
Symptoms from striated musculature	Fatigue, flaccidity, fasciculations, possibly convulsions
Symptoms from the central nervous system	Neurosis- or psychosis-like conditions, agitation, insomnia, headache, hallucinations, phobia, apathy, dysarthria, ataxia, convulsions, tremor, depression, coma, depression of respiratory centre

Source: See ref. [122].

who, prior to the outbreak of World War II—acting on orders from the Wehrmacht—were intensively engaged on work with phosphoric esters intended for CW applications. British teams were also independently working along the same lines during World War II. We now know that, in addition to cholinesterase, a number of other enzymes may also be affected by organophosphorus compounds—particularly chymotrypsin, trypsin, liver esterase, milk lipase, choline oxidase, cytochrome oxidase, carbonic anhydrase, amylase, carboxylase and dehydrogenase.

The symptoms of cholinesterase inhibition predominate in the primary manifestations of poisoning. Knowledge of the processes inhibiting the other above-mentioned enzymes is still incomplete.

Some general observations may be apt here on the part played by cholinesterase and on its importance for the basic processes of nerve transmission.

Cholinesterase—together with other esterases, carbonic anhydrases, proteases and amidases—belongs to the large group of hydrolytic enzymes or hydrolases. Another principal group of enzymes—the desmolases—comprises the enzymes which catalyze the final general breakdown of hydrolytic decomposition products.

Acetylcholinesterase (formerly called “true cholinesterase”) should be distinguished from cholinesterase (formerly called “pseudocholinesterase”, serum or plasma cholinesterase). Acetylcholinesterase has a high affinity for acetyl-

choline and is capable of splitting this choline ester more rapidly than any other choline derivative. It is present in nervous tissue, muscle and red cells. Acetylcholinesterase plays a decisive role in nerve-transmission processes.

Acetylcholine has important physiological functions, such as playing a role in the transmission of impulses from one nerve fibre to another across a synaptic junction. If, for example, a nerve impulse is received by a motor end plate, acetylcholine is released from a bound form (the nature of which is still not precisely known) and transmits the impulse to the muscle which has up to then been in a resting state. Within one thousandth of a second, acetylcholine is hydrolyzed to choline and acetic acid under the catalytic influence of acetylcholinesterase. A resynthesis of acetylcholine into the above-mentioned bound form is effected by choline acetylase; acetylcholine is then again liberated upon arrival of the next nerve impulse. The acetylcholinesterase molecule is capable of splitting approximately 300 molecules of acetylcholine per millisecond.

Acetylcholinesterase is inhibited by organophosphorus compounds and the resulting accumulation of acetylcholine gives rise to the symptoms of endogenous acetylcholine poisoning.

Enzymic inhibition proceeds essentially in three stages. First, the phosphorus derivative responsible for inhibition becomes attached to the enzyme. Shortly after, a nucleophilic substitution occurs, firmly binding the phosphoryl group to the active centre of the esterase. At this stage of inhibition, notwithstanding the existence of a true bond, reactivators like hydroxylamine and oxime are capable of fairly easily detaching the phosphoryl group from the enzyme, and thereby restoring its activity. Dealkylation reactions are also likely to occur at the phosphoryl group at this stage of enzymic phosphorylation [125]. No definitive information is yet available on the extent or quantitative aspects, or the resultant qualitative changes, relating to the course of poisoning. There is likewise a dearth of clinical and toxicological data which might explain the dealkylation and transalkylation processes occurring at this stage of inhibition. A fuller account of alkylation will be given later in this section.

If no reactivator is present to influence the above-described intermediate stage of phosphorylation, the third stage of inhibition (which sets in within minutes or hours, depending upon the type of organophosphorus compound involved) takes the form of a transphosphorylation. The phosphoryl group migrates in a manner not yet fully understood and becomes bound to a serine molecule. Many authors term this step *aging.* According to others, aging is a dealkylation process [129–130]. Any reactivation at this stage is only possible with great difficulty.

For every cholinesterase molecule—and the same applies to chymotrypsin and other enzymes inhibitable by phosphoric acid derivatives—one phosphoryl radical suffices to derange the activity of the enzyme. As approximately 300 molecules of acetylcholine are assumed to be split every millisecond by a single molecule of cholinesterase, it is conceivable that minute concentrations

of organophosphoric inhibitors are capable of initiating disastrous biochemical effects. The organism is, of course, provided with a number of "intrinsic possibilities" for counteracting such malfunctions within certain concentration limits and within its phenotypic makeup, and for compensating for much of this damage with the help of so-called repair enzymes [131–132].

The above statements would require much qualification and supplementation if the so-called Tammelin esters and the related V-agents were to be included in the discussion [128, 133–134]. It is, however, premature in a study of the effects of delayed lesions to appraise the findings of animal experiments using V-materials and related compounds. Medical observations on workers and soldiers charged with handling V-materials are not expected to be published openly for some time due to secrecy regulations.

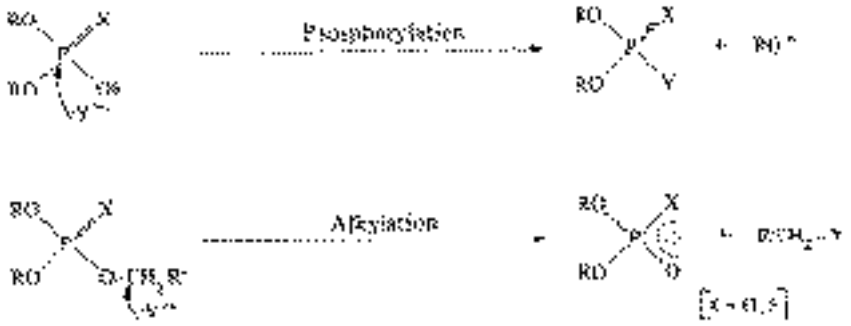
The above discussion has characterized organophosphorus compounds primarily as enzymatic poisons, specifically as cholinesterase inhibitors. We have thereby overlooked a very important fact fundamental to the clarification of the matter of delayed lesions. This fact has likewise been neglected—or, at any rate, inadequately dealt with—by practically all scientists working in this field. This fact is, namely, the alkylating capacity of these organophosphorus compounds.

Alkylation is here to be regarded as an alternative reaction to phosphorylation, as show in figure 5.1.

The reaction formulas below show that in phosphorylation, the nucleophile Y attacks the central phosphorus atom. Alkylation, on the other hand, proceeds via attack by the nucleophile at the α-carbon atom of the residual ester. The type of phosphoric ester employed, the nature of the nucleophile and the reaction conditions determine whether phosphorylation or alkylation takes place, but it is also possible that both reactions occur simultaneously to a large extent [135].

