NITROGEN MUSTARD THERAPY IN HODGKIN'S DISEASE

Analysis of Fifty Consecutive Cases

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INTRODUCTION

MUSTARD gas was first discovered by Ritchie in 1854 and prepared for manufacture by Meyer in 1886. It was first used as a war gas by the Germans at Ypres in the spring of 1915. Five hundred deaths and 14,276 casualties resulted from this initial attack. By the end of the war, there was a total of 400,000 casualties from mustard gas poisoning. The clinical course of these victims was described by Marshall, Mandell and Gibson and others. Pappenheimer and Vance, Warthin and Weller, Lynch et al. studied the effects of mustard gas upon experimental animals. Krumbhaar and Krumbhaar reported upon the hematologic complications.

With the advent of World War II, the Chemical Warfare Service of the United States Army undertook a systematic study of the mustard gases as potential offensive agents. In 1940, these chemicals were submitted, among others, to Drs. L. Goodman and A. Gilman, then at the Yale Medical School, for pharmacologic evaluation. During the course of their investigations they found that following the parenteral administration of an aqueous solution of nitrogen mustard in normal rats, there developed a marked lymphocytopenia together with some degree of anemia and thrombocytopenia. Dr. Thomas Dougherty of the Yale Department of Anatomy studied the effects of the chemical in the spontaneous leukemia and lymphosarcoma of rats. In a number of cases, a marked reduction in the size of abnormal tissues took place.

The possibility then suggested itself that nitrogen mustard might be of some value in the treatment of the leukemias and lymphomata of man. The first patient, a terminal case of lymphosarcoma, was treated at the New Haven Hospital in August 1941 with a dramatic regression of involved glands. One of us (W. D.) was requested to examine the experimental and clinical data obtained in these preliminary studies. Further trial with other patients seemed desirable and a supply of the chemical was given to us for this purpose.

After an initial period terminating with the close of the war, nitrogen mustard was distributed under the auspices of the National Research Council to observers in various parts of the country. Such a cooperative program has made possible a rapid and thorough clinical evaluation of the nitrogen mustards. The historical background, as well as the chemical, pharmacologic, toxicologic, and experi-
mental aspects have been reviewed by Gilman and Philips and the initial clinical results were described by Jacobson and Goodman et al. Favorable results have been reported in Hodgkin’s disease, lymphosarcoma, leukemia, polycythemia vera, mycosis fungoides and Boeck’s sarcoid. The general results obtained by 120 cooperating physicians are currently being analyzed by Dr. David A. Karnofsky at the Memorial Hospital in New York. Tentative detailed analyses have already been submitted for review. Nitrogen mustard has been found to be ineffective in carcinomata (except carcinoma of the lung), Ewing’s sarcoma, melanosarcoma and neuroblastoma. The general results obtained have recently been summarized.

Our work with HN2 was begun in 1942. We were early impressed with its favorable effects in Hodgkin’s disease and in certain cases of lymphosarcoma, although our results with leukemia were disappointing. As our studies continued,

\[
\begin{align*}
&\text{Sulfur Mustard} \\
&\text{HN2} \\
&\text{HN3}
\end{align*}
\]

The chemical formulae of the sulfur and nitrogen mustards are shown in Figure 1. Dichloroethyl sulfide is the formula for mustard gas. The most widely used nitrogen mustard is methyl bis (B-chloroethyl) amine, subsequently abbreviated as HN2. In tris (B-chloroethyl) amine, or HN3, the methyl group is replaced by a third chloroethyl group. The sulfur mustards are soluble only in oils whereas the nitrogen mustards are readily soluble in water.

In aqueous solutions, the nitrogen mustards undergo “intramolecular cyclization” (figure 2). Gilman and Philips have shown that the imino ring possesses an unusual reactivity. It reacts with a great variety of biologically important
groups, i.e., alpha amino, sulfhydryl, phenolic, carboxyl, imidazole, imino, inorganic phosphates, chick pepsin peptodase, choline oxidase, etc. In the presence of chloride ion, the reaction tends to reverse itself with reformation of the parent amine. This probably occurs in the extracellular fluids where the concentration of chloride ion is high. Entrance of the parent amine into the cell where there is little, if any, chloride ion to compete with water, results in a rapid transformation with intramolecular cyclization and alkylation of labile groups. The speed of this reaction was demonstrated by Karnofsky et al. By occluding the circulation to the femoral bone marrow and the small intestine for periods ranging from 2 to 5 minutes, these organs were completely protected from the generalized leukotoxic action of the nitrogen mustards.

\[
\begin{align*}
\text{CH}_3\text{N} & \quad \text{CH}_2\text{OH} \\
\text{CH}_2\text{Cl} & \quad \text{OH} \\
\text{CH}_3\text{N} & \quad \text{CH}_2\text{Cl} \\
\text{CH}_2\text{OH} & \quad \text{OH}
\end{align*}
\]

**Fig. 2.** Intramolecular Cyclic Transformations of Methyl Bis (8 Chloroethyl) Amine

The distribution of radioactive sulfur mustard given intravenously to rabbits was studied by Boursnell et al. The concentration of sulfur mustard in the plasma fell rapidly within a period of four hours while the concentration within the red cell layer remained relatively constant. Seven per cent of the injected sulfur mustard was excreted into the bile in twenty minutes and 50 per cent was excreted within one hour. The amount of radioactive sulfur fixed to the bone-marrow appeared to be of lesser magnitude than that fixed to other organs. However, the quantity per gram of total nitrogen was of the same order.

Friedenwald and Buschke studied the effect of the nitrogen mustards upon corneal epithelium. Cells which were exposed during the active phase of mitosis were unaffected by moderate concentrations of the chemical and went on to complete their division. With continued exposure, however, all mitotic figures eventually disappeared. The resting stage of the mitotic cycle was the most sensitive period. Higher concentrations produced fragmentation of nuclei and abnormal chromosomal patterns which were transmissible through succeeding generations.

Various histologic effects of the nitrogen mustards in experimental animals will be discussed below as related to similar effects noted in cases to be reported.
The dramatic though short-lived effects of the nitrogen mustards in the therapy of Hodgkin's disease were noted early in the course of clinical investigations with the chemical. Jacobson5 reported the occurrence of remissions in 94 per cent of 120 courses administered to 29 cases. There were 8 failures, 3 of which were terminal and 2 radioresistant. One case had a temporary remission of fever for only three weeks. Four radioresistant cases responded well. Remissions lasted up to ten months.


Wintrobe and Huguley16 obtained good improvement in 17 and fair improvement in 5 of 32 treated cases. Fever responded dramatically in almost all cases. Improved well-being and appetite were noted in most cases. Remissions lasted from one to twenty-six months. The average duration of remissions was three months.

Zanes et al.12 noted that remissions occurred in three types of patients with Hodgkin's disease: (1) patients who were radiosensitive or who had had no previous therapy; (2) patients with severe constitutional symptomatology; (3) radioresistant cases. Patients in the last group were occasionally resensitized to x-ray after a course of nitrogen mustard. Remissions averaged 2.8 months in length.

ApThomas and Collumbine13 reported 21 treated cases. All improved following their first course. Improvement was noted in 12 of 13 cases who received a second course, and in 2 of 4 cases who received a third course of nitrogen mustard. The response was usually more rapid than previously noted with roentgen therapy. Remissions lasted from two to six months.

Alpert and Peterson11 reported 8 previously untreated cases, 6 of whom had complete or partial remissions lasting three weeks to four months following HN2 therapy. Heightened responses were obtained by the co-administration of x-ray therapy.

Talbott15 obtained no response in 2 of 10 treated cases of Hodgkin's disease. Hettig16 reported excellent remissions in 2, a partial remission in 1, and slight or no remission in 3 of 6 treated cases. Wilkinson and Fletcher17 obtained satisfactory remissions in 3 of 4 previously untreated cases lasting up to 17 weeks. Sherry17 reported remissions lasting from 44 days to 11 months in six cases of Hodgkin's disease.

Taffe19 reported partial remissions in six cases lasting up to six months.

**Materials and Methods**

Methyl bis (8 chloroethyl) amine* (HN2) was used in the treatment of 50 cases of Hodgkin's disease at the J. H. Pratt Diagnostic Hospital, Boston Dispensary, and West Roxbury Veterans Hospital. The diagnosis of Hodgkin's disease was made in almost every instance by biopsy of a suitable enlarged pe-

* Methyl Bis (8 chloroethyl) amine was supplied in generous amounts by the Merck Chemical Company through the cooperation of the National Research Council.
NITROGEN MUSTARD THERAPY

In 1 cases with intraspinal involvement, the diagnosis was made in the course of laminectomy and examination of excised tissue. No attempt was made in the analysis of this series of cases to differentiate sharply between various types of disease. We recognize that the growth potentiality of Hodgkin's disease, as of all neoplastic disease, varies considerably from case to case, and sometimes in the same case. Our results in the most rapidly growing form of the disease, known as Hodgkin's sarcoma, were often as striking as with the least malignant types. With study of a larger series of cases in the future, it may be possible to analyze more accurately the results of treatment in relation to the histologic picture. In any event, the histologic picture of removed tissue was characteristic of the condition known as Hodgkin's disease and showed the histologic features of reticulum cell hyperplasia, increased reticulum, the presence of Reed-Sternberg giant cells, and a variable degree of necrosis, eosinophilia and polymorphonuclear infiltration. The cases reported in this paper represent patients consecutively treated between December 1943 and December 1947. There were 29 males and 21 females.

Fifteen of the 29 males were treated at the West Roxbury Veterans Hospital. The ages of the patients ranged from 19 to 62 years with a majority of cases below the age of 35. Initially the administration of nitrogen mustard was restricted to radioresistant or terminal cases. In 1946-1947, however, its use was extended to a few radiosensitive and previously untreated cases.

The chemical was packaged in 20 cc. ampules, each containing 10 mg. Initially this was dissolved in 20 cc. of saline and the required dose injected directly into the vein. Because of the frequent occurrence of venous thromboses it became our practice early to inject the material into the rubber tubing of a freely flowing saline infusion. A course of therapy consisted of four to six injections of nitrogen mustard, administered on successive or alternate days. An initial dose of 4 to 5 mg. was given on the first day. If this amount was well tolerated, succeeding doses were increased in 1 mg. amounts.

On each visit the presenting symptoms were recorded, the patient examined, and the blood counts obtained. These usually included white blood counts, hemoglobin and reticulocyte levels, platelet counts and a differential count of the white cell cells. Hemoglobin determinations were made with the Cenco hemoglobinometer. Reticulocyte and platelet counts were performed by the method of Dameshek. Ster nal bone-marrow punctures were performed prior to therapy in most cases and whenever possible at various intervals following HN2 administration. The spinous process was often utilized for marrow aspirations in cases studied serially. Serial lymph node aspirations were performed whenever feasible.

