SCIENCE

Vol. 103, No. 2675 Friday, April 5, 1946

The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

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AT THE CONCLUSION OF WORLD WAR I the theory was generally accepted that mustard gas exerted its vesicant action by releasing hydrochloric acid intracellularly. A few isolated reports appeared describing remote systemic effects of mustard gas on hematopoietic tissues (*1–3*), the gastrointestinal tract (*3–5*), and electrolyte and fluid balance (*3*). Although in the interim between wars the adverse effects of mustard gas on leucopoietic tissues (*6–8*) and on the growth of experimental tumors (*9*) received some attention, biological research on chemical warfare agents remained relatively quiescent. With the advent of World War II research on war gases was resumed, and the newer knowledge and technics of a quarter of a century of scientific progress utilized. New compounds were proposed as potential offensive agents. Mustard, *bis*(β-chloroethyl)sulfide, shared interest with a series of nitrogenous analogues, *bis*- and *tris*(β-chloroethyl)-amines. It was appreciated early that the sulfur and nitrogen mustards were not only contact vesicants but, following absorption, could exert cytotoxic actions on a variety of tissues. Furthermore, cellular susceptibility to these compounds appeared to be related in a general way to the degree of proliferative activity.

With the conviction that only with an understanding of the basic mechanisms of cellular action could significant advances be made in the treatment of vesicant war-gas casualties, the study of the actions of the sulfur and nitrogen mustards on fundamental cell processes was pursued. These studies have revealed a type of action on cells which can be likened to that of no other chemical agent but which resembles in many ways that of X-rays. Cautious preliminary trials have also been made of the possible value of the nitrogen mustards in the treatment of neoplasms, in particular those of lymphoid tissue.

The fact that agents classified as "confidential" were involved in the above studies has heretofore precluded the possibility of presenting the results in the open literature. This report reviews briefly the contributions which have focused attention on the cellular actions of the mustard compounds and gives a general description of their systemic effects as well as a preliminary statement of their possible clinical applications. Because of space limitations important contributions of many investigators will have to go unmentioned.

Chemical Transformations and Reactions of the Nitrogen and Sulfur Mustards

The nitrogen and sulfur mustards owe their physiological activity to a basic chemical reaction which they share in common, namely, intramolecular cyclization in a polar solvent to form a cyclic onium cation with liberation of Cl^-. The reaction may be depicted as follows, Z representing the sulfur or nitrogen atom:

$$R\text{–}Z\text{–}CH_2CH_2Cl \rightarrow R\text{–}{}^{+}\overline{Z\text{–}CH_2CH_2} + Cl^-$$

The onium cation—ethylenimonium in the case of the β-chloroethyl amines, ethylenesulfonium in the case of β-chloroethyl sulfide—reacts readily with anions and various uncharged nucleophilic molecules. It is the great reactivity of the cyclic onium cation which imparts to this group of vesicants their varied actions.

The property of halogenated alkylamines to form cyclic onium cations was known before the war (*10–12*). With the introduction of *bis*- and *tris*(β-chloro-

This paper was prepared as a background for forthcoming articles on the clinical application of the β-chloroethyl amines with the approval of the following agencies: Medical Division, Chemical Warfare Service, United States Army; Division 9, NDRC, and Division 5, Committee on Medical Research, OSRD; Committee on Treatment of Gas Casualties, Division of Medical Sciences, NRC; and Chemical Warfare Representative, British Commonwealth Scientific Office.

ethyl)amines as chemical warfare agents, the importance of the formation of the reactive ethylenimonium ring was appreciated early. Moreover, the study of cyclization of β-chloroethyl amines led to appreciation of the existence of the analogous sulfonium cations. The present knowledge of the chemistry of the mustards, with respect to both the kinetics of cyclization and the reactions of the resultant onium compounds, has been the cooperative contribution of many groups of investigators (*13–22*) whose final publications in the open literature must be awaited. However, so important are the basic chemical findings for an understanding and explanation of the physiological actions of the nitrogen and sulfur mustards that a few pertinent facts will be reviewed here.