While phosphorylation has been the subject of thorough investigation be-

Figure 5.1. Possible mechanisms of phosphorylation and alkylation reactions of organo-phosphate esters



cause of its importance for acetylcholinesterase inhibition and as a hydrolytic decomposition and detoxification reaction, alkylation has hitherto been dealt with almost exclusively from the viewpoint of synthetic chemistry.

Since World War II, biochemists have made comprehensive investigations of the biological aspects of alkylation both in nucleic acid research and in connection with the subject of cytostatic chemotherapeutics [58, 136].

The alkylation of genetically relevant nucleic acids has been discussed as a primary process of molecular biology involving many mutagenic and/or carcinogenic as well as teratogenic, chemical noxae. This question has also been discussed in conjunction with abnormal methylation by suitable methyl group donors in the genesis of schizophrenia [137]. Here it is the alkylation of specific biogenic amines, however, rather than that of nucleic acids which appears to be important. In this connection, special note should be made of the fact that a great number of hallucinogenic agents—for example, mescaline, psilocin and DMT—are methylated derivatives of cerebral neurohormones—for example, serotonin, dopamine and noradrenaline. Figure 5.3 on page 30 shows the O-and N-methylation of serotonin and the N-methylation of dopamine and tryptamine.

For the purpose of classifying bioalkylants it is not important to know whether they exist in a readily alkylating form (“direct” alkylants) or whether they become metabolically so converted (“indirect” alkylants) [70]. Biologically active alkylants are thus found among a wide range of chemical substances—

Figure 5.2. Biological aspects of alkylation

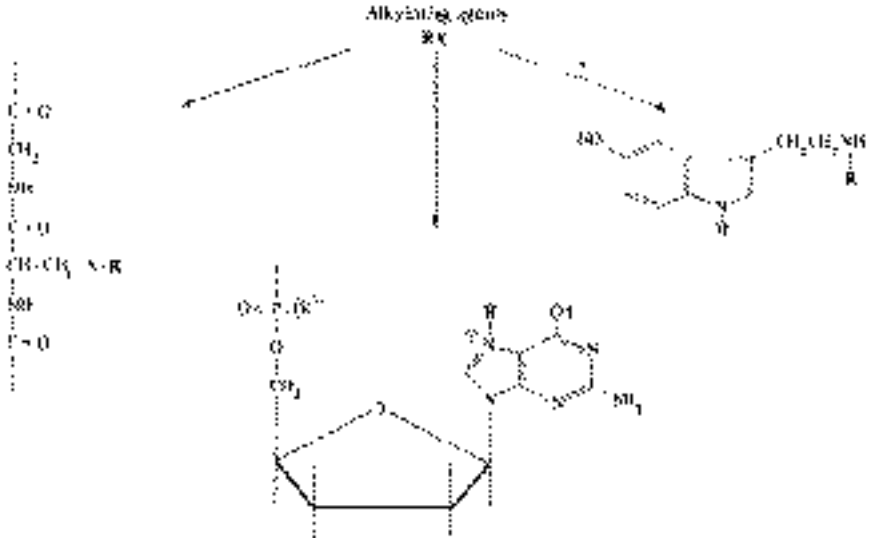
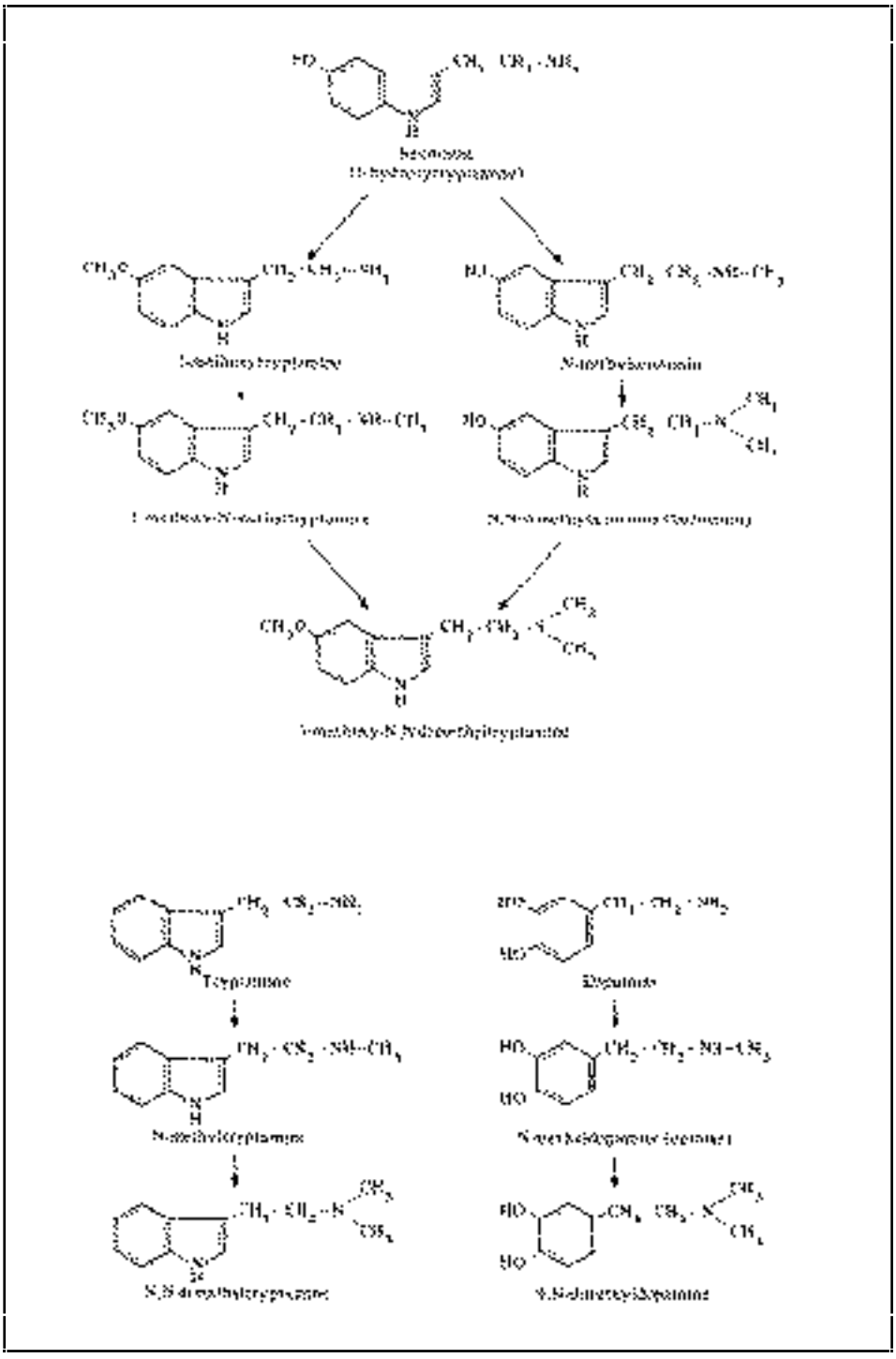


Figure 5.3. Methylation reactions of some biogenic amines



Source: See ref. [193].

for example, alkyl halogenides, mustards, epoxides, ethyleneimine, dialkyl sulphates, alkyl alkanesulphonates, diazoalkanes, organic N-nitroso compounds, hydrazo-, azo- and azoxy alkanes, and aryldialkyl triazines.