RESULTS

Immediate Reactions

Table 1 lists the immediate reactions following the use of 289 doses of HN2. Nausea and vomiting occurred in 93.2 per cent of all cases. This usually began one to three hours after the injection and lasted for two to four hours. The cause of the nausea and vomiting has not been elucidated. It has been attributed to central medullary stimulation and to hemorrhage and necrosis of the gastrointestinal

| Table 1.—Immediate Reactions Following 289 Doses of HN2 |
|---------------------------------|---|
| Nausea and vomiting              | 93.2% |
| Chills                           | 12.4% |
| Fever                           | 6.8%  |
| Headache                        | 1.7%  |
| Thrombosis                      | 1.0%  |
| Cyanosis                        | 0.7%  |
| Dyspnea                         | 0.7%  |
| Diarrhea                        | 0.3%  |
| No reaction                     | 6.8%  |
tract. The marked excretion of the chemical into the bile and subsequently into the second portion of the duodenum may, by causing irritation, be an important factor in the regularity of the occurrence of nausea and vomiting. However, Karnofsky et al. found that the gastrointestinal lesions occurred even when the bile duct was clamped.

There were no reactions in 6.8 per cent of cases. Four of this group responded well making it unlikely that the injected material was inactive. Various attempts were made to reduce the severity of the nausea and vomiting by the co-administration of pyridoxine, morphine and barbiturates.* Pyridoxine was discontinued because of its possible inactivation by nitrogen mustard. Barbiturates had little value. Morphine appeared to allay much of the apprehension incident to the severe nausea and vomiting. It has been our practice to administer one-eighth grain of morphine sulphate subcutaneously in all hospital cases just before HN₂ administration. Shaking chills were observed in 12.4 per cent of cases. These usually occurred one-half to one hour after HN₂ administration and prior to the onset of nausea and vomiting. Chills recurred with successive doses in 7 cases. Morphine tended to diminish such recurrences. Fever either followed the chills or occurred independently in 6.8 per cent of cases. The exact cause for the pyrogenic reactions is unclear. In rabbits, Boursnel, et al. demonstrated an alteration of serum proteins by mustard gas. These proteins possess different immunologic properties. The presence of such foreign proteins may be etiologic in the occurrence of chills and fever.

Headache was a prominent complaint in two patients who had developed a striking aversion to nitrogen mustard. Dyspnea and cyanosis occurred rarely and generally responded well to sedation.

When HN₂ was injected directly into the vein, thrombosis occurred commonly. The incidence of thrombosis disappeared almost completely with the administration of the chemical into the rubber tubing of a rapidly flowing infusion. Two patients who received tris (B-chloroethyl) amine developed thromboses of all injected veins, even when the material was injected into the rubber tubing.

In 4 cases, HN₂ was administered prophylactically in the form of weekly and biweekly injections in the attempt to maintain a remission induced by a course of medication. The reactions were of such severity that this form of therapy had to be discontinued. The same patients, when treated during an active phase of their disease had much milder reactions. It is possible that the actively proliferating granulomatous tissue present in relapse may selectively absorb the nitrogen mustard. During periods of remissions, however, large quantities of unabsorbed chemical may be available for the production of side reactions.

Type and Duration of Response

During the first three years of these studies only terminal or radioresistant cases were subjected to therapeutic trial. The results in this group are not as favorable

* More recently a solution of procaine has been given intravenously immediately following HN₂ administration.
NITROGEN MUSTARD THERAPY

as those obtained in less advanced cases treated during the past year. For purposes of analysis, all cases are however grouped together.

Figure 3 shows the type of response obtained in the first fifty cases of Hodgkin’s disease treated with $10^2$ courses of HN$_2$. In 79.4 per cent a complete or partial response to therapy occurred. In 20.6 per cent, there was no response.

The duration of the response ranged from 17 to 331 days* (figure 4). Remissions lasting less than fifty days were noted in 41.7 per cent; 35.2 per cent developed good responses lasting from 50 to 331 days.

![Figure 3](image_url)

**Fig. 3.** Type of response obtained following $10^2$ courses of HN$_2$ in 50 cases of Hodgkin’s disease

Twenty-three patients received a single course of HN$_2$, 11 patients received 2 courses; 9, 3 courses; 4, 4 courses; 2, 5 courses; and 1, 8 courses of HN$_2$. The general results obtained with successive courses of HN$_2$ are roughly comparable to the composite results for all courses, with the same proportion of successes and failures. The duration of the response obtained in sixteen patients who received multiple courses with varying dosage schedules was approximately proportional to the total dose administered.

Thirty-one patients in this series were regarded as having become resistant to x-ray therapy and in 13 of these, all of whom appeared to be running a progressively downhill course, good remissions following therapy were obtained. Some of the most spectacular results were seen in cases that were virtually moribund on

* The results as reported in this paper are based on findings ending December 15, 1947.
admission (cases 1, 23 and 28). There can be no doubt that many patients of this group have had a moderate prolongation of their life span, as well as a more comfortable existence after having become completely resistant to further x-ray therapy. Nitrogen mustard was particularly useful in 5 cases with severe x-ray dermatitis.

Nine patients failed to show any response following the initial and subsequent courses of nitrogen mustard therapy.

In 7 patients, roentgen therapy was given just before the administration of nitrogen mustard. In 4 of this group (cases 10, 21, 28 and 40), there was definite prolongation of the length of the remission. In 8 cases, x-ray therapy was given following the administration of nitrogen mustard. In 3 of these cases residual lymphoid organs regressed with unusual rapidity when x-ray therapy was given.

Four cases received HN2 as their sole initial therapy. The remissions lasted from 36 to 120 days in 3 cases. Case 9 received three courses of nitrogen mustard which resulted in partial remissions lasting 36, 30 and 51 days respectively. The latter course had been combined with roentgen therapy. Case 49, who developed a severe hemorrhagic complication due to thrombocytopenia has nevertheless had an excellent remission which had continued to the time of this writing.

Case 31, received combined HN2-reontgen therapy following which he had a complete remission lasting 110 days.

The number of patients given HN2 as the first therapeutic procedure is too small to permit statistical evaluation. It appears, however, that the remissions obtained are of much shorter duration than is usually the case following roentgen therapy.

Similar results were reported by Alpert and Peterson.14 The remissions appear to be definitely longer if combined HN2 and x-ray therapy is administered.
NITROGEN MUSTARD THERAPY

EFFECTS OF NITROGEN MUSTARD THERAPY ON CLINICAL MANIFESTATIONS

Systemic Manifestations

A majority of the patients in this series had the characteristic constitutional symptomatology of severe, long standing Hodgkin's disease, i.e., malaise, ease

<table>
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<tr>
<th>Signs and Symptoms</th>
<th>Number of Administra-</th>
<th>Percentage Completely</th>
<th>Percentage Partially</th>
<th>Percentage Unrelieved</th>
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<td>A. Constitutional symptoms</td>
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<td>Fatigability</td>
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<td>31.1</td>
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<td>Incontinence</td>
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of fatigability, anorexia, fever, nightsweats, pruritus and chills. Fatigability and anorexia were relieved (completely or partially) in 82.4 and 87.1 per cent of cases respectively (table 2.)

Following a course of nitrogen mustard therapy and after the immediate reaction had subsided, there usually occurred a marked upsurge in vitality and well-
being. Those patients who had previously received roentgen therapy usually commented upon the greater subjective improvement which followed the administration of nitrogen mustard.

Seven patients were treated with nitrogen mustard shortly after the recognition of their disease. In 2 cases (2.1 and 40) this was administered after a partially effective or ineffectual course of roentgen therapy. Single courses of HN2 resulted in excellent remissions lasting respectively 331 and 169 days and continuing to the time of this writing. Case 2.1 illustrates a striking response in constitutional symptoms and a prolonged remission.

CASE 2.1 (FIGURE 5)

P. D. C., a 36 year old white male, began to notice easy fatigability, weakness, and marked weight loss in 1944. In January 1946 weakness and fatigability became much more pronounced. In September 1946 he was found to have continuous fever. A gnawing sensation in the mid abdomen was relieved by food and medication. He was admitted in October 1946 to the West Roxbury Veterans Hospital.

Physical Examination: Temperature 99.4 F. The patient was a well developed, rather well nourished white male. His voice was hoarse. The eyes were slightly protuberant. The right lobe of the thyroid was more readily palpable than the left. The chest was clear and resonant throughout. A grade II systolic murmur was heard just to the left of the sternum and in the fourth interspace. The heart was otherwise negative. The liver and spleen were not felt. There were bean-sized axillary (right) lymph nodes.

Laboratory Data: Blood counts: leukocytes, 18,800; erythrocytes 3,600,000; hemoglobin 11.1 Gm.; differential: polymorphonuclear neutrophiles, 80 per cent; monocytes 5 per cent; lymphocytes, 15 per cent. The urine was negative. Blood sedimentation rate was 55 mm. per hour, Mazzini test was negative. Sputum was negative for tubercle bacilli. Basal metabolic rate was plus 34.5 per cent. A roentgenogram of the chest showed evidence of mediastinal lymphadenopathy. Biopsy of an enlarged axillary node revealed the presence of Hodgkin’s granuloma.

Course. The patient ran a febrile course with temperature elevations up to 101.4 F. Beginning October 31, 1946 the patient was given 18 roentgen treatments over the anterior and posterior chest and to the right axilla. However, he continued to run a low grade fever and to lose weight. Several right axillary nodes were still palpable. Repeat roentgenograms of the chest showed a complete reduction in the size of the right upper mediastinal mass. A flat plate of the abdomen at this time revealed an enlarged spleen, extending down to about two inches above the iliac crest. On January 4, 1947 a course of nitrogen mustard therapy was begun consisting of 4, 5, 6 and 7 mg. doses administered on successive days. Nausea and vomiting occurred two hours after each administration and lasted from one-half hour to three hours. The fever subsided promptly. Shortly after the nitrogen mustard therapy there followed a reduction in the white blood count from 18,000 to 6600.

The patient developed a marked improvement in his appetite and gained about 60 pounds in weight. He had a remarkable upsurge in strength and sense of well-being. Lymphadenopathy disappeared entirely and the spleen regressed completely. He was then observed at regular intervals in the outpatient department and continued in an excellent state of remission to the time of writing, almost a year later.

Fever, which was a presenting complaint in 30 cases, was completely relieved in 58.7 per cent following HN2 treatment (figure 6). HN2 appeared to be less effective in 13 terminal patients who showed the typical Pel-Ebstein type of relapsing fever. Two of these cases had responded well to a previous course of therapy. Cases 19 and 24 had associated infections, i.e., a chronically draining bronchopleural fistula, and an ascending urinary tract infection respectively. The infections were not affected by the HN2 treatment.

Severe night sweats were relieved in 84 per cent of cases. Of 4 cases, in which night
sweats did not respond to HN$_2$ therapy, 3 were terminal, and case 19 noted above had a chronic infectious process.

Pruritus was present in 10 cases prior to nitrogen mustard therapy. Improvement followed in 73.3 per cent. The pruritus was of such intensity in case 38 that the patient forcefully removed all toenails and produced deep excoriations of the skin.

Pruritus was present in 10 cases prior to nitrogen mustard therapy. Improvement followed in 73.3 per cent. The pruritus was of such intensity in case 38 that the patient forcefully removed all toenails and produced deep excoriations of the skin.

Roentgen therapy could no longer be administered because of severe x-ray dermatitis. Considerable relief and healing of the excoriations followed each of two courses. Four terminal cases showed no response.

Chills were present in 5 patients, 4 of whom responded well to therapy. In one case there was a progressively downhill course.