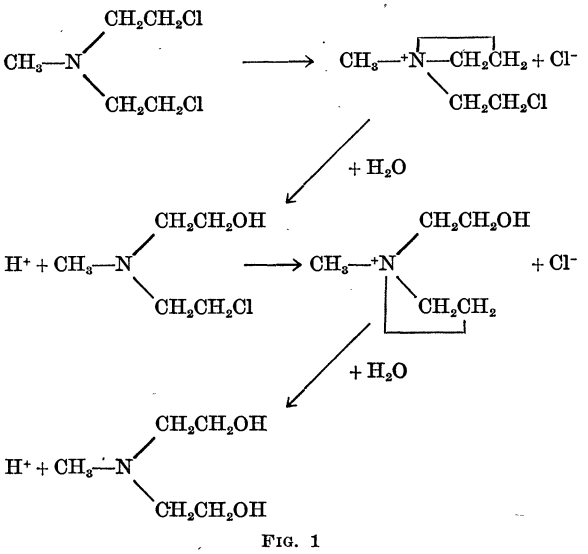

FIG. 1

Two basic distinctions may be made between the chemical behavior of the nitrogen and sulfur mustards. In the case of β-chloroethyl amines, cyclization cannot occur when a proton becomes coordinated with the nitrogen atom. Thus, solutions are stable in strong acid. Hydrogen-ion concentration does not affect the formation of the sulfonium ring. This distinction is of little importance at the pH of body fluids. Secondly, the reactivity of the ethylenesulfonium ring of mustard is so great that it never accumulates in solution in sufficient amount to permit its isolation. On the other hand, the various ethylenimonium compounds are, as a group, less reactive, and several have been isolated. In the case of the majority of the nitrogen mustards, this distinction is of greater chemical than physiological significance in that the reactivity of the ethylenimonium cation is ample to allow the compounds to produce toxic actions in general similar to those of sulfur mustard. For the most part, therefore, the nitrogen and sulfur mustards can be discussed together with respect to the basic relations between chemical structure and physiological actions.

As a prototype of the β-chloroethyl vesicants the behavior of methyl-*bis*(β-chloroethyl)amine may be considered. In dilute aqueous alkaline solution the series of reactions shown in Fig. 1 occurs. Side reactions involving polymerization may occur.

The majority of the nitrogen mustards are *bis*(β-chloroethyl)amines, the third valence of the nitrogen being occupied by one of a variety of alkyl groups. Inasmuch as the rate of cyclization and the activity of the ethylenimonium cation are influenced by substituent groups on the molecule, a large number of nitrogen mustards of different physicochemical and pharmacological properties is available. Thus, the scope of future investigations on the relations between chemical constitution and pharmacological action of the nitrogen mustards is wide.

In pure aqueous solutions at physiological hydrion concentrations the ethylenimonium or sulfonium cation reacts with H_2O. However, if other substances are present, they can react competitively. So reactive are some compounds that in their presence the reaction with water is negligible. Literally hundreds of compounds have been studied in this manner. The objective in many of these studies was the discovery of an effective antidote for the local and systemic actions of the mustards. More pertinent to the present discussion is the ability of ethylenesulfonium or imonium compounds to alkylate the functional groups of compounds of biological importance. Among these may be mentioned the α-amino, imidazole, sulfhydryl, sulfide, phenolic, ε-amino, and imino groups of amino acids and peptides; inorganic phosphate as well as glycerophosphate and hexose phosphates; the amino groups of adenosine and thiamine; and the pyridino-N of nicotinic acid amide and pyridoxine. The carboxyl and amino groups of numerous proteins which have been found reactive with sulfur mustard appear vulnerable to alkylation, although other functional groups are also involved. These proteins include hemoglobin, insulin, gelatin, crystalline egg albumin, tobacco mosaic virus, ovalbumin, silk fibroin, and protamine as well as various purified or crystalline enzymes to be considered below.