In all, there is a wealth of experimental data on alkylants and their molecular–biological mechanism of action. It is thus all the more surprising that organophosphorus alkylants have been neglected for such a long time. One possible explanation might be that this alkylation effect is relatively weak in comparison with that of other alkylants–or that it proceeds only under very definite reaction conditions.

Research scientists working on pesticides were the first to indicate the biological consequences of the alkylating property of organophosphorus compounds. Their publications were, however, primarily concerned with the metabolic problems associated with the use of pesticides.

Löfroth of Sweden was the first to show, by means of experiments with DDVP (2,2-dichlorovinyl dimethyl phosphate) on microorganisms, that such alkylation processes in the case of organophosphorus insecticides can assume far-reaching significance because of their mutagenic effects [138]. His publications attracted great attention—and also aroused much opposition; at any rate, they initiated a number of intensive investigations with DDVP—the basis of important pesticide formulations in worldwide use. The manufacturers of this important class of trade products have naturally shown interest in clarification of the question of alleged mutagenic effects.

In the case of the phosphoric ester CW agents it has been shown that only the V-gases exhibit distinct alkylating properties. Investigations are currently being made on their mechanism of action and on the implications for warm-blooded animals. The exact sites of attack by alkyl phosphates should, in particular, be studied more intensively than hitherto, using modern biochemical techniques [139a–139b, 140–141].

Further anatomical studies are also necessary for the determination of organophosphorus degenerative patterns. Cavanagh has discussed these questions thoroughly in a review [142].

Medical aspects of the effects of delayed lesions caused by organophosphorus compounds

It must again be pointed out that, apart from Spiegelberg’s findings on psychopathological-neurological delayed lesions [2, 50], literature data on delayed lesions caused by organophosphorus compounds relate primarily not to CW agents but to the pesticidal derivatives of phosphoric acid. As mentioned earlier, because of the chemical and toxicological similarity between organophosphorus pesticides and CW agents it appears permissible to draw generalized conclusions.

Health lesions caused by organophosphorus poisons may be grouped as follows from the biological and toxicological viewpoints:

Group 1

Health lesions resulting from acylation—synonymous with the inhibition of cholinesterase, chiefly acetylcholinsterase.

• The clinical picture consists of the acute symptoms of poisoning.

Group 2

Health lesions resulting from alkylation—synonymous with action on the nucleic acids (DNA) or on the biogenic amines of the central nervous system, or on both.

• The major clinical manifestations take the form of delayed and permanent lesions of the central nervous system. Teratogenic, mutagenic, carcinogenic, hepatotoxic and hematotoxic symptoms also arise.

Group 3

Health lesions caused by various—not individually known—metabolites, and so on.

• The major clinical manifestations take the form of, for example, paralysis, impotence and eye diseases—partly in immediate connection with Group 2 lesions.

The division of these lesions into the above three groups is purely formal. The clinical manifestations of any actual case of organophosphorus poisoning are compounded of each of the above components to a varying extent. Precise information on the actual phosphorylation/alkylation ratio *in vivo* for the human body is not yet available. For this reason, clinical toxicology is at present thrown back on indirect conclusions based upon the complex of symptoms and the course of poisoning–subject to marked individual variation.

Some fundamental observations need to be made at this point of the discussion.

From a medical viewpoint it is essential to know in the case of delayed lesions—and this applies not only to poisoning by organophosphorus compounds but also to poisoning by mustard gas or phosgene—whether the test person or patient has a history of acute poisoning by the particular poison or by any other toxic compound, or whether a subacute course of poisoning has been brought on by imperceptible doses. Both alternatives must be borne in mind. When examining a case of delayed lesions, a physician's task is greatly facilitated by verifiable particulars of, say, acute poisoning sustained some years earlier. Conversely, his task is made much more difficult if, on the basis of vague information from the patient, he has to try to piece together a complete picture of the effects of exposure to poisons in the past. The situation is more complicated in the case of personnel employed in military establishments since secrecy regulations, code names for CW agents, and so on, make it more difficult to elucidate the cause of the lesions.

In the civilian sector of industry and agriculture, however, the first epidemiological studies on workers with a history of long occupational contact with pesticides have now been published [143–144].

Where civilian cases are not complicated by secrecy regulations, another factor may make it harder to ascertain facts on delayed lesions—namely, the variety of toxic effects which can be sustained in the normal course of technological operations. Few workers stay in the same production plant year after year; they often change their workplace several times and, of course, production processes are also subject to radical change. Thus a worker employed in pesticide production may be working in the DDT plant one day and in the parathion section the next. After a year or two he may leave the factory altogether and perhaps work for some years in a chemical plant manufacturing petroleum products or pharmaceuticals.

As long as health records do not provide full information on the nature, particulars and duration of contact with toxic products for every worker in such branches of industry—or for those employed in the munitions industry or in the military—it will be difficult to establish any cause-and-effect relationship between exposure to poison and the incidence—years or even decades later—of sequelae or delayed lesions.

In view of the above facts, the following measures would serve as a feasible, preventive medical approach:

1. Thorough epidemiological studies should be carried out on accidental poisoning. In this connection, all known forms of poisoning would have to be evaluated in the light of possible delayed lesions. Based upon these findings, the maximum allowable concentration (M.A.C.) values and other standards applying to the handling of biologically active compounds would have to be steadily improved upon and brought in line with prevailing conditions.