**Lymphoid Involvement**

Lymphadenopathy. Regression of enlarged glands occurred in 70.2 per cent of the cases. In a few patients this was noted as early as twelve hours after the injection of the first dose of nitrogen mustard. Rarely, slight initial enlargement preceded subsequent regression of glands. Twenty-eight of the 44 patients with lymphadenopathy were referred to us for nitrogen mustard therapy because of their radio-
resistant state; of this group, 60.3 per cent showed a complete or partial response. The following case is described in detail to illustrate the response obtained in a patient with a fluctuant supraclavicular mass and a superimposed severe radiodermatitis.

CASE 39

M. V., a 25-year-old white female noted the onset of left supraclavicular adenopathy in December 1945. A biopsy taken in March 1946 revealed the presence of Hodgkin's disease. Roentgen therapy was administered to the left supraclavicular, axillary, and mediastinal areas, with gradual improvement. Adenopathy recurred on October 1946 and continued to increase despite intensive roentgen therapy. The left supraclavicular mass became fluctuant and soon broke through the superimposed skin which showed evidence of a severe radiodermatitis. The roentgenologist referred her for nitrogen mustard therapy in May 1947.

Physical Examination: The patient showed pallor. She presented a large hard but superficially fluctuant left supraclavicular mass, 12 cm. in diameter, superimposed by a deeply pigmented area of skin (fig. 7a). There was a number of smaller cervical, right supraclavicular and left axillary glands. The spleen and liver were not enlarged.

Laboratory Data: Blood counts: Leukocytes, 12,050; erythrocytes, 3,650,000; hemoglobin, 11.0 Gm.; reticulocytes, 0.9 per cent; platelets, 785,500; differential count, polymorphonuclear neutrophiles, 57

FIG. 6.—EFFECT OF HN2 IN REDUCING FEVER IN 3 CASES OF SEVERE HODGKIN'S DISEASE
per cent; band forms, 17 per cent; monocytes, 8 per cent; lymphocytes, 13 per cent. Bone-marrow differential: polymorphonuclear neutrophils, 25.6 per cent; band forms, 14.2 per cent; metamyelocytes, 19.2 per cent; myelocytes, 15.8 per cent; promyelocytes, 1.2 per cent; myeloblasts, 0.5 per cent; reticulum cells, 0.1 per cent; plasma cells, 2.0 per cent; megakaryocytes, plentiful; erythrocytes:granulocyte ratio: 1:7. The urine was negative. The Hinton test was negative. The blood sedimentation rate was 72 mm. per hour. Roentgenograms of the chest showed left supraclavicular and mediastinal masses.

Course: The left supraclavicular mass was incised and drained. The patient was then started on a course of HN2 consisting of 5, 5, 6, 7 and 8 mg. administered on successive days. Each dose was followed by rather severe nausea and vomiting. The wound healed rapidly and all glandular adenopathy subsided completely, leaving only a small area of induration in the left supraclavicular region (fig. 7b). A repeat roentgenogram of the chest showed reduction in the size of the mediastinal and supraclavicular masses. The remission lasted approximately three months when supraclavicular and axillary adenopathy recurred. The patient received a second course of HN2 consisting of 5, 6, 7, and 8 mg. administered on alternate days beginning November 4, 1946. Three-quarters of an hour. Roentgenograms of the chest showed left supraclavicular and mediastinal masses.

Eight cases failed to show any regression of lymph nodes following HN2 therapy. Case 5 had had two previously successful remissions following HN2 and lasting 74 and 66 days respectively. Four patients showed no response to the initial course of the therapy.

Three patients with HN2 resistant glandular enlargements responded unusually well to roentgen therapy given shortly after administration of one course of HN2 therapy. Case 9 is described in detail; and case 14, is presented briefly.

CASE 9

V. K., a 15 year old white female, was first seen in September 1946. She presented a six month history of anorexia, weakness, fatigability, weight loss, fever, and cervical adenopathy. Biopsy of an enlarged gland revealed Hodgkin's disease, probably of the sarcoma type.

Physical Examination: The patient showed moderate pallor and marked weight loss. She had a right Horner's syndrome. There was generalized adenopathy. Supracardiac dullness was 8 cms. in diameter. The spleen was three finger's breadth below the left costal margin.

Laboratory Data: Leukocytes, 10,800; erythrocytes, 3,810,000; hemoglobin, 7.6 Gm.; reticulocytes, 0.3 per cent; platelets, 663,940; differential: polymorphonuclear neutrophiles, 79 per cent; band forms, 10 per cent; monocytes, 4 per cent; lymphocytes, 7 per cent. Bone marrow differential: polymorphonuclear neutrophiles, 21.5 per cent; band forms, 19.9 per cent; metamyelocytes, 11.0 per cent; myelocytes, 10.5 per cent; promyelocytes, 0.5 per cent; myeloblasts, 0.5 per cent; plasma cells, 0.3 per cent; reticulum cells, 0.3 per cent; reticulum cells, 2.0 per cent; megakaryocytes, plentiful; erythrocytes:granulocyte ratio: 1/3.

The urine was negative. The Hinton test was negative. Roentgenograms of the chest showed marked mediastinal widening (fig. 8a).

Course: The patient received 4 mg. of HN2 on September 23, 1946. Three-quarters of an hour later she became moderately dyspneic and cyanotic. This responded gradually to sedation. She received two additional doses consisting of 4 and 6 mg. on September 29 and 30 respectively. These were followed by the usual reactions of nausea and vomiting. A roentgenogram of the chest taken five days after the completion of nitrogen mustard therapy showed marked regression of the mediastinal mass. Further reduction was noted seven days later (fig. 8b). There was complete regression of all peripheral glands.

The patient had a remission which lasted 36 days. Following this she developed recurrent cervical adenopathy. A second course of HN2 consisting of 4, 5, 5, 6 and 6 mg. was administered on alternate days beginning November 4, 1946. Enlarged glands regressed completely. Thirty-three days later the patient noted the onset of anorexia, weight loss, left cervical and bilateral axillary glands and a walnut-sized parasternal mass in the second interspace on the right. The spleen descended one finger's breadth below the left costal margin. A third course of HN2 consisting of 4, 5, 6 and 7 mg. was administered on alternate days beginning January 6, 1946. A chill followed the second, third and fourth doses within
FIG. 7. RESPONSE OF RADIARESISTANT SUPRACLAVICULAR GLAND WITH SUPERIMPOSED BROKEN-DOWN PIGMENTED SKIN EXUDING SERO-PURULENT MATTER (CASE 39).
(a) PRIOR TO HN₂ THERAPY
(b) AFTER COMPLETION OF COURSE OF HN₂ THERAPY
Fig. 8. Response of Mediastinal Adenopathy Following HN2 Therapy (Case 9).

(a) Prior to First Course of Therapy.

Fig. 8.—(b) Same Patients Twelve Days after Completion of First Course of Therapy
one-half, three-quarters, and two hours respectively. The usual reactions of nausea and vomiting followed each dose. The patient had a marked upsurge in well being and gained five pounds in weight. Glandular adenopathies regressed approximately 25 per cent. Roentgen therapy was then administered to the parasternal and left supraclavicular areas (1200 r each). Rapid resolution of residual glands occurred. This remission lasted sixty-one days. Further nitrogen mustard was refused.

CASE 14

This patient, a long standing example of Hodgkin’s disease with the presenting complaint of severe constipation, showed a very large mass in the left lower quadrant, of the abdomen dipping into the pelvis. A course of nitrogen mustard therapy was completely ineffectual. Roentgen therapy was then given to both the left lower quadrant (600 r) and the right lower quadrant (400 r) and was followed by rapid resolution of the pelvic masses and a dramatic relief of constipation.

Splenomegaly. Seventy-one and seven-tenths per cent of the cases with splenomegaly showed complete or partial regression of the enlarged spleen following HN2 therapy. This corresponds roughly to the results obtained with lymphadenopathies. The striking affinity of nitrogen mustard for the various lymphoid organs was noted by Pappenheimer and Vance3 and by Graef et al.35 Atrophy of lymph nodes, spleen and thymus has been demonstrated in normal mice, rats, rabbits, dogs, chickens and pigeons following the administration of nitrogen mustard.

Edema. Edema due to pressure by enlarged lymph nodes or to lymphatic obstruction was present in 12 cases prior to the initiation of nitrogen mustard therapy. Two patients had edema of the lateral half of the breast, secondary to enlarged axillary nodes. Case 12 presented an orange-sized right axillary mass with edema of the lateral half of the right breast. A partial response followed the administration of 2.6 mg. of HN2. Roentgen therapy then brought about rapid and complete regression of the axillary glands as well as edema. Case 2 had very large axillary masses and edema of both breasts. A partial remission lasting one month was induced by the first course of nitrogen mustard. Two subsequent courses, however, were without effect.

Gross edema of the lower extremities was present in four patients.

CASE 30

W. J. O., a 44 year old white male was first seen in March 1947. Six years previously he had noted the presence of a large mass in the left inguinal region. A biopsy revealed Hodgkin’s disease. Intensive roentgen therapy induced a complete regression. Further roentgen therapy was administered as needed with recurrent glandular adenopathies. Increasing radioresistance was noted. Six months prior to admission the patient developed massive edema of the left lower extremity extending to the lumbar area. Roentgen therapy was initially effective in reducing the edema. Three months prior to admission the patient developed extreme edema of the right lower extremity and scrotum. Roentgen therapy was ineffectual.

Physical Examination: The patient had massive edema amounting to elephantiasis of both lower extremities and the scrotum. There was an x-ray dermatitis of the left inguinal, gluteal and lumbar areas. The liver was felt four fingers’ breadth below the right costal margin and the spleen three fingers’ breadth below the left costal margin.

Course: The patient received three daily injections of HN2. Within ten days the edema had completely subsided. The patient remained well for three weeks when he suddenly developed a severe pain in the left groin radiating to the hip and small of back. The edema of the left lower extremity recurred. Three days later, the patient had a sudden massive gastrointestinal hemorrhage. He rapidly lapsed into shock and died twelve hours later.
Postmortem: At autopsy there was a fistulous communication between the pelvis, the retroperitoneal lymph nodes and rectosigmoid. The descending colon contained much freshly coagulated blood. Both ureters were compressed by a large retroperitoneal mass producing bilateral hydronephroses and hydronephroses. There were large nodes in both inguinal regions with compression of the femoral artery and vein on the left.

In another patient (Case 23), massive ascites and marked edema of both lower extremities was present. The energetic use of paracentesis, transfusions, plasma, albumin and HN₂ therapy brought about a marked reduction of the edema and ascites and a well-defined remission.

Edema of the upper extremities was present in 2 cases. Case 8, with scar tissue in the left supraclavicular and axillary nodes, was treated with HN₂ which brought about an approximately 30 per cent reduction in the edema. Two subsequent courses were however, completely ineffectual.

Three patients had edema suggesting superior vena caval obstruction. These will be discussed below, under "mediastinal involvement."

As noted above, edema may be due to lymphatic or venous obstruction, pressure from enlarged glands, or by scar tissue. When due to enlarged glands, nitrogen mustard was found to be moderately effective. When due to scar tissue little or no effect was obtained. It is probable that HN₂ is far less productive of scar tissue than is roentgen therapy.

