gave 35 per cent excretion in one hour. The electrocardiogram was not diagnostic. A roentgenogram of the chest revealed normal conditions. The bacteriologic studies, clinical course and treatment of this patient have already been described.

CASE 3.[2]—The patient was a man aged 42. He had rheumatic fever resulting in a mitral murmur at the age of 18. A simple cold developed in May 1945, from which he did not recover. From May until his admission to Wesley Hospital on Sept. 13, 1945, gradually increasing symptoms of malaise, chills, cough, night sweats, weakness, dyspnea, muscular cramps and loss of weight were present. In June 1945 he was told he had secondary anemia, albuminuria and myocardial damage, but cultures of the blood were not made. On admission, the temperature ranged to 103 F., the pulse rate to 96 and the respiratory rate to 24. The blood pressure was 112 systolic and 68 diastolic. The weight was 105 pounds (48 Kg.). The heart was enlarged; its contour was mitral. A loud harsh systolic murmur and a softer middiastolic murmur were heard at the apex. The liver and spleen were palpable. Petechiae were present on the legs. Urinalysis disclosed 10 mg. of albumin per hundred cubic centimeters. Examination of the blood revealed: erythrocytes 3,150,000; hemoglobin 9 Gm. per hundred cubic centimeters; leukocytes 6,200, and sedimentation rate 45. Roentgenograms of the teeth showed several root fragments with abscesses. Cultures of the blood were positive. The bacteriologic studies, therapy and clinical course of this patient have been described previously.

SUMMARY

Occasionally a case of subacute bacterial endocarditis may be encountered in which the organism is a gram-negative rod insensitive to penicillin. Although a cure may be obtained by the combined use of penicillin and sulfonamides as was true in the boy of 8 whose recovery is recounted, streptomycin should be the drug of first choice when dealing with such organisms.

Strains of streptococci which are highly insensitive to penicillin may be encountered more frequently. These may be relatively sensitive to streptomycin. Three such organisms were encountered in cultures from a group of 34 patients. One was typically Streptococcus viridans after freezing, but was rather atypical in primary cultures of blood. The other two were typical nonhemolytic streptococci. In vitro sensitivity to penicillin ranged from 0.8 to 6 units per cubic centimeter. Sensitivity to streptomycin ranged from 0.1 to 1 unit per cubic centimeter. Streptomycin apparently produced sterilization of the valvar lesions in case 1, resulted in negative cultures of blood after penicillin therapy had failed in case 2 and was solely responsible for the cure obtained in case 3.

The dose of streptomycin used, 500,000 units (0.5 Gm.) per day, is not necessarily that which will be adequate in all cases in which the use of the drug is indicated. In the 3 cases here reported, serum streptomycin levels of 3 to 12 units per cubic centimeter were obtained.

2. In case 3 the streptomycin was furnished by Schenley Laboratories, Inc., Lawrenceburg, Ind.

William Hunter's Entrance Into the World of Affairs.—William Hunter came up from Scotland to London in 1740, at the age of 22, to embark on his chosen career of medical science. After six years in town, while he was yet in his twenties, he considered himself sufficiently well versed in the art of anatomy to start to instruct others. Yet even earlier than this he had begun to contemplate his own field as related to a philosophy which included political as well as physiological phenomena among its materials.—Oppenheimer, Jane M.: New Aspects of John and William Hunter, New York, Henry Schuman, 1946.

NITROGEN MUSTARD THERAPY

Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders

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In a recent report the historical aspects of the use of β-chloroethyl amines (halogenated alkyl amines, nitrogen mustards) in the treatment of certain diseases of the blood-forming organs were presented and the chemical, pharmacologic, toxicologic and animal experimental aspects of these compounds reviewed.[1] The interested reader is referred to that report for orientation.

The present preliminary communication concerns the clinical use of halogenated alkyl amines in the treatment of lymphosarcoma, Hodgkin's disease, leukemia and a limited number of allied and miscellaneous disorders. In all, 67 patients have been studied. These include 7 patients[2] treated by L. S. Goodman and Alfred Gilman at the New Haven Hospital; 34 patients treated by M. M. Wintrobe and Margaret T. McLennan at the Salt Lake County General Hospital; 16 patients treated by William Dameshek, Boston, and 10 patients treated by M. J. Goodman, Portland, Ore. The types of diseases treated are shown in the accompanying table. The youngest patient was 3 years of age and the oldest 76. The sexes were approximately equally represented in the series. Twenty-six of the 67 patients are still alive and under observation or therapy.

No attempt will be made at this time to analyze statistically the results obtained or to compare them with those observed after roentgen irradiation. The reasons for this are (1) the small number of patients in the series, (2) the prior use of radiation treatment for most patients, (3) the terminal nature and radiation refractory character of the disease in the majority of cases and (4) the small number of patients in the early stage of their disease. Rather, our purposes in this report are mainly to summarize briefly the clinical experiences obtained and to present the considered opinions of the various investigators concerned as to the status and the potential value of the β-chloroethylamines in the syndromes enumerated. In subsequent more complete communications, comparison with the results of radiation therapy will be made and detailed hematologic and pathologic data will be presented.

The Jane Coffin Childs Fund for Medical Research, Yale University, defrayed part of the expenses of this investigation.

The chemicals employed in this study were generously supplied by Dr. Milton C. Winternitz, Chairman, Committee on the Treatment of Gas Casualties.