2. Toxicological data from animal experiments on acute and chronic poisoning—or from long-term experiments—should be made to serve as the basis for classing poisons in a provisional rating table or list of noxious substances [145]. The classification of the poisons would only be reappraised if it were conclusively shown that the results of animal experiments were not valid for man. The application of such principles—enforceable by law to a varying extent in some countries, and not at all in others—would make it possible to check pesticides and many other industrial chemicals for carcinogenic effects, and to rate and register them accordingly. The WHO and IUAC have worked out guidelines for this purpose and set up an international research coordination centre at Lyons in France.

These measures are necessary for a proper comprehension of the complex state of medicobiological research and of the effect of clinical-therapeutical treatment of the course of poisoning. The toxicological and preventive medical aspects of poisoning do not have the same vivid impact on the mind of the layman as, for example, the appalling burns wreaked by napalm or the inhuman injuries inflicted by dumdum bullets or nuclear weapons. This detracts from the weight which these aspects should rightfully lend to endeavours for attaining a ban on CW agents.

The difficulties in publicizing the extent of the hazards of CW agents over

and above their acute effects only add to the urgency of making known all aspects of the injuries caused by them.

After this digression on fundamental aspects, let us now revert to the specific subject of organophosphorus poisons.

Psychopathological and neurological lesions caused by organophosphorus compounds

The biological mechanism of action of organophosphorus compounds suggests that they may cause damage to the nervous system in addition to the acute manifestations of poisoning. The derangement of the transmitter function of acetylcholine by the inhibition of the cholinesterases—particularly acetylcholinesterase—brings on manifold dysfunctions, not simply restricted to the nervous system. Not all of these derangements can be offset fully and without complication by the metabolic counterregulatory and repair processes of the organism.

If we disregard the studies carried out in the early 1930s by Smith *et al*. on the neurotoxic effects of *ortho*-tricresyl phosphate and related compounds [146], we first encounter indications of psychopathological-neurological lesions caused by organophosphorus compounds in a publication of 1950 by Rowntree, Nevin and Wilson [147]. Experimental studies on animals were carried out in the late 1940s and early 1950s [148–150]. In their publication of 1953, Bidstrup, Bonnell and Beckett ascribed the mental disorders in two cases of poisoning to the high doses of atropine administered [151].

In the mid-1950s, Spiegelberg of FR Germany began his comprehensive studies on the psychopathological-neurological delayed lesions of workers formerly engaged in CW production plants for the Wehrmacht [2, 50]. His publications will be discussed later in some detail.

The article entitled “Psychiatric Sequelae of Chronic Exposure to Organophosphorus Insecticides” published by Gershon and Shaw in 1961 attracted great attention [152]. The authors chose to carry out their studies on farm workers and agricultural technicians “ . . . to see whether there is any seasonal or geographic variation in the incidence of these conditions in districts where these insecticides are used, and to determine the role of cholinesterase and the levels of acetylcholine in mental disease”. They go on to say that although the toxic manifestations—both muscarinic and nicotinic in type—have been fully reported, the effects on the central nervous system are not so well known. They observed:

Giddiness, floating sensations
Tinnitus, nystagmus, pyrexia
Tremor, ataxia
Paralyses, paraesthasiae, polyneuritis
Speech difficulties:
- slurring
- difficulty in forming words
- changes in speech

repetition of syllables
difficulty in saying what is intended
Memory defect–slowness of recall
Insomnia
Lassitude and weakness
Drowsiness
Concentration difficulty
Mental confusion
Uneasiness
Restlessness
Anxiety
Tremulousness
Emotional lability
Depression with weeping spells and insomnia
Schizophrenic reaction
Dissociation
Somnambulism and excessive dreaming
Fugue

Their summary of the total of 16 cases of injury is given in table 5.3.

Gershon and Shaw summarize their findings as follows:

> . . . only two forms of psychiatric illness were induced—depressive and schizophrenic reactions. This indicates that these insecticides activated a tendency towards depression or schizophrenia. This effect appears to be brought about by the central action of these agents on cholinesterase. It is thus possible that the activation may be related to the anticholinesterase action of the drug on the brain. This effect contrasts with the improvement in schizophrenics produced by intravenous injections of acetylcholine . . .
>
> The effects on the central nervous system produced by these compounds which have been shown to inhibit cholinesterase within the brain suggest that the acetylcholine-cholinesterase cycle plays a positive, though as yet undefined, role in central neural function.
>
> It may be objected that our results are due purely to chance and that exposure and mental change are not correlated. It is true that our results have not been analysed statistically and that they are drawn from the community at large. One group however was distinct (the greenhouse technicians) and in this section the number affected was 8 out of 10 . . .
>
> . . . In 14 men and 2 women exposed for between one and a half and ten years to organophosphorus insecticides, schizophrenic and depressive reactions were observed, with severe impairment of memory and difficulty in concentration.

We have quoted at length from Gershon and Shaw partly because their publication has given rise to much discussion and controversy among scientists working in the same field, and partly in an attempt to allay any emotional public reaction on the subject of the use of pesticides in modern agriculture—regarded by experts as a necessary and prudent measure [153].

Stoller *et al.* took up Gershon and Shaw's studies, and in 1963 they carried out a comprehensive epidemiological investigation with the help of the Statistical-Epidemiological Unit of the Mental Health Research Institute of Victoria [154]. Their aim was " . . . to determine whether areas of high

Table 5.3. Central nervous system toxication

Case number	Exposure *years*	Type of work	Effects on central nervous system
1	9	Technical officer (greenhouse technician)	Depression, headache, impaired memory, fatigue, irritability
2	9	Technical officer(greenhouse technician)	Depression, impaired memory, gastrointestinal symptoms, irri tability
3	4	Technical officer (greenhouse technician)	Dullness, depression, impaired concentration and memory, ir ritability
4	10	Technical officer (greenhouse technician)	Severe depression, headache, impaired concentration and memory, irritability, nightmares
5	4	Technical officer (greenhouse technician)	Headache, impaired concentration and memory
6	2	Technical officer (greenhouse technician)	Headache, fatigue
7	2	Technical officer (greenhouse technician)	Impaired concentration and memory, schizophrenic reaction, paranoidal ideation, ideas of reference
8	1 1/2	Technical officer (greenhouse technician)	Schizophrenic reaction: paranoia (2 episodes) and auditory hallucinations
9	4	Field officer(scientific)	Schizophrenic reaction: auditory religious hallucinations
10	3	Field officer (scientific)	Schizophrenic reaction: apathy
11	4	Farmer	Schizophrenic acute reaction: aggression
12	5	Farmer	Severe depression
13	4	Farmer	Impaired concentration and memory, fugues, somnambulism
14	3	Farmer	Depression
15	8	Scientific officer	Depression, impaired concentration and memory
16	2	Contract sprayer (farmer)	Speech difficulties, waxing and waning of consciousness

Source: See ref. [152].

organophosphorus usage had a higher proportion of admissions for psychiatric disorders than did low-usage areas". Their investigations led them to the conclusion that no correlation existed between the development of psychiatric disorders and the usage of organophosphorus pesticides. Their findings do not, of course, say whether the town and country dwellers covered by their study included any who had actually come in contact with organophosphorus compounds applied in their own particular districts. This publication cannot, therefore, serve as a counterargument to Gershon and Shaw, although some later authors have attempted to treat it as such.