Mediastinal Involvement

Roentgen Changes: X-rays of the chest were performed routinely in all cases. Twenty-one cases showed radiologic evidence of pulmonary or mediastinal involvement. In 7, there was no associated symptomatology. The response of such asymptomatic mediastinal adenopathy to nitrogen mustard therapy is shown in figure 8.

Twelve patients had symptoms referable to their pulmonary pathology, i.e., cough, dyspnea, hoarseness and dysphagia. This group usually had extensive mediastinal involvement. Eleven cases had been previously declared radioresistant. The response to the HN₂ therapy was only moderately effective in this group. The following case illustrates a partial response to HN₂ therapy and a better response to combined HN₂ and roentgen therapy.

CASE 25 (FIGURE 9)

K. D., a 37 year old white housewife, was the first seen on February 3, 1947. Five and one-half years ago she noted the onset of right cervical adenopathy and upon roentgenographic examination of the chest was shown to have a mediastinal mass. A biopsy revealed the presence of Hodgkin's disease. Roentgen therapy was then administered to the cervical and mediastinal areas with prompt improvement. During the following three years the patient received five courses of roentgen therapy each of which induced a short remission. In March 1947 an episode of severe cough, chills, fever (103 F), dyspnea and fatigability developed.

Physical Examination: The patient had a marked radio-dermatitis over the anterior and posterior chest. No adenopathy could be made out. Suprachordal dullness was 17 cm. in diameter. Bronchial breath sounds were present over the left apex. The liver and spleen were not palpable.

Laboratory Data: Blood counts: leukocytes, 8,500; erythrocytes, 4,170,000; hemoglobin, 12.1 Gm.; reticulocytes 1.6 per cent; platelets 638,880; differential: polymorphonuclear neutrophiles 65 per cent; band forms 12 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent; monocytes, 6 per cent; lympho-
cytes, 14 per cent. The urine was negative. The Hinton test was negative. Roentgenograms of the chest showed extensive anterior mediastinal enlargement (fig. 9) and bilateral infiltration of the lung.

Course: The patient was started on a course of HN2 consisting of 4, 5, 6, and 7 mg. administered on alternate days beginning February 3, 1947. Shaking chills occurred two hours after the first, second and fourth injections. The usual reactions of nausea and vomiting followed. The patient experienced a marked reduction of cough and dyspnea, as well as a striking improvement in vitality. The remission lasted for about three weeks when in March 1947 she had another episode of fever (104°F) cough and dyspnea. A similar episode occurred one month later. A roentgenogram of the chest revealed a large mediastinal mass occupying almost the entire upper chest. A second course of HN2 was instituted on April 20, 1947 and consisted of daily injections of 6, 6, 7 and 8 mg. The usual reactions of nausea and vomiting occurred. The fever subsided gradually. Roentgen therapy to the mediastinum in a total dosage of 11,000

![Graph of HN2 therapy](image)

*Fig. 9.—Effects of Nitrogen Mustard in Patient with Massive Mediastinal Involvement Who Had Become Markedly Radiosensitive (Case 25).* A distinct, although temporary response took place with the use of HN2, but best effects were obtained when HN2 was given first and then followed by x-ray therapy.

A marked improvement again occurred with considerable relief of cough, dyspnea, and fatigability. Roentgenograms of the chest showed marked regression in the size of the mediastinal mass. A third course of HN2 was instituted on September 30, 1947 and consisted of daily injections of 5, 6, 7 and 8 mg. Roentgen therapy was also given through axillary portals, 450 r to the right axilla and 525 r to the left axilla. The patient showed an improvement in well being but no further change in the size of the mediastinal mass was noted.

There can be no question that combined HN2 and x-ray therapy was productive in this patient of more prolonged and effective remissions than HN2 alone. A symptomatic response occurred following the third course although no further roentgenographic change could be noted.

Cough. Cough was a presenting symptom in 13 cases. Complete or partial improvement followed nitrogen mustard therapy in 50 per cent of the cases. In the other half, no response occurred and the patients ran a progressively downhill course.

Dyspnea. Dyspnea was notable in 15 cases prior to therapy. Cases 28, 42, and 43
NITROGEN MUSTARD THERAPY

showed no mediastinal involvement but had extensive and generalized involvement with Hodgkin's disease. Case 23 had massive ascites. Cases 22 and 30 had a massive hydrothorax as well as ascites. The results obtained within this group were generally unsatisfactory (table 2).

Hoarseness and Dysphagia. All cases displaying these symptoms represented far advanced radioresistant cases. No improvement was noted following HN2 therapy.

Superior Vena Cava Syndrome. Two patients showed signs of superior vena cava obstruction. Case 11 developed puffiness of the eyelids, suffusion of the conjunctivae, and swelling of the cheek during his course of HN2. This gradually subsided as did the hilar adenopathy. Case 1 is described in detail (previously reported).

CASE I

L. W., a 33 year old housewife, was first seen in 1941 because of axillary adenopathy. Her father had died of Hodgkin's disease and her mother of polycythemia vera. A biopsy revealed the presence of Hodgkin's disease. In rapid succession nodes appeared in the axillae, neck and mediastinum. Roentgen therapy was given with excellent results initially, subsequent results were poor. In the summer of 1944, dyspnea and cough developed and a thoracentesis was required for the 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 bed-ridden and failed to respond to further x-ray treatment.

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

The temperature ranged from 98 to 103 F and the pulse from 100 to 140 per minute.

Laboratory Data: Blood counts: leukocytes, 8500; erythrocytes, 3,910,000; hemoglobin 86 per cent; differential: polymorphonuclear neutrophiles, 73 per cent; eosinophiles, 13 per cent; lymphocytes, 13 per cent. The Hinton test was negative. The urine was negative. The blood sedimentation rate was 40 mm. per hour. Roentgen examination disclosed no mediastinal mass but decided infiltration of the lower two-thirds of both lung fields was present.

Course. On December 7, 1943 the patient was started on a course of tri (B chloroethyl) amine administered on alternate days for four doses (0.1 mg. per kilogram of body weight). This was injected 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 being improved and cough improved. The lymph node masses shrank 60 to 70 per cent, the breasts became smaller, the disfiguring edema of the face and neck receded entirely and the hugely swollen arm returned almost to normal size. Roentgenograms of the chest revealed no change in pulmonary infiltration.

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

The results obtained in cases with extensive mediastinal involvement were on the whole not as satisfactory as those obtained with lesser degrees of mediastinal involvement. However, a more comfortable existence as well as a moderate prolongation of life was achieved with nitrogen mustard therapy. In patients who had been previously subjected to intensive roentgen therapy the resultant fibrosis within and around the mediastinal tumor mass may well occlude the vascular
avenues of approach. With little or no previous Roentgen therapy mediastinal tumors appeared to respond more satisfactorily.

**Hepatic Involvement**

**Hepatomegaly.** Hepatomegaly was present in 15 cases. Thirty-six and six-tenths per cent showed regression following HN₂ therapy. Those who failed to respond were radioresistant terminal cases. Individuals with lesser degrees of hepatomegaly appeared to respond satisfactorily.

**Jaundice.** In four cases hepatic enlargement was associated with jaundice. Two responded well while the other two showed no signs of improvement and in fact became worse following therapy. The following case is illustrative of a possible aggravation of liver dysfunction following HN₂ therapy.

**Case 35**

H. M., a 45 year old white male was first seen on April 16, 1947. Eight months prior to admission he noted the presence of a mass in the right cervical region which gradually increased in size until it filled the entire right side of the neck. He developed marked fatigability, night sweats and pruritus. A biopsy revealed the presence of Hodgkin's disease. Roentgen therapy produced a short remission. Subsequent roentgen therapy was completely ineffectual and the patient became progressively more disabled with severe night sweats and fever.

**Physical Examination:** Temperature 104 F, pulse 126 per minute; respirations, 32 per minute. The sclerae were markedly icteric. There was no adenopathy. The liver descended one finger's breadth and the spleen two fingers' breadth below the right and left costal margins respectively.

**Laboratory Data:** Blood counts: leukocytes, 6100; erythrocytes, 3,010,000; hemoglobin 9.3 Gm.; differential: polymorphonuclear neutrophiles, 45 per cent; band forms 2.1 per cent; monocytes, 16 per cent; lymphocytes, 18 per cent. Bone-marrow: hyperplastic; differential: polymorphonuclear leukocytes, 17.3 per cent; band forms, 30.5 per cent; metamyelocytes, 24.5 per cent; myelocytes, 12.5 per cent; promyelocytes, 1.3 per cent; plasma cells, 1.5 per cent; reticulum cells, 1.6 per cent; erythrocyte:granulocyte ratio: 1:2.5. The urine showed four plus albumin and four plus urobilinogen. The blood sedimentation rate was 125 mm. per hour. The total serum bilirubin was 1.5 mg. per cent. A roentgenogram of the chest revealed hilar adenopathy and increased markings extending down to the right lower lobe.

**Course:** On April 17, 1947, the patient was started on a course of HN₂ consisting of 6, 8 and 6 mg. administered on successive days. The first dose was followed within one-half hour by a chill and within two hours by moderate nausea and vomiting. There were no reactions following the last three doses. Icterus was more intense on the third day of therapy. The patient became increasingly stuporous, lapsed into coma, and died nine days after the institution of therapy.

**Postmortem Examination:** There was a well-defined icterus of the skin and sclerae. The spleen and liver weighed 475 and 840 grams respectively. There was extensive granulomatous infiltration within these organs as well as the tracheo-bronchial, paraaortic and retroperitoneal nodes. Partial compression of the common bile duct resulted from an enlarged node at the head of the pancreas. Microscopic examination revealed numerous foci of necrosis in the liver with swelling and vacuolization of the reticulo-endothelial cells and marked hypoplasia of the bone-marrow.

The progressively downhill course of this patient was probably accelerated by the administration of HN₂ in the face of definite icterus. It is probable that the miliary necroses of the liver and hypoplasia of the bone marrow could be directly attributed to HN₂ therapy.

**Ascites.** Ascites was present in three cases. Partial relief was effected in two cases. Case 5, radioresistant, had marked ascites, pleural effusion, dyspnea, fever, anorexia and malaise. HN₂ therapy and other supportive measures brought about a
satisfactory partial remission. Case 23 is illustrative of a partial response to vigorous therapeutic measures including HN2.

CASE 23

V. C., a 24 year old white female was first seen on January 7, 1947. A diagnosis of Hodgkin's disease had been made two and one-half years prior to admission after a six month period of fever, sweats, hoarseness, adenopathy and splenomegaly. Roentgen therapy was only partially effective in reducing glandular enlargement. She had herpes zoster one year prior to admission. During the past three months she had developed progressive fatigue, anorexia, dyspnea, ascites, and edema of the lower extremities.

The patient had a marked pancytopenia and hypoproteinemia and required frequent transfusions.

Physical Examination: The patient was markedly emaciated. She had a right Horner's syndrome. There was generalized shorty adenopathy, marked ascites, hepatosplenomegaly and pitting edema of the lower extremities.

Laboratory Data: Blood counts: leukocytes, 2000; erythrocytes, 3,380,000; hemoglobin 56 per cent; platelets, 167,020; reticulocytes, 1.6 per cent; differential: polymorphonuclear neutrophiles, 32 per cent; band form, 1.6 per cent; metamyelocytes, 3 per cent; monocytes, 31 per cent; lymphocytes, 7 per cent.