The implication that the systemic toxic action of the mustards is due to the reaction with any single compound listed above is not intended. However, the likelihood that the basic mechanism of the cytotoxic action of the mustards involves a similar reaction with a vital cellular constituent, possibly as yet unknown, is great.

Systemic Pharmacology and Pathology of the Mustards

The nitrogen and sulfur mustards elicit a variety of systemic pharmacological actions. For the most part these are prominent only after the administration of acutely lethal doses. Although the pattern of action of the compounds as a group is similar, certain distinctions are evident. Thus, the possibility exists that changes in chemical constitution can effect a specificity of action.

Cytotoxic action. The outstanding systemic action of the nitrogen and sulfur mustards is that which causes, in a manner still unexplained, the death of cells. The possible relationship between the action of the mustards on enzyme systems and their cytotoxic effects and the details of their more specific action on cell nuclei will be presented below. Pertinent to the present discussion is the relative susceptibility of the various tissues to this cytotoxic action. As a generalization, it may be stated that cellular susceptibility is related to proliferative activity. Thus the formed elements of the blood and the mucosa of the gastrointestinal tract first reflect the cytotoxic action of the mustards. The vulnerability of the blood-forming organs and the intestinal tract was realized as a result of investigations conducted during World War I, (*1–5*) and current studies on the nitrogen and sulfur mustards have contributed a wealth of new knowledge. Briefly, the action of the mustards on the blood-forming organs as reflected in the peripheral blood of both experimental animals and humans results in a lymphopenia, granulocytopenia, thrombocytopenia, and moderate anemia (*23–34*). The severity of the response is in direct relationship to the dose administered. Marked effects on hematopoiesis can be obtained with sublethal doses.

The effects of the mustards on the gastrointestinal tract are equally marked. Nausea and vomiting are evident within a few hours (*26, 35*). This may be a reflex response from the gastrointestinal mucosa or possibly the result of direct medullary stimulation. Diarrhea becomes evident within 24 hours and becomes progressively more severe. Both the vomitus and feces may contain blood. As a result of the loss of fluid and electrolyte from the gastrointestinal tract, marked changes in body water occur (*26, 35, 36*). Furthermore, there is evidence that the action of lethal doses of nitrogen mustards on the kidney may result in a polyuria and a renal wastage of extracellular electrolyte (*37*). A loss of intracellular potassium and water may also occur (*37*). Eventually, circulatory collapse ensues, a typical shock picture is observed, and the animals die of respiratory failure (*26, 35*).

Acute pharmacological actions. The acute pharmacological actions of the mustards are seen only after the administration of supralethal doses. Prominent among these are central nervous system excitation resulting in convulsions and acute death (*26, 28*), parasympathomimetic effects as evidenced by salivation, miosis, etc., followed by a parasympatholytic action (*26, 28, 38*). With subconvulsive doses of nitrogen mustard a progressive muscular paralysis, eventually resulting in death from paralysis of muscles of respiration, is a characteristic finding (*26, 28*).

Relationship between chemical constitution and pharmacodynamic action. A fact which has been pointed out by several investigators is that only those β-chloroethyl compounds which can form a cyclic onium cation are capable of exerting the typical actions described above. Moreover, the toxicity of the members of this series appears to be related to the chemical characteristics of the onium cation. Thus, the toxicity and leucotoxic activity of the nitrogen mustards and sulfur mustard have been correlated with both the reactivity of the onium cation (*26, 28*) and the rate of cyclization of the parent β-chloroethyl compound (*16*).