The following statement in the article "Organophosphorus Insecticides and Mental Alertness" by Durham, Wolfe and Quinby appears to be of importance [155]: "These test results are consistent with the accepted opinion that organic phosphorus compounds may affect mental alertness if absorbed in amounts great enough to cause clinical signs or symptoms of systemic illness. No cases were seen in which mental effects occurred alone."

According to Reinl, an authority on industrial medicine, significant clinical manifestations of industrial phosphorus poisoning—apart from the classical symptoms—are cardiac and mild renal lesions, damage to the hematopoietic system, and neuritic symptoms [156]. He writes: "Considering, however, that the pathophysiologic effect is essentially one of cholinesterase inhibition—that is, it results in interference with the entire enzymic system of the body—a clinical picture rich in symptoms is to be expected since all the organs, particularly the brain, are endangered."

Extensive studies have been carried out in recent years in an endeavour to elucidate the correlation between damage to the central nervous system and cholinesterase inhibition caused by acute and chronic exposure to organophosphorus compounds. As examples may be mentioned the studies of Banks and Russell [157], and the clinical tests performed on aerial-applicator agricultural pilots by Smith, Stavinoha and Ryan [158] and by Dille and Smith (who also report on EEG findings in one case) [159]. Mention should also be made of the investigations of Namba *et al.* [160] and Davignon *et al.* [161] on the chronic effects of organophosphate insecticides on man.

In 1969, Aldridge, Barnes and Johnson succinctly summed up their extensive work of many years on delayed neurotoxicity produced by some organophosphorus compounds thus [124]: "It is clear . . . that many organophosphorus compounds can produce delayed neurotoxicity in low doses. It is also clear that many compounds are inert."

In 1971, Clark summed up his review of organophosphate insecticides and behaviour in the following words [162]:

> Considering the inconsistencies and contradictions in reports of humans exposed to organophosphate insecticides, coupled with the failure in animal studies to note carefully the variations introduced by inadequate attention to experimental design, renders any conclusions decidedly premature. Much further research is needed to clarify the possible behavioral deficits produced by exposure to organophosphate insecticides.

It would exceed the bounds of this SIPRI study to deal further with the large number of still partly controversial publications on correlations between psychopathological-neurological lesions in man and the use of pesticides. Besides, it is not always possible for the independent, outside observer to disentangle purely scientific considerations from the interests of big business. Because of its fundamental importance, the issue of the hazards of using pesticides will continue to remain a prominent item on the scientific agenda in future, notwithstanding further parallel studies on late lesions caused by CW agents.

The overall difficulty and complexity of the problem—together with the variety of external factors influencing uptake of poison by the organism, the susceptibility of the latter, and the relatively limited possibility of protection—were dealt with in an article entitled "Studies on Exposure During the Use of Anti-cholinesterase Pesticides" by W. J. Hayes, Jr., [163]. The author also discussed possible methods for quantitative determination and rating of exposure to toxic doses. He came to the following conclusion, among others: "The expression of exposure in terms of the fraction of the toxic dose may constitute a useful, objective index of hazard, but, because of the number of variables involved, this index can be used only as a guide." Needless to say, the difficulties greatly increase when considering CW agents instead of the relatively easily controllable pesticides. As it was possible for Hayes and others to make use of the services of volunteer test persons—which was also the case during World War II in Britain, for example, even for tests on CW agents—these investigators were naturally in a position to speak much more authoritatively on the compounds then tested.

A marginal note may be inserted here. In view of the risk of causing delayed injury, such experiments on volunteers should, in general, be prohibited. This applies to the "classical" CW agents like mustard gas and phosgene, as well as to organophosphorus compounds—whether important civilian or military products. Even if it were conceded that such experiments yield valuable information for the treatment of victims of poisoning and for the development of antidotes, the burden of responsibility would be too great to bear for such tests. Considering the unforseeable hazards of delayed effects, heroism appears to be misplaced in such cases. In this connection, reference may also be made to the discussions in the USA on the matter of tests with organophosphorus pesticides on human beings [164]. On the other hand, the discussions on the use of beagles by the US Army at Edgewood may simply be dismissed as a farce [165].

Spiegelberg's studies on the psychopathological-neurological lesions of former workers in CW production plants for the Wehrmacht had initially to be based on the working assumption that such delayed lesions were not linked to organophosphorus compounds. According to earlier data from the USA, complete recovery from light or moderate nerve-gas poisoning was held to be possible [166–169]. The authors concerned had either entirely ignored or dis-

missed the question of delayed lesions. It is not clear from their publications whether their findings related only to soldiers and workers engaged in the post-war production of phosphoric ester CW agents or whether they also included the personnel employed at these works and storage depots during World War II.

Up to now, publications dealing specifically with the delayed effects of organophosphorus CW agents have been scant in the literature. Meanwhile, Davies, Holland and Rumens [170] and Durham, Gaines and Hayes [171] have been successful in showing by means of animal experiments that, for example, the neurotoxic phenomena produced by organophosphorus compounds of the nerve-gas type in some poultry varieties are, within certain limits, comparable to the manifestations produced in man. Moreover, as already mentioned, certain groups of organophosphorus compounds have been shown to be basically similar in structure, reactivity and mode of action. The few publications dealing directly with organophosphorus CW agents have confirmed the findings obtained for other organophosphorus compounds. It should be noted, however, that in spite of basic similarities in the action of, and course of poisoning by, for example, DFP (diisopropyl fluorophosphate) and sarin, or Amiton and VX, actual cases of poisoning may exhibit important functional and structural gradations. This is clearly illustrated by the widely varying efficacy of antidotal preparations in the treatment of acute poisoning [172].