Bone-marrow hypercellular; differential: polymorphonuclear neutrophiles, 6.8 per cent; band forms, 16.4 per cent; metamyelocytes, 23.8 per cent; myelocytes, 30.0 per cent; promyelocytes, 10.4 per cent; myeloblasts, 4.0 per cent; eosinophiles, 0.6 per cent; lymphocytes, 0.4 per cent; plasma cells, 0.2 per cent; reticulum cells, 5.2 per cent; megakaryocytes plentiful; erythrocyte : granulocyte ratio, 1:1. The urine showed two plus albumin. The Hinton test was negative. The total proteins were 4.4 Gms. per cent; albumin 3.0 Gm., globulin, 1.4 Gm.

Course: The patient received five doses of HN2 consisting of 1, 4, 6, and 5 mg. administered on alternate days beginning January 11, 1947. She had moderate nausea and vomiting starting two hours after each injection and lasting 3 to 4 hours. The Horner's syndrome disappeared completely. Adenopathy and hepatosplenomegaly regressed partially. The patient received numerous supportive measures, including intravenous blood, plasma, albumin, vitamins and paracenteses. The serum protein rose to 5.1 Gm. per cent. Leukocytes fell to 900 and penicillin was administered. The platelets rose to 410,000. Thirteen days after the initiation of therapy the bone marrow showed a marked decrease in cell larity and a shift of granulocytic elements to more mature forms. Improved appetite and general well being continued for about four months. In May 1947 she developed jaundice and severe epistaxis. A second course of HN2 was instituted but ascites recurred and the patient went progressively downhill and died. Postmortem examination was not obtained.

This patient appeared to be in a terminal state upon admission and HN2 was administered only after considerable hesitation especially since marked leukopenia was also present. However, following therapy the patient had a four month remission and in fact showed partial improvement of her pancytopenia. Rosenthal38 has described the use of nitrogen mustard therapy with splenectomy in those cases having severe leukopenia. Splenectomy was found to be effective in raising the leukocyte level. Remissions tended to be of longer duration with this drastic procedure and the leukocyte count was not lowered. Experience with this form of combined therapy is as yet too limited to permit evaluation.

Case 22 showed ascites, hepatosplenomegaly, hydrothorax and fever.

Patients displaying ascites and extensive hepatic involvement have, on the whole, responded poorly to HN2. Boursnell, et al.39 demonstrated the excretion of as much as 50 per cent of intravenously injected sulfur mustard into the bile of rabbits within one hour. With diffuse granulomatous infiltration biliary excretion is undoubtedly impaired, and the avenue of approach to involved areas obstructed. Roentgen therapy may be of some value in such cases.
Neurologic Involvement

Intraspinal

Intraspinal involvement has been attributed to the following pathogenetic mechanisms: (1) extension from retroperitoneal and posterior mediastinal granulomatous tissue via the intervertebral foramina into the epidural space, (2) extension from an involved vertebra, or compression from collapsed vertebral bodies, (3) mechanical obstruction of blood vessels within the intervertebral foramina or just outside the cord, causing diffuse myelomalacia, and (4) toxic myelitis. Pressure from lesions extending from involved vertebrae was present in one treated case (case 20) and in one untreated case (case 6). In the other cases, there was probable extension via the intervertebral foramina. Thromboses of blood vessels may well have been a contributing factor in some cases.

Spastic Paraplegia. During the course of our observations, 5 patients developed spastic paraplegias. In 3 cases this developed terminally and we did not have the opportunity to treat them with nitrogen mustard. The other 2 cases are described in detail. The results of treatment with HN2 were of only partial and temporary value.

Case 8

G. S., a 31 year old housewife, was first seen in July 1946. She had developed cough, pruritus, cervical and axillary adenopathy and splenomegaly in 1940. Roentgen therapy induced a six year remission. In January 1946 she noted the onset of painful swelling of the left arm and breast. Cough, dyspnea and fatigue were presenting complaints in March 1946. Roentgenograms of the chest showed a massive hydrothorax and bilateral hilar adenopathy. Two thoracenteses brought about considerable relief of dyspnea. This was followed by roentgen therapy to the mediastinum with complete resorption of the left thoracic fluid and regression of hilar adenopathy. The edema of the left breast and arm persisted. Three weeks later, however, a recurrence of the pleural fluid and mediastinal adenopathy was noted and the patient was referred for nitrogen mustard therapy.

Physical Examination. The patient had a marked radiodermatitis of the left supraclavicular area. There were induration and edema of the left breast and upper extremity, a left Horner’s syndrome as well as signs of pleural thickening over the left upper chest. There were no palpable glands; liver, and spleen were not enlarged. Neurologic examination was negative.

Laboratory Data. Blood counts: leukocytes, 7,600; erythrocytes 3,540,000; hemoglobin 11.3 Gm.; platelets 1,176,630; reticulocytes, 1.3 per cent; differential: polymorphonuclear neutrophiles, 81 per cent; monocytes 7 per cent; lymphocytes, 12 per cent. The urine was negative. The Hinton test was negative. Roentgenogram of chest showed enlarged hilar masses.

Course. On July 5, 1946 the patient was started on a course of 4 doses of HN2 consisting of 4, 5, 6 and 7 mg. Chills and severe nausea followed each dose. There followed a moderate regression of the edema of the left arm and breast and complete resolution of both hilar masses. In October 1946, the patient developed a spastic paraplegia and fecal and urinary incontinence. Combined roentgen therapy, (1,025 r to the lower cervical and upper thoracic spine), and HN2 (24 mg.) were administered. Severe nausea and vomiting followed each injection of the latter. During the course of the next three months incontinence completely disappeared and the patient could walk with assistance. Horner’s syndrome persisted.

In February 1947, the patient again developed a spastic paraplegia. Lumbar puncture demonstrated the presence of a partial dynamic block and a spinal fluid protein of 120 mgs. per cent. A third course of HN2 was administered on four successive days (5, 6, 7 and 8 mg.). Spinal fluid dynamics returned to normal and protein level fell to 60 mgs. per cent. Roentgen therapy to the lower cervical and upper thoracic spine (725 r) produced no further effect upon the spinal fluid. There followed a gradual improvement in the use of both lower extremities.
360  NITROGEN MUSTARD THERAPY

In May 1947, the patient developed subcutaneous nodules over the left upper chest. These soon ulcerated and became secondarily infected. Progressive paralysis of the lower extremities resulted in a complete spastic paraplegia and urinary incontinence. The edema of the left arm became especially painful. All forms of therapy were refused. In September 1947 a large sacral ulcer developed and became secondarily infected. The patient ran a fever which did not respond to penicillin therapy. She was continuously sedated with large doses of morphine and pantopon. Death occurred on September 27, 1947. Postmortem examination was not obtained.

CASE 2.4

J. F. K., a 23 year old white male, first noted the presence of left cervical adenopathy in December 1943. A biopsy revealed the presence of Hodgkin’s granuloma. In November 1945, mediastinal involvement was noted. In March 1946, left inguinal glands appeared. Cervical glands recurred in July 1946. Roentgen therapy induced complete regression of enlarged glands. Complaints of anorexia, weakness, nausea, vomiting, epigastric and flank pain were relieved by roentgen therapy to the abdomen and back. In October 1946, the patient complained of left upper quadrant pain and parasthesias of the lower extremities. The upper abdominal pain subsided with x-ray therapy. Complete paraplegia and urinary incontinence developed in January 1947.

Physical Examination: The patient appeared chronically ill. He had enlarged cervical, left axillary, inguinal and femoral nodes. A lime-sized mass was palpable in the lower abdomen. The spleen was two fingers’ breadth below the left costal margin. There was a large sacral ulcer. Neurologic examination revealed a spastic paraplegia and hypesthesia from the level of D12. The patient had both urinary and fecal incontinence.

Laboratory Data: Leukocytes, 18,900; erythrocytes, 3,180,000; hemoglobin, 72 per cent; differential: polymorphonuclear neutrophiles, 89 per cent; monocytes, 1 per cent; lymphocytes 10 per cent. The urine showed a trace of albumin and numerous white cells. The Mazzini test was negative.

Course: Two courses of HN2 were administered: one beginning January 2, 1947 (32 mg.) and the other February 17, 1947 (32 mg.). This was followed by roentgen therapy (3200 r) over the lower dorsal and upper lumbar spine. The neurologic status however remained unchanged. Cervical and inguinal glands appeared about one month later. In June 1947 the patient developed edema of the left leg and scrotum which was unrelieved by mercuhydrin. Bladder incontinence required constant tidal drainage. In August 1947 enlarged cervical glands appeared and the patient had considerable dysphagia. He received 4 mg. HN2 on August 18. The following day at the start of the saline infusion for the administration of nitrogen mustard he became dyspneic and cyanotic and complained of sudden blindness. His face became puffy and neck veins distended. Oxygen and morphine were administered with gradual improvement. A friction rub was heard at the left base twenty-four hours later. One month later a cutaneous ulcer developed at the base of the penis due to pressure from the paraplegic position. The patient died on October 17, 1947.

At autopsy there was granulomatous infiltration of cervical, axillary, inguinal, retroperitoneal, celiac, pancreatic and mesenteric lymph nodes, the spleen and liver as well as infiltration into the psoas muscle, kidneys, adrenals, bladder, pancreas and left lung. There were bilateral pyo-ureters and pyonephroses. A purulent cystitis was present. The lower thoracic portion of the spinal cord was surrounded by an epidural cuff of firm gray tumor 0.3 cm. in thickness. The left half of the cord was greatly compressed. The tumor extended through the dura and pia arachnoid directly into the substance of the cord. There was degeneration of the posterior and lateral tracts of the spinal cord. The vertebral marrow was entirely replaced by necrotic tissue. There was active hematopoiesis in the costal, sternal and calvarial marrow.

Therapy was instituted three weeks and three and one-half months after the initial symptomatology in cases 8 and 24 respectively. In the latter case, irreversible cord changes were undoubtedly present at the time of treatment. The former had a partial remission following combined therapy. The shorter interval between onset of symptoms and therapy is probably responsible for the difference in the results.
obtained. Secondary myomalacia of the cord due to pressure and thrombosis of vessels is an irreversible process.

**Pain:** Pain was a prominent presenting symptom in three patients who showed evidence of intraspinal involvement of Hodgkin’s disease.

In case 8, the initial manifestation of the disease was in the form of agonizing low back pain radiating down the right leg. Roentgenogram of the spine revealed the presence of a destructive lesion in the twelfth dorsal vertebrae. A laminectomy performed one year later revealed an infiltrative mass involving the seventh, eighth, ninth and tenth dorsal spinous processes, laminae and pedicles as well as an extradural mass. Roentgen therapy did not relieve the pain. Because of the excruciating character of the pain the patient required large doses of morphine and demerol to which he became addicted. The patient subsequently had two convulsive seizures with shooting pains down both arms. Four courses of HN2 were administered following which he developed complete remissions from the agonizing pain for the periods of 31, 43, 28 and 21 days respectively. The second course was combined with roentgen therapy. Further HN2 had to be discontinued because of hematemesis. The patient died suffering extreme back pain radiating down both legs. At autopsy the extradural space from the lumbar to the upper cervical area was filled with tumor.