Pathology of systemic mustard poisoning. As might be expected from the above actions of the mustards, the outstanding pathological lesions produced by either nitrogen or sulfur mustards are found in the intestinal tract, bone marrow and lymphatic tissue (*23, 26, 27, 34*). The intestinal lesion progresses from vacuolization and nuclear swelling of the epithelial cells to eventual necrosis and desquamation with hemorrhage. Lymphoid tissue throughout the body is uniformly involved. Lymphatic fragmentation may be evident within 10 hours, leading to a persistent lymphatic atrophy for a number of days. In the bone marrow early changes include swelling and alteration in the staining reaction of hematopoietic cells and a disappearance of mitotic activity. Progressive depletion of the marrow follows, and eventually, almost complete aplasia results.

In Vitro and *in Vivo* Inactivation of Enzymes by the Mustards

The fact that the administration of the nitrogen and sulfur mustards to experimental animals results in widespread systemic intoxication naturally led to the concept that the agents inhibit certain basic metabolic functions which are vital to the maintenance of normal cellular activities. It was reasonable to expect, therefore, that a variety of cells and tissues poisoned by the mustards either *in vivo* or *in vitro* would evidence significant metabolic changes. It has, in

fact, been found that the oxygen consumption and glycolysis of a large number of cells and tissues are inhibited to varying degrees following exposure to the agents *in vitro* and in some instances *in vivo*.

One of the earliest observations which antedated the recent war showed that the addition *in vitro* of sulfur mustard to minced tumor tissue resulted in moderate reduction of oxygen consumption and marked depression of the aerobic and anaerobic glycolysis of glucose (*39*). The anaerobic glycolysis of minced brain and chick embryo tissue was similarly reduced. Similar effects were reported by English investigators to occur in mammalian skin following the application of vesicant doses of sulfur mustard (*40, 41*). It was also determined in early English work that the oxidation of pyruvate by brain brei was significantly inhibited by sulfur mustard (*42*). Later work confirmed the effects of this mustard on the oxidative and glycolytic activities of intact mammalian skin (*43*). Furthermore, the inhibition of the respiration of avian erythrocytes *in vitro* (*13*), of the respiration and anaerobic fermentation of yeast cells (*17, 44*) and of the respiration and glycolysis of isolated mammalian cornea (*45*) was also demonstrated. Following parenteral administration of lethal doses of sulfur mustard significant inhibitions of anaerobic glycolysis and respiration have been noted in bone marrow (*41*) spleen (*41, 43*), and thymus (*43*), as well as inhibition of glycogen synthesis in the liver and intestinal absorption of glucose (*43*).

Certain of the nitrogen mustards have also been shown to inhibit to varying degrees the respiration of isolated slices of such tissues as lymph node, bone marrow, spleen, brain, liver, and kidney (*43, 46*). Moreover, the utilization of pyruvate by kidney slices and the synthesis of urea by liver slices were found sensitive to nitrogen mustard *in vitro* as well as in animals which had been gassed with lethal doses (*43*).

The fact that diverse cells and tissues which had been subjected to the toxic effects of sulfur and nitrogen mustards evidenced marked metabolic defects has fostered the theory that the primary mechanism of action of the vesicants was the inactivation of essential cellular enzymes (*47, 48*). This view has been supported by extensive investigations with skin and other tissues, and in addition it has been postulated that primary inactivation occurs only in a special class of essential cellular enzymes, the phosphokinases, which are concerned with phosphate transfer to or from adenylic compounds (*41*).

The "enzyme-inactivation" theory of the mechanism of toxic action of the mustards served as the impetus for extensive investigations of the *in vitro* sensitivity of a large number of enzyme systems. Briefly, the enzymes or enzymatic systems studied included proteins containing iron, copper, and zinc, and flavin prosthetic groups; dehydrogenases; hydrolytic enzymes such as fumarase, urease, and invertase; catalysts involved in the metabolism of glucose and in reactions concerned with phosphate transfer; intracellular and extracellular proteolytic enzymes; various oxidases such as those of pyruvic acid, ascorbic acid, histamine, and choline; acetylcholine esterase, ribonuclease, hyaluronidase, and carboxylase (*13, 15, 17, 41–43, 49*). The majority of the enzymes proved only moderately sensitive or resistant to inactivation by the mustards. Among the highly sensitive enzymes were hexokinase, creatine and pyruvate phosphokinase, inorganic pyrophosphatase, adenylic acid deaminase, chick pepsin, kidney pepsinase, and peptidases of serum and skin and lung. In addition, choline oxidase, and acetylcholine esterase isolated from brain, were readily inactivated by the nitrogen mustards.