In their above-mentioned study, Davies, Holland and Rumens of the Chemical Defence Experimental Establishment, Porton, England, investigated the correlation between the chemical structure and neurotoxic effect of alkyl phosphates—including DFP, sarin and derivatives—and compared them with trialkyl phosphates [170]. In 1960 they came to the following basic conclusion:

> The neurotoxic hazard which these substances constitute to man is a difficult problem to assess because of (a) known species differences in the response to organophosphorus compounds, and (b) the absence of any direct evidence that organophosphorus compounds other than tri-*o*-cresyl phosphate and mipafox [bis (monoisopropylamino) fluorophosphine oxide] are neurotoxic in humans. Both of these have been extensively examined in the chicken. The delay period, the clinical character of the condition and the distribution and nature of the histological lesions are all the same as those found with dyflos [diisopropyl fluorophosphate, DFP] and the compounds which have, in this study, been reported active for the first time. It must therefore be assumed that all the organophosphorus compounds shown to be neurotoxic in chickens will, under appropriate conditions, produce neurotoxicity in man.

In a study published in 1964 on the behavioural changes produced on administration of a phosphoric acid derivative (code name EA-1701 or VX), similar to sarin, to US Army test volunteers, Bowers, Goodman and Sim arrived at the following conclusion after comparing the results with findings from animal experiments and from production workers in the phosphorus industry [173]: “It seems, therefore, that an excess of the free endogenous amine acetylcholine as produced by anticholinesterase administration leads to a state of altered awareness in man.”

Two studies recently reported from Edgewood Arsenal give very important information about clinical cases of anticholinesterase poisoning [174–175]. Clinical recovery was remarkably slow—the psychiatric sequelae persisted for many weeks and plasma cholinesterase recovery was not complete until several months later. To our knowledge, these two publications are respectively the first report of accidental exposure to these substances and the first report of experiments with VX on volunteers.

In a study of alkyl phosphate poisoning, Pasi and Leuzinger came to the conclusion that delayed lesions only occur, if at all, after severe cerebral anoxia [176]. As regards anatomical changes in the brain (demyelination), these delayed lesions correspond to those caused by peripheral neuropathy in acute and chronic *ortho*-tricresyl phosphate poisoning and are confined to fluorine-containing alkyl phosphates—for example, mipafox, DFP, sarin and soman. A synoptic evaluation of 536 civilian cases of alkyl phosphate poisoning made by the above-mentioned authors led them to the conclusion that acute poisoning by civilian alkyl phosphates did not result in delayed lesions. It should be noted, however, that their period of observation of two to three years was inadequate for investigations of delayed lesions beside the scale of Spiegelberg and others.

To conclude this section, the closing observations from Spiegelberg's monograph will be cited (these remarks do not refer exclusively to organophosphorus CW agents) [2]:

> A psychiatric delayed-effect syndrome was found as a result of systematic investigations on former members of CW production and testing stations for the Wehrmacht. In terms of frequency, two groups of symptoms can be distinguished–each consisting of four separate symptoms or signs.
> (1) The great majority of persons examined showed:
> (a) persistently lowered vitality accompanied by marked diminution in drive;
> (b) defective autonomic regulation leading to cephalalgia, gastrointestinal and cardiovascular symptoms, and premature decline in libido and potency;
> (c) intolerance symptoms (alcohol, nicotine, medicines);
> (d) impression of premature aging.
> (2) Further, one or more symptoms of the second group were found:
> (a) depressive or subdepressive disorders of vital functions;
> (b) cerebral vegetative (syncopal) attacks;
> (c) slight or moderate amnestic and demential defects;
> (d) slight organoneurological defects (predominantly microsymptoms and singular signs of extrapyramidal character).
> Our results are a contribution to the general question of psychopathological delayed and permanent lesions caused by industrial poisoning. On the basis of our studies of the etiologically different manifestations of toxication, the possibility of a relatively uniform–though equally unspecific–cerebro-organic delayed effect syndrome is conceivable.

Hepatotoxic and hematotoxic lesions caused by organophosphorus compounds

Parenchymatous lesions of the liver caused by organophosphorus compounds

were described by Maruyama as far back as 1954 (quoted in ref. [160]) and by Maresch in 1956 [177]. The literature of succeeding years contains references to the hepatotoxic effects of mainly organophosphorus pesticides [160, 178–181].

In 1963, referring to his investigations on CW production workers, Spiegelberg wrote [50]:

> Although all the cases of nerve-gas poisoning investigated up to now show evidence of hepatic lesions, it is not possible to draw any final conclusion at present. A pathogenetic link may be involved. There are analogies to hepatolenticular degeneration (Wilson's syndrome) and to recently reported psychic changes in cases of cirrhosis of the liver . . .

In an experimental study on animals, W. Domschke and G. F. Domagk concluded that the CW agent, soman, has an inductive effect on the entire enzymatic biosynthesis of the liver, which is, however, unspecific for individual liver enzymes [179]. In 1971, on the basis of their investigations of the mechanism of liver-cell damage by alkyl phosphates, S. Domschke, W. Domschke and M. Classen concluded that " . . . the liver-damaging action of alkyl phosphates is . . . to be regarded as indirect, and to be interpreted as the result (like respiratory insufficiency) of general hypoxia caused by cholinesterase inhibition, which also affects the liver" [180]. Their views were partly confirmed by findings from animal experiments published in 1971 and 1973 by Gibel and coworkers on the hepatotoxic effects of trichlorphon and dimethoate, and also amplified with regard to the possible involvement of biochemically pertinent alkylation processes [181]. We shall revert below to the results of Gibel *et al.* in connection with the hematotoxic and carcinogenic properties of organophosphorus compounds.

The hematotoxic effects of organophosphorus compounds became known at a relatively early stage. Thus in 1956, Reinl stated that E-605 (parathion) poisoning might possibly lead to bone-marrow lesions [156]. At the same time, of course, he pointed to the necessity for further observations. In 1971, Namba *et al.* still maintained that the hematotoxic—chiefly coagulatory—effects of organophosphorus insecticides were negligible and were restricted to a few isolated cases [160]. Their viewpoint was supported by a study made by v. Kaulla and Holmes [182]. In the USA, the organophosphorus insecticide, parathion (*O,O*-diethyl *O-p*-nitrophenyl phosphorothioate), was listed by the Panel on Hematology of the Registry on Adverse Reactions of the American Medical Association's Council of Drugs, in its 1965 semiannual tables, as a proven hematotoxic substance [183]. A 1971 monograph by Klimmer—in contrast to other monographs published on insecticides and pesticides—also referred to the possible hematotoxic properties of organophosphorus compounds [121]. In 1972, Reizenstein and Lagerlöf reported on long-term studies on agricultural workers, who—primarily as a result of handling organophosphorus pesticides—showed significantly marked leukocytosis [184]. The study by Davignon and

co-workers on the chronic effects of insecticides also indicates hematotoxic symptoms such as leukopenia [161].

