THE INFLUENCE OF NITROGEN MUSTARD ON MYCOSIS FUNGOIDES

Observations Relating Its Effect to the Reticulo-Endothelial System

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This report deals with the therapeutic effect of nitrogen mustard on 6 patients with mycosis fungoides. The nitrogen mustards, i.e., the B-chloroethylamines, of which the methyl-bis form is being studied clinically, has been shown to be effective in the control of certain types of malignancies. The effects of this group of chemicals, which appear to be on the nuclear structure of the cell, resemble most closely the action of short wave radiation rather than that of any known chemical reaction. The cellular susceptibility to nitrogen mustard is related to the proliferative activity of the tissue. Thus malignant tissue is more susceptible to its action than is normal tissue; while in the normal, the bone marrow elements, the lymph nodes, and probably the liver reflect the cytotoxic action of the mustards. This action may result in lymphopenia, granulocytopenia, thrombocytopenia and moderate anemia as well as nausea and vomiting.

Preliminary clinical experience with the methyl-bis-nitrogen mustard also indicates that a specific effect is exerted upon lymphatic tissues and upon malignancies of lymphatic origin. Nitrogen mustard has been found to be most effective in the treatment of Hodgkin’s disease and lymphosarcoma, and less satisfactory in the treatment of the leukemias. Preliminary trials of the chemical in certain other neoplasms, viz., melanoma, metastatic mammary and cervical carcinoma, multiple myeloma and sympatheticoblastoma, have not been encouraging.

However, sufficiently favorable results have been obtained in carcinoma of the lung and in polycythemia vera to warrant further trial.

The release of this chemical for further clinical investigation under the auspices of the National Research Council has stimulated much interest in its effects upon malignancies, particularly of the lymphatic tissues. It was natural, therefore, that nitrogen mustard was tried in mycosis fungoides because of its relationship to diseases of the lymph nodes. While the origin of the disease has been in dispute for nearly a century, the opinion most generally held is that it is a neoplasm originating in the reticulo-endothelium of the skin, classified, therefore, as a variety of the related diseases now grouped as lymphoblastomas. This group includes mycosis fungoides, Hodgkin’s disease, lymphatic leukemia and the various forms of lymphosarcoma.

Mycosis fungoides was first described, under the name of pian fungoides, by Alibert in 1806. Later the name was changed to mycosis fungoides because of the development of mushroom-like tumors. Two types of the disease have been de-
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scribed. The first type, the most common, begins with superficial inflammatory eruptions known as premycotic lesions, and resemble eczema, psoriasis, parapsoriasis, or dermatitis exfoliativa. These premycotic lesions may be indistinguishable from the chronic dermatoses unless the infiltrates characteristic of the later stages of the disease are present. Intense itching is generally a prominent feature. These lesions may be persistent or recurrent. After variable and generally long periods of time, characteristic infiltrations of neoplastic cells appear in the lesions. This stage of infiltration is then followed, after months or years, by the formation of fungoid tumors. The second type, the so-called "Tumeurs d'emblée," is characterized by tumor development not preceded by the premycotic or infiltrative stages.

Heretofore, x-radiation of the lesions, either during the premycotic, infiltrative or tumor stage, has been the only therapeutic measure of proven benefit. Generally it induces involution of the lesions and relief from the intense pruritis. Sooner or later, however, the eruption becomes radio-resistant. The lesions then spread and may ulcerate; and the lymph nodes may become greatly enlarged. The pruritis becomes more intense. Death finally results from inanition or from intercurrent infections.

CASE REPORTS

Case 1. Mrs. R. G., a 67 year old white female, was first seen in the clinic in August 1945, complaining of a pruritic skin eruption of 10 years duration. This first appeared on her back and then spread to involve the entire body. The itching was characterized by remissions and exacerbations. Gradually, the skin became thickened and brawny. For several years prior to 1945 she received repeated courses of superficial x-ray therapy, with some temporary improvement each time. When first seen at this hospital, physical examination revealed that the skin of the body was markedly thickened, with numerous nodules and small areas of ulceration. There was no enlargement of spleen or lymph nodes. Skin biopsy revealed mycosis fungoides. The blood count was normal. During the next three months she was given filtered x-radiation in divided doses of 300R and 800R over the trunk with little improvement. During the following year she received sodium thiosulphate intravenously and diphtheria toxoid intramuscularly without benefit.