Reports of several of the investigations referred to either have not been published or have not been recorded in the open literature. The date given is the year in which the work was carried out.

Dr. L. S. Goodman, Dr. Wintrobe and Dr. McLennan are from the University of Utah School of Medicine; Dr. Dameshek is from Tufts College Medical School; Dr. Morton J. Goodman is from the University of Oregon Medical School, and Major Gilman is from the Medical Research Division, Edgewood Arsenal.

The following physicians have generously cooperated in providing cases for study: Drs. Gustaf E. Lindskog, Grover F. Powers, Francis G. Blake, G. G. Richards, M. J. Taylor and L. A. Wheelwright.

1. Gilman, A., and Philips, F. S.: The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides, Science **103**: 409-415, 1946.

2. Gilman, A.; Goodman, L. S.; Philips, F. S., and Dougherty, T., 1943.

CHEMISTRY AND DOSAGE

The chemistry and the pharmacodynamics of the nitrogen mustards and particularly of the two compounds employed in this study have been described recently.[1] The water soluble hydrochloride salts of the *tris*(β-chloroethyl)amine and methyl-*bis*(β-chloroethyl)amine were injected intravenously. The doses of the two were the same.

The standard single dose of 0.1 mg. per kilogram of body weight was injected daily or every second day until three to six doses were administered, but the single dose never exceeded 8 mg. This was considered to represent the initial treatment required to induce remissions in suitable cases. In an occasional very ill patient the single dose was reduced to 0.05 mg. per kilogram. Subsequent treatment varied with each patient, depending on the clinical response, the hemopoietic status, the duration and completeness of remission and the like. As a rule an additional dose of nitrogen mustard was not given oftener than every six to eight weeks, and subsequent treatments usually consisted of but two to four doses.

METHOD AND TECHNIC OF ADMINISTRATION

The nitrogen mustards must be administered only by the intravenous route, great caution being observed to prevent extravasation of the solution. The solution was freshly made by adding 0.9 per cent sterile aqueous sodium chloride solution to sterile glass bottles each containing exactly 10 mg. of the dry salt. Injection was accomplished within five minutes after preparation of the solution, because of the rapid hydrolysis which may occur, with consequent loss of efficacy. In the majortiy of the 20 patients receiving *tris*(β-chloroethyl)amine hydrochloride the direct syringe method was employed, the dose being contained in 25 to 50 cc. of saline solution. Pain during injection and subsequent thrombophlebitis of the injected vein were frequent with this technic. In all other cases 10 mg. of the drug was dissolved in 10 cc. of saline solution (1 mg. per cubic centimeter), and the calculated dose was injected into the rubber tubing during the course of an intravenous infusion of glucose or saline solution, special attention being given to assure free and rapid flow of the infusion and rapid injection of the nitrogen mustard solution. Considerable caution was exercised to prevent the solution from touching the skin or mucous membranes of the patient or physician. All patients were hospitalized, no ambulatory therapy being attempted.

CLINICAL RESULTS AND REPORT OF CASES

Hodgkin's Disease.—Twenty-seven patients with this disease, verified pathologically by biopsy, were treated with nitrogen mustard, 22 with methyl-*bis*(β-chloroethyl)amine hydrochloride and 5 with *tris*(β-chloroethyl)amine hydrochloride. All but 3 had previously had radiation therapy. The majority were in the advanced or terminal stage of their illness and also were considered resistant to roentgen irradiation. In nearly every case some benefit was obtained from chemotherapy. Indeed, the clinical results were sometimes dramatic. Whether the halogenated alkyl amines are superior to radiation treatment cannot be stated at this time, but sufficient experience has been obtained to permit the conclusion that remissions may be induced in patients whose disease no longer responds to roentgen irradiation. In fact, in 3 patients sensitivity to irradiation may have been restored after a course of nitrogen mustard. In 1 patient who had Hodgkin's disease for seven years and who was still responsive to radiation therapy a more satisfactory remission was obtained from nitrogen mustard than from any previous course of radiation treatment. In another patient who did not respond adequately either to radiation therapy or to halogenated alkyl amine therapy alone, good results were obtained by combining the two agents.

In addition to rapid partial or complete disappearance of Hodgkin's tumor masses, most patients experienced improvement in appetite, weight, strength and sense of well-being; fever, if present, disappeared. A number of persons were able to return to work. Symptom free remissions varying from two weeks to at least seven months have been observed.

The following abbreviated case report serves to illustrate a dramatic remission induced by therapy with the *tris*(β-chloroethyl)amine hydrochloride in a radiation refractory case of terminal Hodgkin's disease.

CASE 1.—L. W., a woman aged 33, a housewife, was first seen in 1941 because of axillary lymphadenopathy, and biopsy revealed Hodgkin's disease. Her father had died of Hodgkin's disease, her mother of polycythemia. In rapid succession nodes appeared in the axillas, the neck and the mediastinum. X-ray therapy was given with initial excellent but with subsequent

Distribution by Disease of Cases in Which Nitrogen Mustard Therapy Was Used

Hodgkin's disease	27
Lymphosarcoma	13
Chronic myelocytic leukemia	7
Acute and subacute myeloblastic leukemia	4
Chronic lymphocytic leukemia	5
Subacute lymphoblastic leukemia	3
Miscellaneous diseases *	8
Total	67

* Melanosarcoma (2), undiagnosed retroperitoneal mass, undiagnosed tumor (probably Hodgkin's disease), reticuloendotheliosis, metastatic mammary carcinoma, metastatic cervical carcinoma and giant follicular lymphoma.

poorer results. In the summer of 1942 dyspnea and cough developed, and thoracentesis was required for pleural effusion. Complete motor and sensory paralysis of the right arm appeared in the spring of 1943, and the limb gradually increased threefold in size. Cough, weakness and dyspnea became worse, lymph node masses increased, and in the fall of 1943 the patient was bedridden and failed to respond to further x-ray treatment.