Case 38 was completely relieved of pain following the first and partially relieved following the second course of nitrogen mustard.

The following case, showing remarkable pain relief following HN2 therapy, is described in detail:

**CASE 10 (FIGURE 10)**

B. D., a 38 year old white male was first seen in October 1946. He had discovered a mass in the left axilla two and one-half years previously and the diagnosis of Hodgkin’s disease had been made following biopsy. Roentgen therapy was then administered to the left axilla, left supraclavicular region and mediastinum. In September 1944 the patient developed fever, night sweats and right axillary adenopathy. A submental gland appeared in December 1944.

Roentgen therapy was administered on these and subsequent occasions with progressively increasing radioresistance. The patient developed marked fatigue, lassitude, night sweats and anorexia.

**Physical Examination:** (October 2, 1946) The patient was moderately pale. A large mass was present in the eleventh left intercostal space. There was no cervical, axillary, or inguinal adenopathy. The liver was felt three fingers’ breadth below the right and the spleen five fingers’ breadth below the left costal margin.

**Laboratory Data:** Blood counts: leukocytes, 15,650; erythrocytes, 3,390,000; differential: polymorphonuclear neutrophiles, 44 per cent; band forms, 10 per cent, lymphocytes, 34 per cent, monocytes, 10 per cent.

**Course:** The patient received four doses of HN2 consisting of 4, 4, 5 and 6 mg. administered on alternate days. Moderate nausea and vomiting followed each injection and lasted for three to five hours. Within a few days the patient had a marked increase in vitality, an increased appetite, and began to gain weight. The mass in the eleventh intercostal space and the hepatosplenomegaly regressed completely. The leukocyte level dropped to 3,950. This remission lasted for two and one-half months. At that time the patient noted the presence of enlarged preauricular glands. On examination he was found to have generalized adenopathy, recurrent eleventh left intercostal mass, and hepatosplenomegaly. A second course of HN2 was instituted on December 26, 1946 in the form of weekly and biweekly injections. The nausea and vomiting were of such severity that further attempts at prophylactic therapy had to be discontinued. Adenopathy and hepatosplenomegaly regressed completely.

In February 1947, the patient noted the onset of headache and irritability. This was soon followed by intermittent pain in the right quadriceps muscle, severe sweats and anorexia. About one month later the patient complained of low back pain radiating down the right extremity, aggravated by coughing, sneezing, and straining at stool. Neurologic examination was essentially negative. The pain shifted to the left lumbar area and radiated to the left hip and left thigh anteriorly. Roentgen therapy (300 r) to
NITROGEN MUSTARD THERAPY

the lumbar spine had no effect. The pain localized at L3 and became progressively more intense. A lumbar puncture revealed a complete dynamic block, xanthochromic fluid and 872 mg. per cent spinal fluid protein. Other physical findings and hematologic data are depicted in figure 10.

Beginning April 25, 1947 the patient received daily injections of 4, 5, 6 and 7 mg. HN2. Moderate nausea and vomiting followed each dose. Within twelve hours after the first dose 90 per cent of the pain had subsided and moderate reduction in preauricular adenopathy was noted. The pain was almost completely relieved at the conclusion of therapy. A repeat lumbar puncture was performed on the following day and revealed normal dynamics clear fluids and 39 mg. per cent spinal fluid protein. Sweats and hepatosplenomegaly subsided completely. The usual fall in the leukocyte level occurred.

In July 1947, the patient noted a recurrence of weakness, anorexia and dizziness. On examination he was found to have marked pallor and hepatosplenomegaly. Blood counts were as follows: leukocytes, 6000; erythrocytes, 3,010,000; hemoglobin, 6.9 Gm.; reticulocytes, 6.6 per cent; platelets, 303,000; differential, normal. The blood sedimentation rate was 68 mm. per hour. The urine urobilinogen was positive in 1:32 dilution. The fourth course of HN2 was started on August 9, 1947 and consisted of daily doses of 3, 6, 7 and 8 mg. The usual reactions of nausea and vomiting followed each dose. 1000 cc. of whole blood were given to correct the anemia. There followed a marked improvement in anorexia and sweats. The hepatosplenomegaly subsided completely. The leukocyte level fell to 3600.

The remission lasted until October 10, 1947 when the patient again noted the onset of fatigability and anorexia. On examination he was found to have moderate pallor, preauricular and submental adenopathy and hepatosplenomegaly. The erythrocyte count had fallen from 4,040,000 to 3,300,000 with corresponding hemoglobin levels of 11.3 and 9.3 Gm. respectively. A fifth course of HN2 was started on October 23, 1947 consisting of 5, 6, 7 and 8 mg. administered on alternate days. The patient had a prompt improvement in general well being as well as complete regression of adenopathy and hepatosplenomegaly. The leukocyte level dropped to 3600. The platelet count rose to 404,500.
Following each of the five successive courses of HN\textsubscript{2} this patient demonstrated an unusual sensitivity to nitrogen mustard therapy with objective signs of improvement occurring as early as 12 hours after the initial dose. The response of pain and the regression of the intraspinal tumor were indeed remarkable. The consistent fall in erythrocyte and hemoglobin levels and reticulocytosis were quickly corrected with HN\textsubscript{2} therapy.

In this group presenting pain as the predominant symptom the results were far more striking than in those cases showing paraplegia, probably because pain is an early sign of intraspinal involvement and may therefore cause the patient to seek help before irreparable spinal cord damage has taken place. Thus pain was completely relieved in 71.4 per cent and partially relieved in 28.6 per cent of the cases.

**Peripheral**

*Paralysis of the Upper Extremity*. In 2 cases, paralysis of the upper extremity, secondary to pressure upon the brachial plexus was present. In neither case was nitrogen mustard effective in relieving the paralysis. Case 1, had a large mass filling the entire left side of the neck. Case 8 had extensive scar tissue in the supraclavicular region which resulted from previous intensive roentgen therapy. The cervical mass in former case showed partial regression but sudden death occurred before any improvement in the paralysis could be noted.

**Pain**. Back pain in the absence of specific intraspinal disease was present in 7 patients. Complete subsidence of pain in all cases followed nitrogen mustard therapy. It is probable that dorsal root compression by granulomatous tissue was quickly relieved before irreversible changes had occurred.

*Hirschner's Syndrome*. Seven patients having eleven administrations of HN\textsubscript{2} had Horner's syndrome. No change followed therapy in nine of eleven administrations.

**Osseous Involvement**

Roentgenograms of the skeletal system revealed lesions in 6 patients. Vertebral lesions were present in 4 cases, pelvic and vertebral lesions in 1 case, and pelvic lesions alone in 1 case. A destructive lesion of the sternum was present in 1 case. Despite successful clinical remissions following nitrogen mustard therapy the destructive lesions as visualized roentgenologically showed no improvement. This lack of response may be due to the inhibitory effect of the nitrogen mustards upon osteoblastic and other enzymatic activities necessary for osseous regenerations.

**Effects on Hematologic Constituents**

**Peripheral Blood**

*Erythrocytes*. Figure 11 illustrates the hematologic changes which followed HN\textsubscript{2} therapy. Fifty-eight and five-tenths per cent of cases showed a well defined decrease in the erythrocyte level. This was manifest within five to six days after the initiation of treatment, and persisted until the twenty-first to twenty-fifth day, after which a gradual increase to normal levels occurred. The maximum reduction in the erythrocyte count was 16.2 per cent. In 18.8 per cent of cases, erythrocytes rose
following therapy. The average rise was 12.2 per cent on the ninth to tenth day and 23.3 per cent on the twenty-sixth to thirtieth day. Twenty-two and seventen-ths per cent of cases showed slight if any change in red cell count. The routine examination of all peripheral blood films failed to reveal any striking morphologic changes in the red blood cells.

It is possible that the effect on red cell count may be due to a direct action of the chemical upon the circulating red cell. Bournell, et al. have demonstrated in rabbits, that one-third of the injected radioactive sulfur mustard remains affixed to the red cells. Increased urilibiligen excretion into the feces has been reported by Jacobson and Urteaga following the administration of nitrogen mustard. Serial serum bilirubin studies, performed in many of our cases, revealed no change. No spherocytosis or altered osmotic fragility of the red cells could be demonstrated.

Case 10, with each relapse, showed a marked fall in erythrocyte and hemoglobin levels and developed a spherocytosis and reticulocytosis. Following each course of nitrogen mustard therapy the erythrocyte and hemoglobin levels rose and sphero-cytes and reticulocytes diminished.
Hemoglobin. A parallel fall in the hemoglobin level to that noted above occurred in 59.0 per cent of cases. A 7.1 per cent reduction was present on the fifth day, and a 12.1 per cent reduction on the fifteenth to twentieth day. Gradual improvement followed. In 41.0 per cent of cases, a rise in the hemoglobin levels to a maximum of 19.3 per cent on the twenty-first to twenty-fifth days was noted.

Reticulocytes. Eighty-five and one-tenth per cent of cases showed a depression in the reticulocyte level following nitrogen mustard therapy. This was maximal on the sixth to tenth day (0.0 to 0.2 per cent).

Leukocytes. A fall in the leukocyte level occurred in 87.7 per cent of cases. Those patients with initial leukocyte counts ranging from 4000 to 15,000 tended to develop leukopenic levels; while those ranging between 15,000 and 27,250 tended to fall to normal levels. The maximal fall in the leukocyte count occurred on the twenty-first to the twenty-fifth day after the initiation of treatment and was followed by a gradual return to normal levels on the thirty-sixth to fortieth day.

Five cases (6.9 per cent) with initial leukopenias after a slight decrease in the leukocyte count showed a progressive increase beginning on the sixteenth to twentieth day. Case 23 had an initial leukocyte count of 2600 which fell to 900 on the eleventh day and subsequently rose to 6920 on the thirty-third post-therapy day.

Case 49 showed the most marked leukocyte depression falling from 22,350 to 600 and lasting for forty days (fig. 12). This was associated with a corresponding reduction in the erythrocytes and platelets and progressive bone marrow hypo-
NITROGEN MUSTARD THERAPY

plasia. The etiologic role of tris-mustard in the production of this reaction is discussed below.

The decrease in the leukocyte count was predominately a reflection of the simultaneous decrease in granulocytes (figs. 5, 9, 10, 12). Lymphocytes and monocytes showed moderate reductions only when their initial levels were high. Repeated examinations of the blood films revealed no qualitative changes in any of the white cell elements.

Platelets: The platelet level was affected in only 2.0.5 per cent of the cases. In these cases, an average reduction of 69.4 per cent was present on the twentieth to thirtieth day following which a gradual increase occurred. Two patients with initially low platelet counts after a slight depression showed increases of 43.8 and 54.4 per cent.

Hemorrhagic Manifestations

Upon the usual therapeutic schedule, 3 patients developed hemorrhagic manifestations following one or more courses of HN2. Case 20, who had received a total of eight courses, developed moderate bleeding of the gums following her last course. Severe hematemesis followed the third and fourth doses of the fourth course in Case 28 and well as the fifth dose of the fifth course. Hematemesis occurred terminally eleven days after the first course in Case 22. The most severe hemorrhagic complications due to marked thrombocytopenia, occurred in Case 49 who received 18 mg. of the tris compound (HN3) and 8 mg. of HN2. Her case is described in detail.

CASE 49 (FIGURE 12.)