On October 31, 1946 she was admitted to the hospital for nitrogen mustard therapy. Physical examination at this time revealed an extensive papular, eczematoid eruption involving the entire body except the head, the palms and soles. The skin was thickened, dull red in color and covered with superficial excoriations (figure 1). There were a few discrete nodes in the cervical and inguinal regions. The ankles were slightly edematous.

Laboratory examination. The urine, Kline test, blood N.P.N. and uric acid determinations were normal. The blood count was R.b.c. 4.3 M., Hgb. 81 per cent (13.0 Gm.), W.b.c. 8,120 with polymorphs 67 per cent, eosinophils 3 per cent, lymphocytes 11 per cent and monocytes 9 per cent. The serum albumin was 3.0 Gm. per cent, and the serum globulin was 3.5 Gm. per cent. Sedimentation rate was 12 mm. in 1 hour (Linzenmeier). The electrocardiogram was within normal limits. Sternal marrow puncture showed a slight increase of the mature eosinophils and the eosinophilic myelocytes. A biopsy of the skin was reported as follows: "Section of the skin reveals a moderate acanthosis. The epithelium in places is atrophic and an occasional small ulcer is seen. There is slight parakeratosis of the surface. The superficial portion of the corium and papillae shows striking infiltration by cells which vary considerably in size and shape. Many of the cells are plasma cells. There are also a number of lymphocytes. In addition, there can be seen large mononuclear cells with abundant cytoplasm and large vesicular nuclei. There are many dilated capillaries with prominent endothelial cells. Diagnosis: Mycosis fungoides" (figure 1).

Treatment and course. On November 11, 12 and 13, 1946 the patient was given 5 mg. of nitrogen mustard for a total of 15 mg. Under treatment the white count dropped from 5400 with P. 79 per cent and L. 17
Fig. 1. Case I (R. G.) Extensive Eczematoid Lesions Prior to Treatment

Fig. 2. Case I (R. G.) Skin Biopsy Prior to Treatment, Showing Extensive Infiltration with Lymphocytes and Reticulo-endothelial Cells

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per cent on November 11, to 3,600 with P.76 per cent and L.14 per cent on November 19, 1946, a decrease in the lymphocytes from 918 to 504 per c.u. mm. There was the usual toxic reaction with nausea and vomiting several hours after each injection. There was prompt response to therapy. Four days after the beginning of treatment, there was a definite involution of the eruption and marked reduction of pruritis. One week later the skin of the entire body was clear, except for some large inflammatory eczematoid patches extending across the right scapula and right breast (figure 3). At this time small groups of minute vesicles were noticed interspersed among the eczematous and infiltrated patches. The patient's only complaints were itching and pain (radicular in character) confined to these areas. X-ray examination of the spine on November 27, 1946 showed a compression of the fourth dorsal vertebra. A second biopsy of the skin was taken, immediately adjacent to the area of the first biopsy, on the ninth day after treatment was started. The pathological report is as follows: "The section shows epithelium of average thickness with slight keratinization. There are a moderate number of dilated capillaries in the superficial corium and papillae. A number of pigmented chromatophores are seen. There are a small number of lymphocytes and mononuclear cells located perivascularly. The intense infiltrate of the earlier sections is gone (figure 4). Diagnosis: Chronic dermatitis, slight."

During the months of December 1946 and January and February 1947, the patient remained free of symptoms. The radicular rash subsided considerably. However, in mid-February 1947, itching of the skin recurred. By February 16, 1947, about a dozen noninflammatory papules appeared on the forearm and left chest indicating a recurrence of the original disease. On April 2, 3 and 4, 1947, a second course of nitrogen mustard was given consisting of 6 mg. doses, for a total of 18 mg. By April 7, the new lesions had begun to disappear and by April 14, the skin had again become clear except for the previously noted radicular eruption. During this course of therapy, the lymphocyte count dropped from 1,560 (26 per cent of 6,000) to 240 (8 per cent of 3,000), 8 days after the onset of the treatment. By April 24, the count had returned to normal. When last seen on May 18 the patient was free of all lesions except for the ever present radicular lesion on the right breast and chest. The itching had completely disappeared.
Comment. This patient suffered extensive lesions of the body for 11 years. The lesions reacted to x-radiation at first but in recent years have been radio-resistant. Two courses of treatment with nitrogen mustard, totaling 33 mg., caused a disappearance of the infiltration of the skin and the pruritis. The skin now appeared normal except for a radicular herpetic lesion over the right mid-back and breast which is associated with x-ray evidence of a destructive lesion of the fourth dorsal vertebra. The patient remained clinically well for 3 months, following the first course and for 2 months following the second course to date of report.