On admission to the hospital in December 1943 the patient was extremely ill and very cyanotic, with a shallow dry cough and gasping respiration. The face and neck were greatly swollen and distorted, and the left side of the neck bulged with a hard irregular mass extending into the supraclavicular fossa. There was pitting edema over the upper thorax. Both axillas were occupied by hard irregular masses of nodes, extending on the right side to the lower chest wall. The percussion note was dull to flat over both thoraces, and breath sounds were diminished. The breasts were large and edematous. The right arm was greatly swollen and completely paralyzed. There was no enlargement of the spleen or liver and no inguinal lymphadenopathy.

Roentgen examination disclosed no mediastinal mass, but decided infiltration of the lower two thirds of both lungs was present. Blood values were not remarkable except for a mild eosinophilia and a total absence of lymphocytes. The temperature ranged from 98 to 103 F. and the pulse from 100 to 140.

Treatment consisted of four doses of *tris*(β-chloroethyl)amine hydrochloride, 0.1 mg. per kilogram of body weight every other day, given intravenously by the direct syringe method. Improvement started after the second dose and continued over a period of two weeks. The patient felt much better, the fever and cyanosis disappeared, the dyspnea and cough improved,

the lymph node masses shrank 60 to 75 per cent, the breasts became much smaller, the disfiguring edema of the face and neck entirely receded, and the hugely swollen right arm returned almost to normal size. Roentgenograms of the chest revealed no change in the pulmonary infiltration. Treatment was well tolerated and only minimal blood changes occurred (a slight reduction in the hemoglobin content and red blood cell count, a moderate decrease in the number of white blood cells).

The dramatic therapeutic remission persisted until it was interrupted at the end of four weeks by a sudden severe attack of pulmonary edema which quickly resulted in death. Postmortem examination was not obtained.

Lymphosarcoma.—Thirteen patients with lymphosarcoma were treated with nitrogen mustard, 5 with *tris*(β-chloroethyl)amine hydrochloride and 8 with methyl-*bis*(β-chloroethyl)amine hydrochloride. Most of the cases were terminal. In all but 4, prior radiation therapy had been given. Of the patients who had received such treatment, nearly all had reached the radiation resistant stage of their disease.

The clinical results observed were qualitatively similar to those previously described for Hodgkin's disease but were more frequently unsuccessful. Therapeutic remissions, when obtained, lasted from three weeks to several months; but with each recurrence renewed therapy seemed to be less and less effective, and the remissions became shorter. At least 5 complete failures were encountered without obvious explanation for the lack of satisfactory response. It was impossible to predict beforehand which patients would or would not respond satisfactorily. This was likewise the experience with the nitrogen mustard therapy of experimental lymphosarcoma in mice,[3] in which syndrome it was also observed that the tumor cells became more resistant to the chemicals with successive courses of treatment.

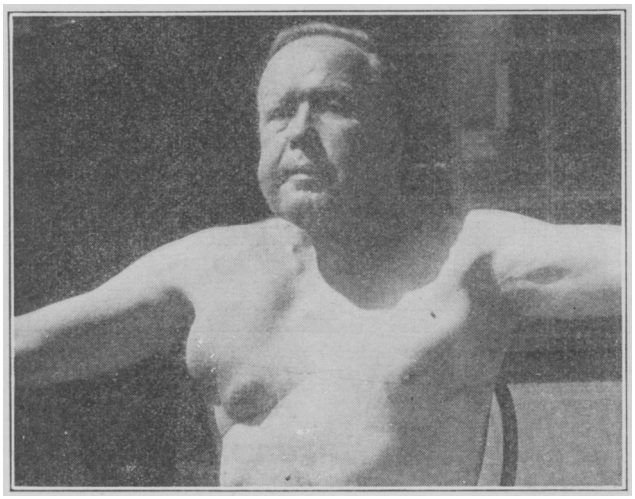

Fig. 1 (case 2).—Appearance in terminal lymphosarcoma in the radiation resistant stage four days after initiation of *tris*(β-chloroethyl)amine hydrochloride therapy. Improvement in well-being, strength, appetite and temperature but no visible change in size of tumor masses.

Dramatic results against lymphosarcoma in the terminal stages were observed in several patients near death. In 1 patient, sensitivity to radiation was restored by halogenated alkyl amine therapy. As was also true for Hodgkin's disease, satisfactory responses were obtained even in radiation resistant patients. In addition to definite reduction or complete clinical disappearance of lymphosarcoma masses and the signs and symptoms attributable thereto, the therapeutically induced remissions frequently were associated with an improvement in appetite, strength and weight and with reduction of fever and a sense of well-being.

The following brief case report serves to illustrate the salutary effect of β-chloroethylamine therapy in terminal lymphosarcoma which had become refractory to radiation. The case is of further interest because it is the first in which nitrogen mustard therapy was employed and also because it illustrates the severe toxic effects which excessive dosage produces.