In their work of recent years, from an oncologic angle, on a selected range of organophosphorus pesticides, Gibel *et al.* also became alert to the hematotoxic properties of such compounds [181]. They observed marked hyperplasia of the blood-forming parenchyma of the bone marrow—varyingly affecting all three hematopoietic cell systems (erythropoiesis, granulopoiesis and megakaryopoiesis)—and pronounced extramedullary myeloid metaplasia, primarily in the liver and spleen, in 34 and 59 per cent of the trichlorphon and dimethoate test animals respectively. In addition, they observed a varying incidence of leukocytosis (mostly granulocytosis) in the peripheral blood.

More pronounced leukocytosis affected 33 per cent of the trichlorphon test animals and 22 per cent of the dimethoate test animals. (Infections, particularly pneumonias, were excluded by histological examination, as the cause of leukocytosis.) On the basis of these findings, the investigators diagnosed panmyelosis in a large number of the test animals, with partly concomitant myeloid metaplasia, corresponding to the myeloproliferative syndrome[1] in man. The secondary or symptomatic form, following a transitional preleukemic stage, was myelogenous mature-cell leukemia. The myeloproliferative changes amply demonstrated the considerable hematotoxic effects of the organophosphorus compounds used.

It is thus high time to check other organophosphorus compounds for hematotoxic properties, and to rate them accordingly. The hematological findings from workers engaged in production plants for phosphoric ester CW agents during and after World War II should now be released in view of the urgency of appraising the actual hazards. This also applies to other clinical-diagnostic findings obtained in these production plants.

Carcinogenic, mutagenic and teratogenic lesions caused by organophosphorus compounds

The question of the carcinogenic properties of, and the hereditary damage caused by, CW agents has been discussed repeatedly in the literature since World War I, as well as in the daily press—albeit at a less qualified level. Discussion and conjecture have, however, strayed far beyond the bounds of established fact and an altogether unsatisfactory state of affairs has prevailed. There have been failures of omission and commission in the matter of carrying out experimental investigations where needed, and attempts have been made at playing down clinically attested results where available so as to obscure their true cause-and-effect relationship with CW agents. Nonetheless, a body of in-

[1] The myeloproliferative syndrome is a proliferative disease of the blood-forming parenchyma characterized by simultaneous granulopoiesis, erythropoiesis and megakaryopoiesis; it is also characterized by extramedullary hematopoiesis, mainly in the liver and spleen.

controvertible evidence has been built up over the years in relation to the "classic" CW agents—particularly those, like the mustards, with alkylating properties—indicating a significantly higher incidence of tumours in persons handling such substances [53, 78].

No open publication has yet appeared on observations on the incidence of cancers in workers and soldiers who have handled organophosphorus CW agents. The few publications which at all refer to a possible connection between the development of cancer and the action of organophosphorus CW agents, deal with CW agents as a whole. They either do not single out the various substances or do so simply from a medical angle, within individual classes of substances. Only A. Weiss, in his previously mentioned investigation of 1951–53, provides the first concrete basis for a possible link between the development of cancer and contact with organophosphorus CW agents. He points out, however, that the extremely small number of patients examined does not allow of any conclusive statement to be made. Hence, in any appraisal of the cancer problem *vis-à-vis* organophosphorus compounds, we are for the time being obliged to resort to animal experiments using these compounds. Such studies are indicated all the more urgently in view of the practical significance of the large number of organophosphoric esters in use in agriculture, medicine, veterinary medicine and various branches of industry. The side effects of this class of substances no longer, therefore, simply constitute an interesting scientific problem but are a basic concern of preventive medicine [185].

As already mentioned, for a proper appreciation of the biological action of organophosphorus compounds, their alkylating properties must be taken into account in addition to their phosphorylating properties. This does not, of course, exclude the possibility that some other property may also be at work in influencing the biological action pattern of these substances.

The possibility of a link between alkylating capacity and carcinogenic and mutagenic effect has figured prominently in the majority of known studies hitherto made on alkylating agents. Gibel and co-workers carried out the first studies on carcinogenesis using trichlorphon and dimethoate [181]. Although they did not use any CW agents in their animal experiments, they consider that their findings justify the statement that those working in the organophosphorus industry run an increased cancer risk. Gibel *et al.* came to the following conclusions:

> The hematological and hepatotoxic findings and the development of benign and malignant tumours make it necessary to revise the view held up to now—namely, that trichlorphon and dimethoate, as well as related organophosphorus pesticides, are to be considered innocuous from the point of view of long-term biological effects because of their relatively rapid hydrolytic decomposition in warm-blooded animals. Moreover, a Soviet team working on pesticidal alkyl phosphates has succeeded in demonstrating a teratogenic effect. It now remains for further parallel investigations on the alkylating capacity of similar alkylphosphoric and alkylphosphonic pesticides to yield detailed information on the biochemical mechanism of alkylation—in the sense of the already mentioned alternative reaction to phosphorylation—and to clarify the relationship

between chemical constitution, reactivity and carcinogenic effect. Knowledge of this relationship is not simply of theoretical interest for the problem of carcinogenesis, it will enable possible hazards to be assessed properly—thus contributing to practical cancer prophylaxis. In this connection, the investigations performed using trichlorphon and dimethoate seem decisive for the optimization of health protection and work safety in direct contact with such alkyl phosphorus derivatives in manufacturing industry and in applications in agriculture and hygiene.

The publications of Löfroth on the mutagenic properties of organophosphorus pesticides [138] have attracted far greater attention than other publications of recent years on the carcinogenic effects of organophosphorus compounds. As already mentioned, Löfroth's findings from investigations on microorganisms were heavily attacked by the pesticide industry on account of the relatively high dosages employed. However, the investigations carried out in the hope of refuting his findings have not been successful up to now. The value of all these investigations lies in the fact that they have stimulated thorough studies of the alkylating properties of alkyl phosphates and of the biological consequences entailed [186–187]. In the light of the findings of Löfroth and of others, Dyer and Hanna of Monash University in Australia recently raised the question of a ban on organophosphorus pesticides [188], but it must be said that banning an entire class of compounds would be a case of throwing out the baby with the bath water. The problem of organophosphorus insecticides—unlike that of organophosphorus CW agents—must be dealt with in such a way that a proper balance is struck between their known hazards to human health and the need for using them in agriculture and hygiene.

Only a few experimental investigations have been carried out on the teratogenic effects of organophosphorus pesticides in animals [160]. Few observations have been made on human beings [189–190].