Case 2. Mr. R. H., age 72, had been followed in the clinic several years for a persisting pruritic, eczematoid eruption of 8 years duration. These lesions were present chiefly on the legs and thighs. During the past year many similar patches appeared on the trunk and upper extremities. Many of these had become thick and leathery. Concomitantly, several painless nodes appeared in the axillae and groins. On August 2, 1946 a biopsy taken from a lesion on the back was reported as showing "a massive infiltration of the cutis by reticulum cells causing obliteration of the rete pegs and atrophy or disintegration of the overlying epidermis. The lesion is compatible with mycosis fungoides as seen in late stages but lacks some of the features such as pleomorphism of cells, intra-epidermal focal cellular masses and clumping pseudogiant cell formation. It is indistinguishable from lymphosarcoma of the skin." A sternal marrow puncture showed hyperplasia of the myeloid elements of the marrow. His past history, personal history and review by systems were noncontributory.

On January 7, 1947 he was admitted to the hospital for nitrogen mustard therapy. Upon physical
examination he presented a generalized eruption consisting of about a dozen coin to palm sized patches located on the upper back, the legs, the back of the hands and forearms. These patches were pink in color, scaly, fairly well marginated and moderately thick and infiltrated. Pruritis was evidenced by superficial excoriations of all the lesions. There were several enlarged, firm, nontender and freely moveable lymph nodes in the axillae, posterior cervical and inguinal regions. These measured 2 to 3 cm. in diameter. The remainder of the physical examination was normal.

**Laboratory examination.** The blood count showed R.b.c. 5.0 M., Hgb. 93 per cent, W.b.c. 5,200 with P. 65 per cent, E. 2 per cent, L. 18 per cent and M. 15 per cent. The blood platelets were 135,270 per cu. mm. The Kline test was negative. The urine and the blood sedimentation rate were normal. Blood N.P.N. 32 mg. per cent, serum albumin 4.7 Gm. per cent, serum globulin 4.0 Gm. per cent. X-ray examination of the chest was normal.

**Therapy and course.** The patient was given 4 doses of nitrogen mustard of 6 mg. each intravenously on January 11, 13, 15 and 18, 1947. By January 20 there was a marked decrease in the itching, and a noticeable involution of the lesions. The skin became much softer. There was no significant change in the blood counts. The patient was discharged from the hospital on January 28, 1947 with only a faint erythema remaining at the sites of some of the lesions, and considerable shrinking of the enlarged lymph nodes. A repeat skin biopsy on January 21, 1947 showed some of the cells characteristic of mycosis fungoides but a marked decrease in the amount of cellular infiltration. Throughout the course of treatment, the blood counts remained unchanged. To date, 5 months after onset of treatment, he has remained well.

**Comment.** This patient has had mycosis fungoides for 8 years which was radio-resistant. The skin biopsy was unusual in that extensive infiltration of reticulum cells was found with but little pleomorphism. Twenty-four mg. of nitrogen mustard resulted in a clinical remission for the period of 5 months of observation.

**Case 3.** Mr. F. S., age 61, was admitted to the hospital on January 23, 1947 complaining of an eczematoid pruritic eruption of twelve years duration. The eruption first appeared on the hands and wrists later spreading to the legs and thighs. For the past 6 years the eruption has been generalized and intensely pruritic. Since the onset of his illness the patient has received a number of courses of superficial x-ray radiation. During the past 3 years x-radiation has produced only partial temporary remissions. For the past 6 months the lesions have been totally radio-resistant. Three months prior to admission to the hospital, a diagnosis of mycosis fungoides was made from a biopsy of the skin. In addition, during the past 3 years the patient has become progressively more dyspneic on exertion. In the week prior to admission he developed a productive cough.