CASE 2.—J. D., a man aged 48, a silversmith, entered the hospital[4] in August 1942 in the terminal stages of lymphosarcoma. He had been seen first in January 1941 complaining of pain and swelling due to a mass on the right side of the neck. Physical examinations and biopsy revealed lymphosarcoma, primary in the tonsil. Radiation therapy was instituted in March 1941 with considerable reduction in the tumor mass. Palliative local resection was performed in June 1941. The patient remained well until December 1941, when masses appeared on both sides of the neck. A second course of x-ray therapy gave relief, but by May 1942 a rapid enlargement and spread of the tumor masses had occurred, the axilla, mediastinum, face and submental region being involved. Additional therapy was given almost continuously, but the masses increased in size.

Physical examination revealed the aforementioned tumor masses (fig. 1), cyanosis, venous dilatation and edema of the face and the upper part of the chest, anisocoria and paresis of the right facial nerve. Chewing and swallowing had become almost impossible, and the axillary nodes prevented adduction of the arms. The spleen and liver were not enlarged. The patient was severely orthopneic, and a tracheotomy set was kept close at hand for immediate use. The results of laboratory examinations were not remarkable, and the blood picture was within normal limits.

Ten consecutive daily doses of *tris*(β-chloroethyl)amine hydrochloride were injected intravenously by the direct syringe method, 0.1 mg. per kilogram of body weight per dose. (This dosage, subsequently found to be too large, was arrived at on the basis of results obtained in experimental lymphosarcoma in mice.)[3] On the fourth day of treatment the patient felt better, was able to swallow and could sleep lying down. By the tenth and last day of treatment the cervical masses were no longer palpable, and the axillary masses receded completely four days later (fig. 2). All signs and symptoms due to the disease disappeared.

Tumor masses recurred after one month, and a second course of treatment (three consecutive daily doses) was given. Improvement was transitory and a third course (six consecutive daily doses) was administered three weeks later without sustained benefit. However, at the time of death, three months after the start of therapy and three weeks after the third course of chemotherapy was completed, the tumor masses were relatively small. Death was hastened by the untoward effects of the drug on the bone marrow, especially thrombopenia.

The panmyelopathy caused by the first course of the drug may serve to illustrate the toxic potentialities of the nitrogen mustards.[5] The earliest action was observed on the circulating lymphocytes, which disappeared completely by the time of the fifth daily dose and then slowly returned. The total white blood cell count fell gradually and progressively from the time of the first daily injection until a low of 200 cells per cubic millimeter was reached (despite two blood transfusions) one month after the initiation of therapy, at which time the differential count indicated 52 per cent lymphocytes, 4 per cent monocytes, 12 per cent eosinophils and 32 per cent neutrophilic granulocytes. The total leukocyte count returned to pretreatment values over a three week period. Despite the leukocyte picture, the clinical signs and symptoms of agranulocytosis were absent except for moderate fever. Thrombocytopenia was most pronounced (22,000 platelets per cubic millimeter) at the height of the leukopenia and was accompanied with gingivitis, periodontitis and cutaneous purpura. The platelets rose to normal

3. Dougherty, T.; Gilman, A., and Goodman, L. S., 1942. Unpublished observations.

4. Dr. Gustaf E. Lindskog, Department of Surgery, Yale University School of Medicine, gave the authors permission to study and report this case.

5. A complete description of this case has appeared elsewhere.[2]

values over a three week period. At no time was anemia more than moderate. The red blood cell count did not decline until the first course of therapy was completed and the lowest values (red blood cells 3.28 million, hemoglobin 9.9 Gm. per hundred cubic centimeters) occurred simultaneously with those for leukocytes and platelets. Recovery from anemia paralleled that for the other formed blood elements and was hastened by blood transfusions.

An instance of complete failure of halogenated alkyl amine therapy to influence the course of a radiation refractory and terminal case of lymphosarcoma is illustrated in the following brief case report:

CASE 3.—E. W., a woman aged 42, a housewife, was first seen in September 1943, when she complained of severe pruritus, substernal pain, cough and dyspnea. Study disclosed a rapidly growing mediastinal lymphosarcoma, verified pathologically by biopsy (cervical node). Radiation therapy gave temporary relief but finally failed to retard the growth of the mediastinal mass. Observations on final hospital admission in February 1944 included fever, generalized severe pruritus, cough, dyspnea, bilateral pleural effusion, cervical nodes and the intrathoracic mass. The blood picture was not remarkable. Five doses of methyl-*bis*(β-chloroethyl)amine hydrochloride were given (0.1 mg. per kilogram of body weight per dose, every other day). There was no objective or subjective improvement; the ingravescent course progressed, and death occurred five weeks after the start of nitrogen mustard therapy. Postmortem examination verified the diagnosis of lymphosarcoma, which was found to involve the lungs, pleura, pericardium, myocardium, diaphragm and ribs.

Chronic Leukemias.—Twelve patients with chronic leukemia have been treated with nitrogen mustards, 10 with methyl-*bis*(β-chloroethyl)amine hydrochloride and 2 with *tris*(β-chloroethyl)amine hydrochloride. Seven cases were of the chronic myelocytic type, and 4 of chronic lymphocytic leukemia. In 6 terminal or nearly terminal cases the treatment was of no appreciable value. In 6 other patients, however, the results of treatment with the β-chloroethylamines were comparable with those obtained with radiation therapy. In addition, even when concomitant clinical and symptomatic benefits did not occur, nitrogen mustard often caused a reduction in the leukocyte count, a more normal differential formula, improvement in the appearance of the bone marrow and more persistence in the effect of blood transfusion. In 1 patient with chronic lymphocytic leukemia the signs and symptoms of hypermetabolism were considerably relieved. Further experience is needed to determine the status of these agents in chronic leukemias.