On the basis of the results obtained from studies of *in vitro* inactivation it is generally conceded that the phosphokinases as a group are highly susceptible to the mustards but share this sensitivity with other types of enzymes. In view of this finding, some doubt has been expressed concerning the possibility that the inactivation of phosphokinases *in vivo* represents the primary and specific mechanism of toxic action of the mustards, especially since no obvious correlation has been found between susceptibility of enzyme systems *in vitro* and *in vivo* (*49*).

At present it is not possible to present a final statement concerning the merits of the "enzyme-inactivation" theory of mustard intoxication. That some enzymes possess a high order of sensitivity to the agents *in vitro* cannot be questioned. Whether the inactivation of the same enzymes *in vivo* represents a primary step in the course of events leading to cell pathology is, however, open to serious question. The consensus of opinion of many investigators is that the specific chemical lesion responsible for the changes that eventually lead to cell death has not yet been defined by studies on the inactivation of enzymes. The difficulties attending the clarification of the characteristics of such a lesion are apparent in cytological studies of mammalian cornea (*45*) and yeast (*44*), where concentrations of the mustards below those which affect either respiration or glycolysis have been found to produce fundamental changes in mitotic activity.

Nucleotoxic Action of the Mustards

Although diverse systemic effects can be elicited in the mammalian organism by the administration of toxic amounts of the mustards, threshold doses evoke pathological changes only in cells and tissues which normally exhibit relatively high rates of proliferation

and growth. Considerable attention has been focused on the morphological changes exhibited by such cells in response to the mustards in the hope that such studies might provide a better understanding of the basic cellular disturbances involved. As a result it has been shown that the mitotic activity of a variety of cells from representative unicellular, invertebrate, amphibian, mammalian, and higher plant organisms is peculiarly sensitive to inhibition by minimally effective doses. For example, mild exposure of yeast cultures to sulfur mustard can produce an immediate reduction in growth rate which may be sustained at reduced levels by several succeeding generations of daughter cells before recovery is apparent (*50, 51*). Similarly, the early cleavage of the sea urchin egg is inhibited or retarded by brief immersion of either the unfertilized egg or the early zygote in minimally effective concentrations of the mustards (*52*). The exposure of young salamander larvae elicits an immediate cessation of growth which can be attributed to an inhibition of mitotic activity in the proliferating regions of all the tissues of the embryo (*53*). Those cells in which mitotic activity has been completed at the time of exposure continue functional differentiation in a normal manner. Following direct application of threshold amounts of the mustards to the intact eye or after parenteral administration of minimal lethal doses, the corneal epithelium of mammals can be largely depleted of mitotic figures for a period of several days without visible evidence of concomitant cytoplasmic or nuclear damage (*54*). Moreover, for several days after the parenteral administration of doses sufficient to cause lymphopenia and granulocytopenia in rats, mitotic activity is decreased in lymphoid, myeloid, and erythroid cells of hematopoietic tissues which have escaped the initial destruction caused by the agents (*27, 34, 54*) as well as in the intestinal mucosa (*54*). Finally, the mitotic rate of regenerating cells following partial hepatectomy has been found to be significantly lowered by the intravenous injection of sulfur mustard (*55*). In this regard it is important to note that similar doses do not evoke visible pathological changes in normal, nonproliferative hepatic tissue.