**Physical examination.** The face, trunk, and all extremities were covered with scattered pink to red patches ranging in size from a silver dollar to saucer-like plaques. Some of the patches were scaly, some moist and eczematoid, and all were infiltrated. The skin of both legs was completely covered with these lesions. There was slight adenopathy in the cervical regions but not elsewhere. Liver and spleen were not palpable. The fundi showed grade I arteriosclerosis; the chest was emphysematous with increased resonance, diminished breath sound and numerous coarse rales. The heart was normal in size, but there was considerable ankle edema. The blood pressure was normal. The prostate was enlarged, but firm, smooth and nontender.

**Laboratory examination.** The R.b.c. varied between 6,170,000 and 5,950,000, Hgb. 114 per cent (19.3 Gm.) and the W.b.c., 7,400 with P. 76 per cent, E. 3 per cent, L. 11 per cent, M. 10 per cent. The sedimentation rate was 11 mm. in 314 minutes (Linzenmeier). Urinalysis and sputum studies were normal. The blood N.P.N. was 32 mg. per cent; the blood Wassermann and Kline tests were negative; the serum albumin was 4.0 Gm. per cent and the serum globulin was 4.0 Gm. per cent. X-ray of chest revealed an increase in bronchovascular markings and some adhesions in both costophrenic angles, suggestive of a chronic bronchitis. The heart was normal in size and configuration. EKG showed left axis deviation and "myocardial impairment." Biopsy of the skin showed a moderate amount of acanthosis. The underlying corium showed scattered small groups of poorly defined cells, a moderate number of round cells, probably lymphocytes, and occasional large mononuclear cells, probably histocytes.

**Therapy and course.** Because of his chronic bronchitis, the patient was given penicillin aerosol, 75,000 units daily, from January 29 through February 7, 1947, with considerable improvement of his pulmonary symptoms.
On January 31, February 1, 3, and 4 he was given 6 mg. of nitrogen mustard intravenously for a total of 24 mg. By February 4, there was a great diminution in the pruritis and by February 9 there was noticeable involution of all the lesions with complete disappearance of the lesions on his arms. However, itching and a new type of papular eruption appeared on his lower extremities. This was diagnosed as a penicillin reaction and was associated with an eosinophilia of 4–13 per cent. During the nitrogen mustard therapy, the blood counts remained unchanged, but in the following 1 weeks there was a progressive drop in the leukocyte count to a level of 3000 with P. 64 per cent and L. 10 per cent.

By February 19 it was evident that the remaining lesions were not involuting. He was then given a second course of nitrogen mustard of 6 mg. each on February 14, 16, 18 and March 1. This was followed by a considerable reduction in the number and size of the remaining lesions with a corresponding reduction in the itching. On March 18 however, a slight recurrence was evidenced by the appearance of a few superficial pink spots. On March 25, 1947 he was readmitted for further treatment. His general condition was poor due primarily to an increase in his pulmonary and cardiac symptoms. He was markedly dyspneic and cyanotic and showed signs of right heart failure. He was digitalized with some improvement.

Further nitrogen mustard was withheld. Instead he received spray x-radiation, 3 times weekly (for 3 weeks), 308 units on each side of his body, and urethane, 0.3 Gm., 3 times a day. After the third x-radiation he began to improve even though he had been radio-resistant previously. Itching was much relieved although still present. His cardiac status remained poor with dyspnea, cyanosis and orthopnea and he died on March 25, 1947 in congestive heart failure. No autopsy was obtained.

Comment. This patient had extensive premycotic lesions of the skin for 12 years which responded partially to x-radiation. For 6 months there was complete radio-resistance. Two courses of nitrogen mustard of 24 mg. each, totaling 48 mg. induced a rapid involution in the lesions and pruritis. Improvement was first noted on the fourth day of treatment. One and one-half months after the onset of treatment, relapse was noted. X-radiation, plus urethane, in spite of previous radio-resistance, was effective in controlling the disease. He was clear of lesions and relatively asymptomatic until the day of death 3½ months after the onset of therapy.