The following case abstract serves to illustrate the beneficial effect of nitrogen mustard therapy on a patient with chronic myelocytic leukemia:

CASE 4.—B. C., a white man aged 52 with typical chronic myelocytic leukemia of four years' duration, had received radiation therapy at approximately yearly intervals from 1941 to 1944 inclusive, with remission of symptoms following each course of therapy. In May 1945 fatigability had returned, the leukocyte count was 293,000 and the red cell count was 3.11 million per cubic millimeter. The spleen extended 3 cm. below the umbilicus and the liver 5 cm. below the costal margin. Five doses of methyl-*bis*(β-chloroethyl)amine hydrochloride (0.1 mg. per kilogram per dose) were given over a two week period, and two blood transfusions of 500 cc. each were administered during this same period. Six weeks later the patient had no anemia (hematocrit 50) and the leukocyte count was 25,800 per cubic millimeter. The spleen and liver had decreased appreciably in size. The patient had gained 10 pounds (4.5 Kg.) in weight and was able to do light work. Eight weeks later (four months after the start of therapy) the patient was still feeling well, was doing regular work and maintaining the gain in weight but because of a slight anemia (hematocrit 40) and a leukocyte count of 50,400 per cubic millimeter he was hospitalized and given four more doses of the drug. Following this second course of therapy he felt well, the hematocrit again rose and the leukocyte count decreased to 11,300. Two months later he was found to be slightly anemic (hematocrit 37) and the leukocyte count had risen to 103,000. Three more injections of drug were given and again an increased hematocrit and decreased leukocyte count were obtained. At the present time, nine months after the first course of therapy, the patient is in a state of fairly complete remission, both hematologically and clinically.

Subacute and Acute Leukemias.—Seven patients with acute or subacute leukemia were treated with nitrogen mustards, 5 with *tris*(β-chloroethyl)amine hydrochloride and 2 with methyl-*bis*(β-chloroethyl)amine hydrochloride. Four cases were myeloblastic in type and 3 were lymphoblastic. The clinical results in most of the cases were not particularly encouraging, but in 3 partial clinical and hematologic remissions were obtained. In 1 patient with subacute lymphoblastic leukemia a brief but definite clinical remission with a decrease in the total leukocyte count and in the size of the spleen occurred, but the ultimate fatal outcome

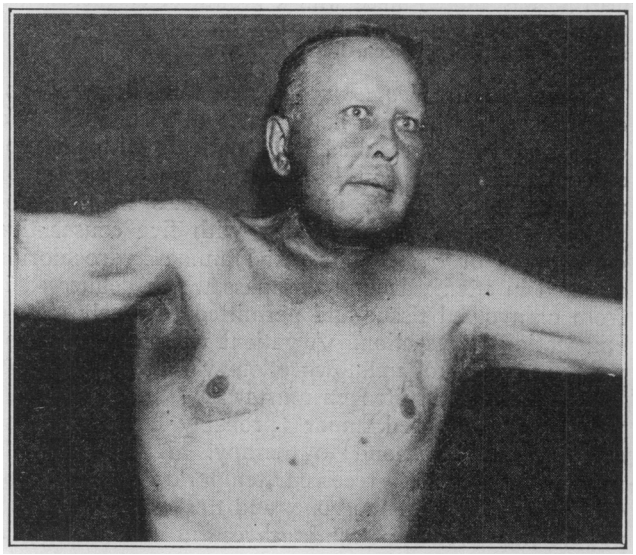

Fig. 2 (case 2).—Eight days later and two days after the last dose. Complete disappearance of tumor masses in axillas, neck, jaw and thorax, with decided improvement in the patient's condition.

was only briefly postponed. The decrease in thrombocytes caused by halogenated alkyl amines was a complicating factor in the use of this agent in several patients with platelet values which were already quite low. Improvement in the white blood cell count, differential formula or bone marrow picture was not always paralleled by clinical or subjective gain. Indeed, in at least 2 patients there is the possibility that β-chloroethylamine therapy may have accelerated the fatal termination.

The brief case report which follows illustrates the failure of nitrogen mustard therapy in a patient with subacute myeloblastic leukemia:

CASE 5.—S. C., a woman aged 66, a housewife, was hospitalized in October 1943 in the terminal phase of subacute myeloblastic leukemia. Symptoms had existed for five months; they were becoming progressively worse and included fatigue, dyspnea, anorexia and dizziness. Examination revealed moderate fever and tachycardia, pallor, cutaneous purpura and ecchymoses. The spleen and liver were not palpable, and there was no lymphadenopathy. Examination of the blood revealed moderately severe anemia (hematocrit 21) with 68,000 leuko-

cytes (89 per cent myeloblasts) and 50,000 platelets per cubic millimeter. Study of the bone marrow revealed almost a "pure culture" of primitive cells (many of them peroxidase positive) and numerous other cells of the granular series.