The inhibition of mitosis caused by mild exposure to the mustards does not in itself imply a primary nucleotoxic action of the agents; in fact, the mitotic arrest appears to be confined to the resting phase of the mitotic cycle (*52, 54*). Cells in active mitosis at the time of exposure complete their division with the result that ultimately the inhibited tissue may become depleted of mitotic figures (*54*). However, evidence of a more direct toxic action on nuclear mechanisms is the appearance of extensive nuclear fragmentation in cells of the corneal epithelium which have been exposed to doses somewhat higher than those which effect only a mitotic inhibition (*54*). The nuclear fragmentation and resultant chaotic chromatin dispersal can be considered as a pathological and incomplete mitosis (*56*). More convincing of the association of mitotic arrest with primary nuclear damage are studies on the inhibition of mitosis of pollen grains following exposure of *Tradescantia* inflorescences to minimal concentrations of sulfur mustard (*57*). The fate of the treated cells was shown to vary with the extent to which chromosomal abnormalities were elicited. Thus, severe exposure in association with complete mitotic arrest caused multiple chromosome breaks resulting in fragmentation, pycnosis, and ultimate death of the cell. Mild exposure which prolonged the resting period of the pollen grains caused chromosomal breaks in many of these cells. If these were not too numerous or followed by translocation, they were transmitted to daughter cells in the subsequent mitosis as heritable chromosome abnormalities.

Perhaps the most significant demonstartion of specific nucleotoxic action has been obtained from observations on the profound disturbances produced by the mustards on the structure and function of chromosomes in *Drosophila melanogaster* (*58*). Exposure of both male and female adults to sublethal doses was found to reduce or suppress fertility through disturbances of miosis and mitosis in the gametogenesis of both sexes. However, following exposure of adult males to lower doses which did not reduce fertility unduly, the genetic analysis of the X-chromosomes revealed a high incidence of sex-linked lethals greatly in excess of the natural rate of mutation as well as a significant number of translocations and inversions. No other class of chemical agents has been shown to have such specificity of action on chromosomal mechanisms. Indeed in the past similar effects have been attained to the same degree only by the use of short-wave radiation (X-ray and ultraviolet).

That the mustards can exhibit a primary nucleotoxic action is attested by the above demonstration that in threshold doses they act directly on the intimate structure of chromosomes, without apparent influence on other cellular entities, to produce an inheritable chromosomal abnormality which can be reproduced indefinitely by normal processes of cell division and thereby transmitted from ovum to ovum through several successive adult generations. The precise mechanism whereby changes in the chromosome are effected, whether by direct chemical reaction with its component compounds or as the result

of structural instabilities induced by inactivation of intimately associated nuclear enzymes, is a subject of future investigation. Of possible importance in this regard are observations on the inactivation of the infectivity of the nucleoprotein tobacco mosaic (*20, 59*) and bushy stunt (*59*) viruses. Although reaction of the viruses with the mustards resulted in extensive inactivation, moderate exposure which did not appreciably reduce infectivity was not accompanied by significant increases in mutation. It has been shown that under the latter conditions the virus molecule sustained multiple reactions with mustard groups.