Eye lesions caused by organophosphorus compounds

The therapeutical application of a range of organophosphorus compounds in ophthalmology as, for example, miotics, has been common for the past 25 years or so. The best known of such drugs continue to be diisopropyl fluorophosphate (DFP) and *O,O*-diethyl *O-para*-nitrophenyl phosphate (paraoxon)—both highly toxic compounds related to organophosphorus CW agents. Eye lesions have also been reported in the therapeutic use of these and other compounds [190].

Remarkable scientific findings have been obtained in recent years in the USSR and in Japan on eye damage caused by the handling or agricultural application of organophosphorus compounds [191–192]. The Soviet study covered 1 995 workers and 2 272 students. The Japanese study dealt with the effects of aerial application of the organophosphorus pesticides, parathion, malathion, EPN, sumithion, and so on, in a fruit-growing area, and discussed the findings obtained from a group of 71 children in the 4–16 year age-group. Since these findings were reproducible in dogs by the use of organophosphorus com-

pounds, the authors concluded that the syndrome was induced by chronic poisoning by these chemicals. They observed:

(1) reduction of vision 98%
(2) narrowing of peripheral visual fields 95%
(3) refraction anomaly with high astigmatism 88%
(severe case shows keratoconus)
(4) neurological abnormalities with EEG abnormalities 71%
(5 disturbance of smooth pursuit motion of the eyes 57%
(6 insufficiency of the pupillary sphincter 52%
(7 optic neuritis and/or retinochoroid atrophy 65%
(8) dysfunction of liver
(a) reduction of serum cholinesterase 33%
(b) increment of serum phosphorus 30%
(c) increment of acid phosphatase 62%
(d) increment of alkali phosphatase 10%
(e) abnormalities of cephalin-cholesterol-lecithin flocculation test 46%
(9 reduction of ocular tension 25%
(10) paresis of accommodative convergence 20%
(11) cycloplegia 12%
(12) nystagmus or fixation disability 6%

The authors state that the above conditions seemed to be induced in lesions of the retinochoroid vessels, the sphincter muscle of the iris, the ciliary ganglion, the ciliary muscle, the slow fibre of extraocular muscle, the accessory nucleus, the pyramidal tracts and the dorsal part of the spinal cord–where cholinesterase activity is higher than in other organs.

These eye lesions point to an entirely different side of the effects of organophosphorus compounds–which can scarcely be explained on the basis of present-day knowledge of biochemical mechanisms–and to the need for research on the subject. It remains for future investigations to clarify the mode of action of this most important class of compounds.

Chapter 6. Summary and conclusions

The foregoing chapters may be summarized as follows:

1. In addition to causing acute effects, most CW agents are liable to cause delayed effects. This applies to persons who have survived acute poisoning, as well as to those who have sustained subacute—even imperceptible—poisoning.

2. The main delayed effects take the form of: (a) psychopathological-neurological changes; (b) malignant tumours (cancer); (c) increased susceptibility to infectious diseases (primarily of the lungs and upper respiratory tract); (d) disturbances of liver function; (e) pathological changes in the blood and bone marrow; (f) eye lesions; and (g) premature decline in vigour, rapid aging and related functional disturbances, such as decline in potency and libido.

3. In addition to these neural and organ-specific effects, mutagenic effects in human beings–although not conclusively proven–must be taken into account. The occurrence of teratogenic and embryotoxic effects in human beings—likewise not proven in all respects—is highly probable.

4. What has been said of CW agents also applies to a large number of compounds related to them in structure and action. These compounds are of scientific and practical interest either as by-products or as “model” compounds.

5. The biochemical mechanism of the delayed effects of most CW agents and related compounds is not yet known. In the few cases where concrete information is available, research work is still incomplete.

6. No effective prophylactic or therapeutic measures are available, at present, against the delayed effects of CW agents. This means that the handling of these poisons—no matter how slight—in the course of their manufacture, storage or use carries the risk of imperceptible poisoning and can lead to any of the above-mentioned types of related delayed lesions. Thus it is not only the victims of attack by CW agents that run the risk of grave injury to their health but also those engaged in the manufacture of these chemicals or in preparing them for use.

The following conclusions may be drawn from the above-mentioned facts:

1. The hazards of CW agents are by no means adequately described simply by their acute effects.

2. A thorough appraisal should be made from the delayed-lesion angle of the results published from both World Wars on illnesses proved or presumed to be delayed effects. Moreover, all classified findings—especially those relating to work at CW production plants and storage sites—should be declassified. The material released could be deposited with the WHO and appraised by a panel of experts, provided that medical ethics are observed.

3. The inquiry into CW agents should also be extended to nonmilitary poisons as these products are related to CW agents in structure and action.

This applies particularly to organophosphorus pesticides, some carbamates and a range of pharmaceuticals—especially psychopharmaceuticals. The results of such an extended inquiry would, among other things, help in promoting improvements in work and health conditions in these civilian occupations.

4. The personal safety of the individual and the disarmament measures desired—particularly a ban on the production, storage and use of CW agents—require that every worker and research scientist in the chemical industry be issued an international health certificate. The latter, apart from stating the nature and duration of work with chemicals, should give an up-to-date health record—particulars of diseases, infections, accidents, surgical operations, blood transfusions, inoculations, and so on.

5. All chemicals directly or indirectly related to CW agents should carry a compulsory declaration. This should state the physical and chemical properties of the particular substance, together with any known or suspected risk of delayed illness associated with it.

6. Endeavours should be made to attain an international ban, in principle, on toxicological studies on volunteers—irrespective of the motives behind such studies or of the type of volunteer.

7. The following research projects are urgent for the clarification of outstanding problems on the causes and therapeutic treatment of delayed effects:

• Investigations of the metabolism of CW agents, including studies of their primary, intermediate and by-products in human beings, animals and plants under specific environmental conditions. Studies on human beings would only be permissible in the course of necessary therapeutic treatment of poisoning.

• Investigations of the structure/action relationship in CW agents and related compounds with reference to reaction mechanisms—such as, alkylation and aging of the inhibited enzyme—which may be of significance for delayed effects.

• Epidemiological and catamnestic studies of workers in the chemical industry who are known to have handled chemicals directly or indirectly related to CW agents. Particular attention to be paid to diseases of the respiratory organs, liver, blood-forming system, digestive system and nervous system. Studies of fertility, incidence of cancer, and any hereditary defects in children.

• Intensification of research on antidotes with reference to their use in counteracting acute effects and preventing the onset of delayed poisoning, and also with reference to the elimination of the risk of delayed lesions from the antidote itself–the present-day “antidotal therapy” provided by the methanesulphonate and methyl iodide derivatives of pyridinealdoxime in phosphoric ester poisoning is a case in point.

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