After several blood transfusions, *tris*(β-chloroethyl)amine hydrochloride 0.1 mg. per kilogram of body weight was given every other day for three doses intravenously by the direct syringe method. Severe nausea, vomiting and weakness resulted. There occurred a rapid fall in the total leukocyte count over a period of one week (to 600 cells per cubic millimeter) with an absolute and relative reduction in primitive cells. But the complete disappearance of platelets and rapid progression of the anemia were concomitant (but not necessarily causally related) features. As the granulocytes and platelets returned during the second week after therapy, more differentiation into myelocytes and metamyelocytes was observed. Although there was a specific effect on proliferating primitive cells, this was short lived and not associated with objective or subjective clinical improvement. The condition of the blood soon deteriorated, cerebral hemorrhage occurred one month after completion of nitrogen mustard therapy, and the patient died shortly thereafter.

Postmortem examination revealed hyperplasia of the bone marrow, diffuse hyperplasia of the lymph nodes of the abdomen and pelvis, multiple punctate cutaneous, pleural and peritoneal hemorrhages and fresh intracranial hemorrhage. The bone marrow was entirely filled with a growth of undifferentiated cells suggesting atypical plasma cells. Similar cells were found in the lymph nodes, spleen, liver, kidney and skin.

Miscellaneous Neoplasms.—Eight miscellaneous diseases were treated with halogenated alkyl amines. No observable benefit resulted for 2 patients with melanosarcoma. However, in 1 patient in whom the tumor appeared as a diffuse infiltrating mass in the submaxillary region, chemotherapy with five consecutive daily doses of *tris*(β-chloroethyl)amine hydrochloride resulted in edema around the mass which delineated it from uninvolved tissue and permitted relatively simple enucleation at resection. A patient with a large retroperitoneal mass of unknown etiology failed to respond to treatment with nitrogen mustard. A second patient with an undiagnosed tumor (probably Hodgkin's disease) did not respond to therapy. A patient with reticuloendotheliosis received temporary relief from excruciating pain in the bone, and the leukemoid blood picture improved; but the ingravescent course and the ultimately fatal outcome were not altered. An elderly woman with pleural metastases from a mammary carcinoma which had been resected two years previously required less frequent thoracenteses after chemotherapy with four consecutive daily doses of *tris*(β-chloroethyl) amine hydrochloride, but the causal relationship could not be established with certainty. The clinical course of a patient with carcinoma of the cervix and mediastinal metastases was unaltered by treatment with nitrogen mustard. An elderly woman with giant follicular lymphoma exhibited a moderate reduction in the size of the lymph nodes and spleen after six consecutive daily doses of methyl-*bis*(β-chloroethyl)amine hydrochloride but experienced no corresponding clinical benefit and died three weeks later.

The results of the limited experience here described with neoplasms other than lymphomas and leukemias suggest that the halogenated alkyl amines employed are fairly specific in their tissue affinities, a tentative conclusion supported by animal studies employing experimental virus tumors in fowl,[6] testicular interstitial cell carcinoma in mice, and mammary carcinoma in mice.[3]

6. Duran-Reynals, F.; Goodman, L. S., and Gilman, A., 1942. Unpublished observations.[2]

TOXICITY

Immediate Local and Early Systemic Effects.—Local extravasation during the injection of solutions of the β-chloroethylamine hydrochlorides resulted immediately in pain and subsequently in tender indurated swellings which resolved slowly. Thrombophlebitis of the injected veins was observed in a number of cases but was probably less prone to occur with methyl-*bis*(β-chloroethyl)amine hydrochloride than with *tris*(β-chloroethyl) amine hydrochloride. The incidence of thrombophlebitis as well as of pain during administration was decreased by injecting the nitrogen mustard solutions into the lumen of the rubber tubing while an intravenous infusion was flowing rather than into the vein by the direct syringe technic.

Nausea and vomiting were commonly observed after nitrogen mustard therapy, occurring within one to three hours after the injection and subsiding within a few hours. Nausea and vomiting were more apt to follow the first one or two injections in a course. Anorexia was infrequent and transient. Diarrhea was not observed in the patients of this series. Preliminary sedation with a barbiturate and the withholding of food (usually an overnight fast) prior to treatment tended to decrease untoward gastrointestinal symptoms. Febrile response to the therapy was not observed, but 1 patient had a chill shortly after treatment.

Late Systemic Effects.—The toxic effects of the halogenated alkyl amines on the blood and blood-forming organs have been carefully investigated in a variety of laboratory animals and in man. As numerous reports [1] are available in this field, it is necessary here only to summarize briefly what may occur during the therapeutic administration of these agents to man. The toxic effects of the β-chloroethylamine hydrochlorides on the hemopoietic tissues are in some respects merely extensions of the therapeutic effects. Although the chemicals seem to have a selective action on primitive cells and abnormal hemopoiesis, in sufficiently large doses the compounds affect all elements of the bone marrow, producing a decided leukopenia and thrombocytopenia and a moderate normochromic anemia. The objective in treatment against lymphomas and leukemia is to keep the dosage within the relatively narrow range of safety, so that maximal salutary clinical results can be obtained with a minimal untoward effect on the formed elements of the blood. The dosage schedules employed were specifically designed to accomplish this end. Nevertheless the leukotoxic action was usually evident. Lymphopenia and neutropenia of moderate degree occurred in most patients within the first week or two after a course of therapy, the lymphopenia sometimes appearing first. Mild reduction in the volume of packed erythrocytes was also observed in a number of patients and reached its peak in about three weeks; but frequently a preexisting anemia improved as a result of the beneficial effect of the nitrogen mustards, for example on myelophthisic anemia.