On the basis of the marked susceptibility of nuclear mechanisms it is provocative to associate the cytotoxic action of the mustards with primary disturbances of nuclear function. Even the necrotization of hematopoietic and intestinal cells of mammals following fatal intoxication might conceivably be considered the eventual outcome of a primary nuclear derangement. However, it must be pointed out that abnormalities which cannot be readily interpreted as arising from a primary nuclear intoxication have been reported to result from exposure of cells to the mustards. Thus, the response of avian erythrocytes or their nucleated ghosts to the swelling action of applied detergents was demonstrated to be highly susceptible to inhibition by prior immersion in dilute solutions of the mustards (*60*). The inhibition of swelling has been interpreted to result from a primary change in the properties of the cytoplasmic stroma. Similar observations obtained with suspensions of rabbit bone marrow and lung cells (*60*) indicate that the effect is not limited to the avian erythrocyte. Although the significance of this cytoplasmic change is not clear, it does represent one of the most sensitive cellular reactions so far demonstrated to result from exposure to the mustards. Similarly, the application of dilute solutions of sulfur mustard to *Nitella flexilis* caused a marked loss of turgor associated with a loss of the normal semipermeability of the surface films to electrolyte (*61*). Finally, cytoplasmic changes have been noted in response to minimally effective doses of the mustards under circumstances which have not permitted an exact analysis of the sequences of morphological events. Thus, concentrations which inhibit the growth of cultures of choroid and sclerotic chick tissue cause a simultaneous swelling of cytoplasmic fat globules (*62*). Similarly, in cultures of embryonic membrane bone the first signs of injury are evident in the mitochondria, which undergo marked structural changes (*63*). It may also be mentioned that ameboid movement of leucocytes and metamyelocytes in suspensions of rabbit bone marrow is readily inhibited in the presence of nitrogen mustard (*46*).

Clinical Applications

The marked effects of the mustards on lymphoid tissue, coupled with the finding that actively proliferating cells are selectively vulnerable to the cytotoxic action of the mustards, suggested the therapeutic use of these compounds in the treatment of neoplasms of lymphoid tissue. Because of its undesirable physical properties and extreme chemical reactivity, sulfur mustard does not lend itself to parenteral administration. However, nitrogen mustards in the form of their hydrochloride salts are water-soluble, crystalline compounds, which can be readily dissolved in sterile saline for intravenous administration. Experiments on transplanted lymphosarcoma in mice revealed that dissolution of such tumors could be rapidly effected although the dose required bordered on the toxic, and the tumor invariably returned (*64*). The first clinical trial of the nitrogen mustards (*65*) was conducted on a group of six patients in the terminal stages of various neoplastic diseases. In two cases of lymphosarcoma in which X-ray therapy had been discontinued, a rapid dissolution of large tumor masses followed a course of injections. The results were sufficiently encouraging to warrant further clinical experimentation. To date approximately 150 patients have been treated by several groups of investigators (*66–68*). For the most part observations have been limited to selected cases of Hodgkin's disease, lymphosarcoma, and leukemia. The findings may be summarized in general terms. The most favorable effects have been obtained in patients with Hodgkin's disease. Remissions characteristic of those which follow careful X-ray therapy have been observed. Symptoms were quickly alleviated, and physical evidence of lymphadenopathy, splenomegaly, and hepatomegaly regressed. It was necessary to repeat treatment at intervals varying from one to eight months. Less favorable results have been obtained in cases of lymphosarcoma. The response in acute and chronic lymphogenous and myelogenous leukemias has been disappointing.

The action of the available nitrogen mustards on lymphoid tissue has not yet reached that degree of specificity which precludes undesirable actions on the hematopoietic system. At present, dosage is limited by the occurrence of moderate granulocytopenia, thrombocytopenia, and anemia. However, if care is taken with dosage, an adequate clinical response may be obtained without affecting to a serious degree the formed elements of the blood. In addition, nausea and vomiting are very likely to occur for a brief period after each injection. No other undesirable effects on the gastrointestinal tract have been observed.

Comments. Although some patients receiving ni-

trogen mustards have been observed for a period of 28 months, the evaluation of the clinical status of this group of compounds will require many more years of careful study. At present there is no basis for assuming that the therapeutic efficacy of the nitrogen mustards is any greater than that of X-ray.

It is possible that the potential value of the nitrogen mustards in the treatment of neoplastic diseases will be fully realized only when the opportunity to explore the relationship between chemical constitution and pharmacodynamic action has been exhausted. At present only two of the nitrogen mustards have been investigated clinically, namely, *tris*(β-chloroethyl)amine and methyl-*bis*(β-chloroethyl)amine. These have been the product of a screening program designed for the evaluation of toxic chemical warfare agents rather than of compounds of therapeutic interest. Literally hundreds of congeners remain to be synthesized and evaluated. Thus, a series of compounds which can reproduce in many ways the cellular effects of X-rays is available for chemical and biological investigation. It may be hoped that the previous successes which have characterized the evolution of chemotherapeutic agents by chemical alteration of a parent compound may be duplicated in the case of the β-chloroethyl amines. The result would be a compound having a sufficiently specific toxic action for certain types of proliferative cells to possess therapeutic value.