Case 4. Mrs. A. C., age 58, was admitted to the hospital on December 23, 1946. She had been under observation and treatment for mycosis fungoides at several clinics for many years. Her present illness began 30 years ago with an itching rash on the upper back. Similar patches appeared over the entire body during the next few years. The lesions resembled psoriasis, but 6 years ago a diagnosis of mycosis fungoides was established. Since then she had received x-radiation at various intervals with partial remissions. For the past year her disease had been radio-resistant. Upon physical examination she presented a universal eruption of coin to saucer-sized plaques, which were dull red, infiltrated and covered with moderately thick adherent scales. Many lesions were weeping (figure 5). The heart was slightly enlarged to the left, with a grade III blowing systolic murmur at the apex.

Laboratory examination. The R.b.c. was 4,300,000, Hgb. 79 per cent, W.b.c. 11,800 with P. 57 per cent, E. 14 per cent, L. 20 per cent, B. 3 per cent and M. 7 per cent. Urinalysis, blood Kline test, and total blood proteins were normal. A biopsy of the skin, showed the typical histological picture of mycosis fungoides, with a dense polymorphous infiltrate and scattered histiocytes.

Therapy and course. The patient received 3 injections of nitrogen mustard intravenously on December 24, 26 and 27, 1946 for a total of 18 mg. The blood count and differential remained unchanged. By December 30, there was a marked decrease in the infiltration of the patches. The scaling had greatly decreased, the color was now pink rather than a deep red, but the pruritis remained unchanged. On January 2, a repeat biopsy, taken from the same lesion, showed a considerable decrease in the number of cells composing the infiltrate. A second course of therapy was begun 3 weeks later. On January 14, 17, 21 and 22, 1947, she received 4 injections of nitrogen mustard intravenously, for a total of 24 mg. On January 14, the white count was 2,000 and on January 18, it had dropped to 1200 with a normal differential count. By February 5, the white blood cell count had returned to 7,800 with a normal differential. The R.b.c., Hgb. and platelet counts were unaffected. Following the second course of treatment, there was a further decrease in the intensity of the erythema and infiltration in the patches and a complete disappearance of the exfoliation.
The pruritis still persisted, but was much less intense. A third skin biopsy on January 30, 1947, from the same patch, was reported as "mycosis fungoides with further decrease in cellular infiltration of the cutis." Six weeks later, itching became more intense. Some of the lesions on the arms and legs became more infiltrated and nodular. Superficial ulcerations involved some of the nodules on the left foot. The latter ulcerations progressed, coalescing to form a palm-sized area of painful ulceration on the instep of the left foot. On March 17, 18 and 20 a third course of nitrogen mustard was given with simultaneous x-radiation to the ulcer. In the course of 3 weeks there was rapid healing of the ulcer with disappearance of pain.

By April 10, however, there was some recurrence of a generalized pruritis and a fourth course of nitrogen mustard consisting of 6 mg. doses was given on April 11, 12, 15 and 16 for a total of 24 mg. The pruritis and infiltration again improved. Following this, however, all elements of the blood were depressed. The R.b.c. dropped to 1,800,000, Hgb. 54 per cent, W.b.c. 2,500 with P. 42 per cent, E. 6 per cent, L. 44 per cent, M. 8 per cent, and platelets 40,000. The bleeding time was 4\(\frac{1}{2}\) minutes. The tourniquet test was positive. A purpuric eruption was manifest. No secondary infection set in, but she was given penicillin,
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800,000 units daily, prophylactically for about a week and 1,500 cc. of whole blood. By May 15, the platelet count had risen to 145,000. On May 28, the W.B.C. had returned to a level of 2,800 with P. 53 per cent, E. 6 per cent, L. 31 per cent and M. 10 per cent. At the time of writing, the skin is generally somewhat indurated. Pruritis is mild. The ulcerations of the left foot have not returned.

Comment. This patient suffered from mycosis fungoides for 30 years. For 1 year her lesions had been radio-resistant. Four courses totaling 84 mg. of nitrogen mustard were given over a period of 3½ months. Each course of treatment was followed by a marked regression of the lesions. This, in turn, was followed in several weeks by a partial relapse. Six weeks after the second course a recurrence of the lesions was accompanied by painful ulceration of the foot. A third course of nitrogen mustard of 24 mg., together with x-radiation of the foot, produced healing of the ulcer with relief of pain. The fourth course of nitrogen mustard of 24 mg., together with x-radiation to the foot, produced healing of the ulcer with relief of pain. The fourth course of nitrogen mustard of 24 mg. was followed by a temporary pancytopenia. Five months after the onset of therapy, the patient has considerable symptomatic relief and about 50% clearing of her mycosis fungoides lesions. In this instance the combined use of nitrogen mustard and x-radiation of ulcers on her foot seemed to give reasonably good results.