Detailed and repeated laboratory tests (urine, renal function, liver function, blood chemistry and others) failed to indicate any abnormal or untoward responses to the β-chloroethylamines in the doses employed, other than those previously enumerated.

In the 2 patients who were the first ever treated with *tris*(β-chloroethyl)amine hydrochloride, before optimal dosages could be determined for man, toxic hemopoietic effects were observed in the following sequence: the

complete disappearance of circulating lymphocytes, definite leukopenia and granulocytopenia (without mucosal lesions or other signs or symptoms of agranulocytosis except fever), thrombocytopenia of severe grade with purpura, and moderate anemia. Repeated blood transfusions were necessary, and the return of blood values to pretreatment levels required several weeks.

CLINICAL STATUS OF THE NITROGEN MUSTARDS

The halogenated alkyl amines would appear to be able to produce the same qualitative clinical results in Hodgkin's disease, lymphosarcoma and leukemia as does radiation therapy. In general these chemicals have the same "total" effect on lymphoid cells and those of the bone marrow and on the hyperplasia of the reticulum cells in Hodgkin's disease as does radiation therapy. Whether they have any imperative advantages over the best possible type of radiation therapy remains to be determined. It is fairly certain that the β-chloroethylamines are capable of producing salutary effects and even therapeutic remissions in patients who have become resistant to roentgen irradiation. However, the term "resistant to roentgen irradiation" is variously employed by radiologists, and it was not always ascertainable in the cases herein reported whether the term was truly applicable in the sense that the tumor cells would no longer respond to properly applied radiation.

In 4 patients there was evidence that sensitivity of the tumor tissue to radiation therapy returned after a course of nitrogen mustard therapy. This is not too unexpected, as new generations of tumor cells are involved. In 1 patient who was unresponsive either to radiation or to nitrogen mustard therapy a favorable response was obtained when the two agents were used simultaneously.

Whether the β-chloroethylamines can or should either replace or supplement radiation therapy in any or all categories of cases in which they have been found effective cannot be stated at this time, particularly because the majority of the 67 patients concerned in the report were in the terminal stages of their disease. Nor can it yet be stated whether halogenated alkyl amine treatment may be expected to yield remissions as complete or as lasting as does radiation therapy. The question as to whether the chemicals should be used as agents of choice in "fresh" (i. e. previously untreated) cases also remains unsettled, but there is sufficient evidence to warrant investigation of this problem. Obviously there is as yet no adequate backlog of clinical experience with the nitrogen mustards, such as exists for radiation therapy, to serve as a basis for judging their value in comparison with other therapeutic measures.

As a rule, local and immediate systemic reactions would appear to be less severe after chemotherapy with the β-chloroethylamines than after irradiation, and dermatitis due to the latter is avoided. Certainly therapy should prove to be less expensive, particularly in cases in which ambulatory treatment schedules would be feasible. No costly equipment is required. It must be emphasized, however, that the margin of safety in the use of the nitrogen mustards is quite narrow. The maximal tolerated dose (that which does not cause harmful hemopoietic effects) is usually not much larger than the optimal therapeutic dose. Considerable care must therefore be exercised in the matter of dosage, and repeated examination of the blood is mandatory in all cases as a guide to subsequent therapy.

The answers to numerous other questions which occur to investigator and reader alike cannot even be approximated at present. For example, optimal dosage schedules remain to be determined both for initial therapy and for prophylactic treatment during remissions. Various combinations and schedules of two or more agents (radiation, halogenated alkyl amines, radioactive phosphorus, arsenicals and the like) may prove superior to any one agent alone. The indications and contraindications for the use of nitrogen mustards cannot be stated definitively. Although immediate but transitory side effects may be more prominent with *tris*(β-chloroethyl)amine than with methyl-*bis*(β-chloroethyl)amine, further comparison of the clinical efficacy of these two agents is not as yet possible. Numerous congeners of the two halogenated alkyl amines employed in this study are known, and a number of them are available. It is possible that certain of these congeners may be more selective and potent in action and less toxic than the β-chloroethylamines employed up to the present. Certainly the subject is deserving of investigation.

Encouraging clinical results, sometimes dramatic, have been obtained particularly in Hodgkin's disease and lymphosarcoma and occasionally in chronic leukemia. It is not understood why some patients respond and others do not. Varied results have been seen in acute and subacute leukemia. Giant follicular lymphoma (1 case) did not respond to therapy nor did a small group of miscellaneous disorders including melanosarcoma and reticuloendotheliosis. Like roentgen irradiation, the β-chloroethylamines do not constitute a cure but only offer symptomatic palliative therapy. In our opinion the use of these agents would seem to represent a definite but limited advance in the management of lymphomas and leukemias, though perhaps the clinical implications are less impressive than the heuristic.

COMMENT

This brief preliminary communication presents the clinical results obtained for 67 patients treated with the nitrogen mustards (halogenated alkyl amine hydrochlorides) for Hodgkin's disease, lymphosarcoma, leukemia and certain related and miscellaneous diseases. Complete reports including pathologic observations and detailed hematologic data will be submitted later.

Salutary results have been obtained particularly in Hodgkin's disease, lymphosarcoma and chronic leukemia. Indeed, in the first two disorders dramatic improvement has been observed. However, some patients fail to benefit from β-chloroethylamine therapy, and the cause of this failure is not known. Varied responses have been observed in acute and subacute leukemias. Diseases other than those of the blood-forming organs would not seem at present to constitute indications for the use of the nitrogen mustards.