M. S., a 19 year old white female first noted the presence of a right supraclavicular mass in October 1947. Within two weeks she began having severe night sweats and fever. Other glands appeared in the left cervical and axillary regions. The biopsy showed features of both Hodgkin's granuloma and sarcoma. The patient was first seen about one month after onset at which time she complained of cough.

Physical Examination: The patient was moderately pale. There was a large left axillary mass, 6 cm. in diameter. There were numerous bean-sized axillary and cervical glands. Supracardiac dullness was increased. The liver and spleen were not palpable.

Laboratory Data: Blood counts: leukocytes, 15,180; erythrocytes, 4,310,000; hemoglobin 10.4 Gm.; reticulocytes, 0.5 per cent; platelets, 689,600; differential: polymorphonuclear neutrophiles, 82 per cent; eosinophiles, 3 per cent; monocytes, 4 per cent; lymphocytes, 11 per cent. Bone Marrow: hyperplastic: differential: band forms, 36 per cent; metamyelocytes, 11.5 per cent; myelocytes, 11.6 per cent; plasma cells, 1.2 per cent; megakaryocytes, markedly increased; normolasts: A, 0.8 per cent; B, 2.8 per cent; C, 4.0 per cent. The urine was negative. The Hinton test was negative. The blood sedimentation rate was 95 mm. per hour. The total blood proteins were 7.1 Gm. per cent; albumin 4.4 Gm. per cent; globulin, 2.7 per cent. A roentgenogram of the chest showed large mediastinal and hilar masses.

Course: The patient received three doses of HN3 (5, 6 and 7 mg. respectively) and one dose of HN2 (8 mg.) on alternate days beginning November 18, 1947. There was a strikingly rapid regression of cervical and axillary glands. On the fifth day following the initiation of therapy the mediastinal masses regressed 60 to 70 per cent. The patient's hematologic course is shown in figure 12. A marked pancytopenia with extreme thrombocytopenia developed. Severe menorrhagia, petechiae, ecchymoses, bleeding of gums and a retinal hemorrhage occurred eighteen days after the initiation of therapy. Thromboses of the right and left antecubital veins were present. Serial bone marrow aspirations revealed progressive hypoplasia (fig. 13). The patient ran a febrile course for ten days. During this time she received penicillin and sulfadiazine. A total of 3500 cc. of fresh whole blood was administered. Protamine, 137 mgs., was
administered intravenously but without apparent effect upon the hemorrhagic manifestations. These subsided spontaneously with an improvement in the platelet count. Definite evidence of bone marrow regeneration was noted on January 5, 1948.

The $\text{HN}_3$ administered to this patient was undoubtedly largely responsible for the severity of the hemorrhagic complications. This form of nitrogen mustard was found to produce unusually severe depressions of leukocyte, erythrocyte and platelet levels. Thromboses of injected veins were likewise more common. Further use of tris-mustard appears to be unwarranted.

**Bone Marrow**

Serial bone marrow studies were performed in 11 cases of Hodgkin's disease treated with nitrogen mustard. Within twenty-four hours after the initiation of nitrogen mustard therapy the clumps of marrow began to show a decrease in size and cellularity. Fat-spaces were increased.

Polymorphonuclear neutrophiles showed hypersegmentation. Erythropoiesis was suppressed. Within two to four days there was a reduction in the number of myelocytic cells and a relative increase in the number of more mature forms. Bizarre, distorted myelocytes, metamyelocytes, polymorphonuclear neutrophiles and megakaryocytes were noted with moderate frequency. Marked hypoplasia of the bone marrow followed nitrogen mustard therapy in 7 cases. The serial bone-marrow changes obtained in 1 case are shown in fig. 13. Case 46 showed a marked decrease in cellularity within 24 hours after the initiation of therapy. Increasing hypoplasia was found two days later. Bone marrow regeneration was noted six days after the cessation of therapy. The pretherapy bone-marrow of case 35 was markedly hyperplastic. Severe hypoplasia was present nine days after the initiation of treatment.

A moderately active bone-marrow was present in Case 16 who died fifteen days after the completion of the last course of nitrogen mustard. Hyperactive marrows were found at autopsy in 2 cases (Cases 15 and 24) who died five and ten months, respectively, after their last course of therapy.

Suppression of erythroid activity was noted within twenty-four hours after the initiation of $\text{HN}_3$ therapy. No immediate reflection of this depression was noted in the peripheral erythrocyte and hemoglobin levels, in all probability because of the normal red cell survival time of one hundred and twenty days.

Bloom and Bloom showed that the chick erythroblast was the most sensitive cell in the marrow following the administration of x-ray therapy.

Suppression of granulopoiesis was noted within two to four days. The fall in the peripheral leukocyte level occurred shortly thereafter reaching a maximal leukenopemia on the twenty-fifth day. This prompt reflection of an effect on the marrow is undoubtedly due to the short survival time of the leukocyte in the peripheral blood.

Megakaryocytes proved to be the most resistant of all marrow elements and platelet reduction occurred in only 20.2 per cent of cases.

Except for terminal cases dying shortly after their course of nitrogen mustard therapy no cases of irreversible aplasia of the marrow were encountered in this...
FIG. 13.—Hypoplastic Response of Bone Marrow Following Injection of 18 mg. Tris (8-Chloroethyl) Amine and 8 mg. Methyl Bis (8-Chloroethyl) Amine (Case 43).

(a) Prior to Initiation of Therapy.

FIG. 13.—(b) Eight Days after Initiation of Therapy.
FIG. 13.—(c) Twenty Days after Initiation of Therapy

FIG. 13.—(d) Thirty-eight Days after Initiation of Therapy
series. However, we have been informed of such instances from other clinics where a higher dosage schedule of HN₂ and more frequent institution of therapy have been in vogue. Our experience indicates that the tris compound has a much greater cytotoxic effect upon the bone marrow than does the methyl Bis (B chloroethyl) amine.

In experimental animals, the rapidity of the cytotoxic action of the nitrogen mustard has been demonstrated by Karnofsky et al. This occurs within a period of five minutes after injection. The fixation of radioactive sulfur mustard to the bone marrow was shown by Boursnell et al. Kindred studied the reaction of the femoral bone marrow of the albino rat to sulfur and three nitrogen mustard preparations. A marked suppression of erythroid and granulocytic elements was noted two days after injection. Mitotic activity was diminished. Megakaryocytes showed some signs of injury but no reduction in number. Reticulum cells and plasma cells were unaffected. Similar results were obtained in dogs, rabbits, and in mice.

Severe aplasia of the bone marrow following mustard gas poisoning was reported in 6 fatal cases by Krumbhaar and Krumbhaar in 1919. Spurr, et al. using the marrow aspiration technic found a more prolonged depression of the marrow and a less rapid return to normal than noted in our cases. Block et al. studied the serial marrow changes histopathologically. The "atrophic stage" was between eight and twenty days after initiation of HN₂ therapy. In the post-mortem findings reported by Spitz, severe marrow hypoplasia was noted following a cumulative dose of 0.5 to 0.6 mg./kilo of HN₂ administered eight days prior to death.

Barron et al. showed that the addition of choline, dimethyl amino ethanol and methionine to bone marrow in vitro protected it from the inhibition of respiration by the nitrogen mustards.

**Lymph Nodes**

Serial lymph node aspiration were performed in six treated cases. The typical appearance of the lymph node aspiration in Hodgkin's disease is shown in fig. 14a. This is characterized by a pleomorphic cellular pattern consisting of lymphocytes, polymorphonuclear neutrophiles, eosinophiles, plasma cells, reticulum cells, and Dorothy Reed cells. Within a period of twenty-four hours after the initiation of therapy there was a decrease in cellularity and pyknosis and smudging of lymphocytic cells. Four days after the initiation of therapy, these findings were more marked (fig. 14b). Polymorphonuclear neutrophiles showed vacuolation and hypersegmentation. Reticulum cells were bizarre and degenerate and showed frequent vacuolation.

No change was noted in the lymph node aspirations of a case of Hodgkin's sarcoma (Case 46) who was resistant to treatment. Case 49, having some features of both Hodgkin's granuloma and sarcoma showed a marked reduction in the pleomorphism present before therapy with large numbers of sarcoma cells still present after therapy. The lymph nodes of Case 30, who died from an exanguinating gastrointestinal hemorrhage twenty-four hours after receiving 4 mg. of HN₂, showed marked pyknosis and diminished mitotic activity. Figure 15 shows a mili-
FIG. 14.—EFFECTS OF NITROGEN MUSTARD ON LYMPH NODE OF CASE OF HODGKIN'S DISEASE (CASE 17)
(a) PRIOR TO INITIATION OF THERAPY

(b) SAME PATIENT FOUR DAYS AFTER INITIATION OF THERAPY
ary focus of necrosis within a lymph node obtained at postmortem examination seven days after the institution of nitrogen mustard therapy (Case 28).

Similar results were noted by Block et al. and Spitz. Focal necrosis of the splenic pulp was reported by the latter following cumulative doses of 0.5 to 0.8 mg./kilo, administered seven to eight days before death. Kindred showed marked lymphoid atrophy and lymphocytic degeneration in the albino rat on the second postinjection day. Similar changes were present in the thymus and the spleen. The peripheral lymphocytopenia coincided with decreased production within lymphoid organs rather than a direct effect upon the peripheral lymphocyte. Mice and rabbits showed essentially the same changes.

Liver

Case 30 who died one day after a single injection of 4 mg. HN₂ showed an increase in the number of polymorphonuclear cells within the sinusoids. Miliary foci of necrosis of the liver were noted at postmortem examination in 3 cases (Cases 16, 28 and 35), who died nine, ten and nineteen days, respectively, after the initiation of therapy. The liver cells showed extensive necrosis with very little leukocytic reaction (fig. 16). Four cases who died from fifty-four days to eight months after their last course of treatment showed no evidence of such miliary foci of necrosis.

Nitrogen mustard appears to exert a karyolytic effect upon liver cells. Polymor-
phonuclear infiltration is present within twenty-four hours. Resolution of the necrotic foci probably takes place between nineteen and fifty-four days after the institution of therapy. Boursnell, et al. demonstrated the ability of the rabbit liver to concentrate as much as 50 per cent of the injected radioactive sulfur mustard within the bile within one hour. It is probable during this time that the hepatotoxic effect occurs. Zimmerman reported focal necroses in the liver of cats after the oral administration of nitrogen mustard.

We prefer to classify Hodgkin's disease as a malignant proliferation of reticulum cells originating in lymphoid tissue, perhaps as a result of various stimuli including infections. The Sternberg-Reed giant cell, the "type" cell of this proliferative process, may represent a malignant type of reticulum cell. As with all neoplastic processes, Hodgkin's disease varies greatly in growth potentiality from case to case. In the most benign types giant cells are scarce and a tendency to fibrosis is marked. In the most highly malignant (Hodgkin's "sarcoma"), giant cells are
NITROGEN MUSTARD THERAPY

common and but little tendency to fibrosis is present. Dissemination of the disease ordinarily occurs by way of the lymphatic channels and by contiguity, and only rarely by way of the blood stream. Whatever the growth potentiality of the disease may be in a given case its course is relentlessly progressive. From peripheral lymph nodes, it extends to the mediastinum and the spleen. Thence, it spreads to visceral organs and constitutional symptoms of fever, night sweats, increasing weakness and itching appear. Terminally, it may block large lymphatic channels and cause huge tumor masses in various parts of the body.