(See p. 436 for list of references.)

Science and Our Future

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THE WAR'S DESTRUCTION FAR EXCEEDS that of any catastrophe yet known. The war ended with the application of a new weapon that is a thousand times more frightful than the weapons which produced most of the war's frightfulness. And already we have responsible statements from scientists who effected this development that bombs a thousand times more powerful than those already used are capable of being made in the near future. There are men living who know how to make a single bomb whose destructiveness is equal to a million ten-ton blockbusters. One such bomb, dropped on Washington or any other major city, may be expected to wipe out its population, to destroy its buildings utterly, and to render the site uninhabitable due to poisoning by radioactive materials.

In the face of this situation, people react essentially in one of two ways. One group says: "It's just another weapon. Mankind learned to adapt to the long bow, and the cross bow, and the B-29. We have always had wars." An extreme expression of this kind is found in a speech delivered in Philadelphia last December by Prof. Leslie A. White, of the Anthropology Department of the University of Michigan, who said: "As for the extermination of the human race as a consequence of hurling atomic thunderbolts, this too may be admitted as a possibility, and all we can say is that if it is to come, it will come." This is indeed a rather coldly hopeless, fatalistic expression. Prof. White further says: "Extravagant expressions of horror will not alter the course of events."

There is a certain rhetorical trick here in that, in our language, "extravagant" connotes exaggeratedly inaccurate, and thus emotionally detracts from the serious warnings which responsible physicists are trying to give us. I would agree that expressions of horror *alone* will not alter the course of events. But I insist that if we look at what civilization has suffered in World War II, even before the atom bomb, and couple it with the picture of a war with plentiful use of the old-fashioned "one-hoss shay" atom bombs, and further with the picture of a war with both sides equipped with the really potent 1950 models—then no expression of horror of which our hearts are capable can be exaggerated or extravagant. We need not, and should not, fatalistically await death, reading papers to an academic society meeting in a museum in Philadelphia.

The second kind of people react differently. We say: "This is the end." Mankind has brought down suffering and death on its head, spiritual values have been destroyed, hatreds have been nourished and developed into great social cancers by war, war fears, and war suspicions and divisions among men.

From an address delivered 5 March 1946 in Washington, D. C., at the conclusion of the Fifth Annual Science Talent Search (*Science*, 1946, 103, 336). The guests for the evening were the 40 winners from the Science Clubs of America who received the Westinghouse Scholarships and scientists from the Washington area. The event was arranged by Science Service, whose director, Watson Davis, served as toastmaster.

change, and it is something of a shock to learn that the uncomfortable benches in use for generations were not replaced until 1939, when "others of modern type more suitable for meetings which lasted long and demanded the close attention of the audience" were installed.

As treasurer of the Royal Society for many years, Sir Henry Lyons had access to its records and was well qualified to write its administrative history. The great wealth of information in this book concerning the finances and administration of the Royal Society make it particularly useful to specialists in the history of science. Inasmuch as there has been no comprehensive history of the Society for a hundred years, the book should also be of interest to those who are not specialists for it is much more than a treasurer's report. Each chapter has a useful short bibliography and there is an excellent index. It is to be regretted that this book was published in such a small edition that it is already out of print.

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B-Chloroethyl Amines and Sulfides

(Continued from p. 415.)

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[1] The majority of the references cited above are to classified documents which are not generally available. Reference is therefore made to authors and the time at which their work was conducted. Those references preceded by an asterisk refer to unpublished British work.