In an impressive proportion of terminal and so-called radiation resistant cases, especially of Hodgkin's disease and lymphosarcoma, the β-chloroethylamines have produced clinical remissions lasting from weeks to months. There is evidence to suggest that responsiveness to radiation therapy may occasionally be restored after a course of nitrogen mustard therapy.

The margin of safety in the use of these chemicals is narrow, necessitating the exercise of considerable caution. The blood picture must be carefully followed at frequent intervals as a guide to subsequent dosage.

Immediate local or systemic side effects (pain on injection, thrombophlebitis of injected veins, nausea and vomiting, malaise, anorexia and headache) are relatively inconsequential and can sometimes be avoided or mitigated by careful technic. More serious late toxic effects are concerned with the blood-forming organs (leukopenia, granulocytopenia, thrombocytopenia, anemia) and can be largely avoided by adherence to safe dosage schedules.

Optimal dosage schedules—as well as possible combinations of this treatment with radiation or other agents—for initial, continuation or interim prophylactic therapy remain to be determined. It is not known whether the β-chloroethylamines used in this study represent the best compounds of their chemical group.

Although indications and contraindications for the use of the nitrogen mustards remain to be established definitively, it is felt that these agents are deserving of further clinical trial in Hodgkin's disease, lymphosarcoma and leukemia. Like radiation, they do not cure.

Chemicals discovered to be therapeutically active in neoplastic disease deserve close study by clinicians, experimental pathologists, enzymologists and others interested in cancer and in cellular biology. From this point of view the heuristic aspects of the actions of the β-choloroethylamines here reported may eventually prove of greater importance than the clinical results obtained to date.

RECURRENT HIATUS HERNIA

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It is a frequent observation that symptoms and the roentgenologic findings of hiatus esophageal hernia appear and disappear over varying periods of time and in response to certain conditions. Several years ago von Bergmann [1] wrote of "free hiatus hernia," and Hurst [2] of "recurrent hiatus hernia," but neither attracted the attention which their communications warranted. As Levy [3] stated, "We have observed, not infrequently, the presence of a hernia fluoroscopically and also demonstrated it upon a film, only to find it impossible to locate any hernia at another examination." Any program for the management of this condition demands some consideration of why such a herniation should occur and under what conditions it should appear and disappear.

OBSERVATIONS FROM THE LITERATURE

It would seem improbable that any congenital shortening of the esophagus could play a large part in the production of a condition which is infrequent before the age of 40, and in which the average age of onset is 55. Akerlund's [4] original article figures several patients with a redundant esophagus. This is a frequent observation in the obese, or when the hernia is consequent on other sources of increased intra-abdominal pressure. Cases in which there is a congenitally short esophagus and cases of thoracic stomach certainly occur, but they are not relatively frequent. Cases due to a shortening of the esophagus as a result of inflammatory changes are infrequent.

It is probable that most cases of hiatus hernia of the stomach begin as the free or recurrent variety. They may continue to be recurrent, or they may become fixed because of inflammatory changes or other secondary anatomic conditions or because of a continuation of the factors which originally caused their appearance.

Hiatus hernia is not at all an infrequent condition. Just how frequent it is, we do not know. Root and Pritchett [5] found hiatus hernia in 1.3 per cent of all patients examined. Weintraub and Tuggle [6] quoted Rude as observing an incidence of 2.4 per cent in an unselected series of patients. Knothe,[7] quoted by Hurst,[2] found an incidence of 4.5 per cent in symptomless controls. Schatzke, also quoted by Hurst,[2] demonstrated such hernias in 70 per cent of patients over 60 years of age. As Hurst commented, however, this high frequency was probably due in large part to his technic, which greatly increased the intra-abdominal pressure. Many patients may not have had such a hernia either before or since.

Even though the tissues at the hiatal orifice are normally lax and permit a certain amount of play of the esophagus, it appears certain that some extensive deviation from normal must precede the occurrence of a hiatus hernia. It may be that in some patients there is a congenital deficiency of the tissue at the hiatal orifice which may predispose to a herniation. Hurst [2] and others have suggested that, because of the age of incidence, there may be senile changes in the tissues which result in relaxation. The large incidence in hiatus hernia in patients past the age of 60, as shown by Schatzke, would support this belief. Frequent episodes of increased intra-abdominal pressure due to coughing or retching, or emesis, could possibly tear and stretch the tissues, as would the constant effect of increased intra-abdominal pressure due to obesity or pregnancy, to abdominal tumor or to ascites. An increase in intra-abdominal pressure caused by trauma might also initiate a hernia.

Granted some relaxation of the tissue about the hiatal orifice, it is easy to see why an esophageal hiatus hernia could occur in cases of increased intra-abdominal pressure due to obesity or other causes, especially in patients with a firm and muscular abdominal wall. Rigler and Eneboe [8] found that 18 per cent of 195 pregnant women showed a hiatus hernia on roentgenologic examination. In 3 of 10 of these women who were examined again post partum a hernia was still present.

Decreased intrathoracic pressure may be a causative factor, as is shown when the hernia is demonstrated fluoroscopically with a deep inspiration. In the experimental animal we found it difficult to produce a hernia with the chest closed and the abdomen open. Just how important intrathoracic pressure is clinically is doubtful. The deep inspiration in constant coughing might be a factor, as well as the increased intra-abdominal

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