The course of Hodgkin’s disease may be terminated by complete extirpation of a single node or a small group of nodes if this is the only source of the disease. Such a successful end result is extraordinarily rare since once the diagnosis has been made, the disease has already spread. X-ray therapy has been used for many years to shrink the tumor masses and produce remissions. We have been impressed with the better results obtained in early cases by drastic x-ray therapy as opposed to the use of just enough x-ray to induce a reduction in lymph node size to normal. Sooner or later, despite x-ray therapy, new lymph node masses develop and constitutional symptoms become marked. At this point, x-ray therapy often has but little effect. The use of HN₂ has to our mind revolutionized at least this phase in the treatment of the disease.

In the course of our studies it became apparent that HN₂ is a valuable therapeutic tool in the treatment of Hodgkin’s disease; in many cases, indeed, it presents distinct advantages over the more standard form of therapy by x-ray. HN₂ has been particularly valuable in the “terminal” cases of Hodgkin’s disease, i.e., in individuals completely disabled by their disease, having visceral involvement, and running an irregular or relapsing fever. The use of a single course of HN₂ in such cases has often resulted in a termination of the febrile state and its associated symptom, the drenching night sweat. Frequently, there is a dramatic upsurge in vitality and a resumption of normal or almost normal activity. Severe itching of the skin, with its common accompaniments of excoriations and ulcerations due to scratching has usually yielded to HN₂ when previous x-ray therapy has proved completely ineffective.

In those cases that have become refractory to x-ray therapy, whether the Hodgkin’s process is generalized or of a more or less localized character, the use of HN₂ may be invaluable. A single therapeutic course of HN₂ often results in a very rapid and striking response with a marked simultaneous reduction in large lymphoid masses and spleen and in amelioration of both local and constitutional symptoms. The pain of peripheral nerve or spinal cord involvement has yielded quickly in all our cases to HN₂ therapy even though previous x-ray therapy has been completely ineffective. A frequent finding is the enhancement of sensitivity to x-ray therapy following a course of HN₂.

Thus, HN₂ has proved invaluable in salvaging some of the apparently hopeless cases of Hodgkin’s disease and in increasing their life span by periods ranging from two months to more than two years. Although the results in “terminal” cases have at times seemed almost miraculous, they have nevertheless been of temporary nature. Treatment with HN₂ should in no sense be considered as curative.
The new sense of well being obtained with HN$_2$ has however proved of great psychologic value and has often given the patient a renewed determination to cope with his illness.

Our experience with the treatment by HN$_2$ of early or only slightly advanced cases has been too limited to warrant any definite therapeutic evaluation. In such cases, in which only a single group of nodes is apparently involved, the distinct possibility is present that some of the abnormal cells of the disease have already progressed beyond the local lesion. Although a sufficiently high dosage of x-ray therapy is usually productive of a sustained remission, the use of HN$_2$ under these circumstances may help to destroy abnormal cells at a distance from the local process. Particularly in the early cases of Hodgkin's disease, drastic therapy by all available means is important. This may include radical extirpation of a mass of glands, heavy dosage of high voltage x-ray and HN$_2$.

There seem to be few contraindications to the use of HN$_2$. In the presence of leukopenia, the granulocytes should be carefully watched and treatment with penicillin given when a distinct granulocytopenia develops. When jaundice is present HN$_2$ should be given with particular care since further injury to the liver may develop. If anemia is present, transfusions should be given either prior to the course of HN$_2$ or during its administration.

We have had better results in our cases with the use of smaller rather than larger doses of HN$_2$. A complete remission is usually attended with the use of doses smaller than the customarily recommended amount of 0.1 mg. per Kg. of body weight. Reactions, particularly those of a hematologic nature, are usually slight. Larger doses of HN$_2$ may be productive of extremely severe and indeed irreversible reactions.

Although x-ray therapy is still the method of choice in the early cases of Hodgkin's disease and is productive of longer remissions than is HN$_2$, the combined use of x-ray and HN$_2$ may prove to be better than that of either therapeutic method given alone. We have obtained the impression that HN$_2$ is more specific against reticulo-endothelial cellular proliferations than against those of any other cell type. HN$_2$ must therefore be considered as a definite addition to our present therapeutic armamentarium of attack against Hodgkin's disease, which we consider to be a form of reticulum cell proliferation. It is realized that the use of HN$_2$ leaves much to be desired, since it destroys abnormal cells leaving others which continue to maintain neoplastic potentialities. These ultimately proliferate, leading to relapse. However, it is hoped that further research will result in the development of even more potent chemotherapeutic agents for the ultimate control of the disease.

**Summary**

1. Methyl bis (B chloroethyl) amine (HN$_2$) was given by intravenous route for the treatment of 50 successive cases of Hodgkin’s disease, most of them severe and far advanced. Doses somewhat smaller than the usually recommended amount of 0.1 mg. per Kg. were used in courses of four to six injections.

2. Nausea and vomiting followed administration of the drug in 93.2 per cent
of cases. Chills and fever occurred in 12.4 and 6.8 per cent of cases respectively. Dyspnea, cyanosis and diarrhea were rare.

3. In previously untreated cases, remissions were of much shorter duration than those obtained with Roentgen therapy. However, striking remissions were commonly obtained in x-ray resistant cases. Remissions lasted from 17 to 331 days and in individuals receiving multiple courses were roughly proportional to the total dosage administered. A moderate prolongation of the remission period was obtained when HN₂ was combined with roentgen therapy.

4. Constitutional symptoms such as fever, night sweats, weakness and itching responded exceedingly well in most cases to HN₂ therapy. Many previously incapacitated patients were completely rehabilitated for several weeks to several months after a single course of HN₂ therapy.

5. Adenopathy and splenomegaly regressed in 70.2 and 71.7 per cent of cases respectively. Lymphoid masses previously resistant to x-ray therapy appeared to develop increased sensitivity to x-rays after a course of HN₂ therapy.

6. Patients with extensive mediastinal involvement and obstructive symptoms responded only moderately well while those with lesser degrees of involvement showed a better response.

7. Paraplegia due to intraspinal involvement was partially relieved in half the cases while pain due to similar involvement was dramatically relieved in all cases. Pain due to pressure upon peripheral nerves was similarly relieved in all cases.

8. A slight but definite fall in the erythrocyte and hemoglobin levels occurred within five to six days after the institution of therapy. Reticulocytes were maximally depressed on the sixth to tenth days. Of the leukocytic elements, the granulocytes were predominately affected, with maximal cytopenic levels on the twenty-first to twenty-fifth day. The leukocytes gradually returned to normal by the thirty-sixth to fortieth day. Cases presenting an initial leukopenia tended to develop normal leukocyte counts after an initial drop to low levels. The platelet count was affected in only 20.5 per cent of cases. Terminal cases at times developed marked pancytopenia.

9. In one case severe hemorrhagic complications due chiefly to thrombocytopenia followed the administration of the tris form of nitrogen mustard and gradually subsided after a very stormy course.

10. Progressive but temporary marrow hypoplasia followed nitrogen mustard therapy in eleven cases studied with serial marrow punctures. Erythroblastic depression was noted within twenty-four hours and granulocytic depression within forty-eight to seventy-two hours. The megakaryocytes proved to be the most resistant of the marrow elements. The marrow picture usually returned to normal spontaneously within a period of six to eight weeks after the cessation of therapy.

11. Lymph node punctures revealed degeneration and pyknosis of lymphocytes within twenty-four hours after the institution of therapy with a subsequent gradual disappearance of polymorphonuclear neutrophiles, eosinophiles, plasma cells, reticulum cells and Dorothy Reed cells. Miliary foci of necrosis were demonstrated in a gland obtained at post mortem seven days after the institution of HN₂ therapy.

12. Miliary foci of necrosis were demonstrated in the liver of 3 cases dying be-
tween nine and nineteen days after the institution of HN$_2$ therapy. No such findings could be found in a case in which death occurred fifty-four days after the initiation of therapy.

13. The therapeutic results with HN$_2$ in Hodgkin’s disease appeared to have little relationship to the histologic appearance of the involved tissue. The immediate response in so-called Hodgkin’s sarcoma was particularly striking, and in one case, a remission lasting about a year took place.

**Conclusions**

1. Nitrogen mustard (HN$_2$) is a useful drug in the treatment of Hodgkin’s disease, particularly in severe cases with marked constitutional symptoms and visceral involvement. In these cases, a period of complete rehabilitation and a definite increase in life span of from two months to two years may follow the use of one or several courses of HN$_2$.

2. HN$_2$ appears to have an almost specific affinity for the abnormal tissues of Hodgkin’s disease. Although a chemical without any radioactivity, its effects resemble closely those of x-ray. It is however often effective in producing complete remissions in cases that have proved completely refractory to continued x-ray therapy. A resumption in radiosensitivity may follow the use of a course of HN$_2$ therapy.

3. HN$_2$ offers certain advantages other than simplicity of administration over x-ray therapy. Its quick action by intravenous route often results in a simultaneous reduction of all affected lymphoid tissues. In involvement of the spinal cord or peripheral nerves, HN$_2$ is far more effective, particularly in pain relief, than is x-ray. HN$_2$ is likewise more effective in bringing about relief of fever and severe generalized itching than is x-ray. The one outstanding characteristic of the drug is its effectiveness in inducing complete or partial remissions in certain generalized or febrile cases that have been completely unaffected by persistent x-ray therapy. Repeated remissions may be induced by giving repeated courses of HN$_2$.

4. In relatively early cases of Hodgkin’s disease, x-ray therapy is the treatment of choice, primarily because longer remissions can be obtained than with HN$_2$. However, it is possible that the best form of therapy, even in these cases, is that of the combined use of HN$_2$ and x-ray, the HN$_2$ being given for its effect upon proliferating cells which may either be at a distance from the local lesion or else so situated as to remain untouched by x-ray.

5. With cautious use of the drug, the reactions following HN$_2$ therapy are rarely severe enough to militate against its use. Severe granulocytopenia can be handled prophylactically by the use of penicillin. Severe thrombocytopenia rarely occurs. The only definite contraindication to the use of HN$_2$ is the presence of jaundice, indicating some degree of hepatic dysfunction.

6. Doses of HN$_2$ somewhat smaller than the generally recommended one of 0.1 mg. per Kg. of body weight are usually completely effective and are furthermore productive of minimal reactions.

7. As with all very quickly acting and potent drugs, HN$_2$ must be used with
great care. Properly used, it has a well defined place in the treatment of Hodgkin’s disease. Although cures are not to be expected and remissions are temporary, such remissions offer great comfort to the patient seriously ill with Hodgkin’s disease. It is possible that HN₂ may be the forerunner of other even more effective chemotherapeutic agents.

REFERENCES

DAMESHEK, WEISFUSE AND STEIN

26 ——: A tentative analysis of results obtained with nitrogen mustard in miscellaneous types of neoplastic disease. Unpublished data.
36 ZIMMERMAN, H. Quoted in reference 37.
NITROGEN MUSTARD THERAPY IN HODGKIN'S DISEASE: ANALYSIS OF FIFTY CONSECUTIVE CASES

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