Case 3. Mr. K. S., age 50, first noted an itching rash on his right leg 3½ years ago. This soon spread to his right hip. He was given sulfa drugs and penicillin without effect. Later, a biopsy established the diagnosis of mycosis fungoides. X-radiation was then given with almost complete remission for 6–7 weeks, until about October 1945. These recurrent lesions were acute and fulminant in character, commencing as vesicles and bullae that rapidly became infiltrated. The infiltrated lesions then assumed a nodular and ulcerated character. Since October 1945 he received large amounts of x-radiation with little effect. He also received arsenic without benefit.

On January 18, 1947 he was admitted to the hospital for study and treatment. Physical examination was normal, except for the extensive lesions of the skin. X-ray showed the chest was normal. The trunk and extremities were covered with numerous annular, serpiginous, infiltrated lesions which had a tendency to clear in the center and spread peripherally. Some involved fairly large plaques of skin, without central clearing, and with tendencies toward coalescence. On the left hand, in the upper right groin and on the feet, extensive sloughing of the skin had taken place leaving large areas of denudations and deeper ulcers. In the right groin the area of denudation measured about 1½ by 6 inches. The right foot was completely denuded over the anterior ⅓ of the foot and toes leaving an intensely red and painful ulcer that was secondarily infected. A somewhat smaller area of the left foot was similarly involved. These lesions were intensely pruritic.

Laboratory examination. Urinalysis was normal. R.B.C. 4,030,000, Hgb. 11.8 Gm., W.B.C. 7,700 with P. 66 per cent, L. 30 per cent, M. 11 per cent, E. 1 per cent and B. 1 per cent. The smear was normal and the platelets present in normal amounts. Biopsy of a skin lesion confirmed the diagnosis of mycosis fungoides, but showed few specific changes.

Treatment and course. The patient was given a concentrated course of nitrogen mustard consisting of 7 mg. per dose on January 18, 19, 21, 24, 25 and 27, a total of 41 mg. By the fifth day of treatment there was marked decrease in the number and size of the lesions and in the intensity of itching. The lymphocytes dropped from 1,540 at the onset of treatment to 461. Upon completion of the course of therapy the extensive lesions had almost completely disappeared. At this time there were only several scattered annular lesions about the trunk. The denudations of the left foot and right thigh had healed completely. The right foot, which was the most extensively involved, showed considerable, but not complete healing. New areas of skin began to appear and the secondary infection cleared without other therapy. Two weeks later, however, reactivation of the disease was evidenced by a dozen or so tiny new lesions and an increase in exudation over the pre-existing ones. By February 16, the new lesions had become fairly large and all lesions were oozing considerably. He was given one injection of 7 mg. of nitrogen mustard on
February 19 with the thought of trying weekly "suppressive" doses. By February 16, the progression of the lesions demanded a full course of treatment. On February 16, 17 and 18 and March 1, 3 and 4 he received a second course of 8 mg. doses for a total of 48 mg. The lymphocyte count dropped from 1,800 (30 per cent of 6,000) to 125 (11 per cent of 1,050 on March 5) which forced the abandonment of heavier therapy. By March 1, the lesions began to regress. There was steady improvement and by March 10 about half the lesions had disappeared and the remainder had regressed to at least one-half their original size. The denuded area of the right foot remained but was covered with patches of new skin. He was able to walk without pain in his foot for the first time since the onset of this ulceration. This improvement was short-lived. In a few days the ominous signs of recurrence, namely an increase in oozing, appeared. He continued to regress rapidly and was readmitted to the hospital on April 10, 1947 for further treatment. At this time the entire body was covered with circinate, crusted lesions, and the epithelium of both feet and hands was extensively denuded. His admission blood count showed R.b.c. 3,360,000, Hgb. 58 per cent, W.b.c. 5,000, P. 68 per cent, E. 1 per cent, B. 0.5 per cent, L. 17.5 per cent, and M. 12.50 per cent. The platelets were present in average numbers. He was given a third course of 6 doses of 7 mg. each of nitrogen mustard on April 11, 12, 15, 16, 19 and 21. To this was added colchicine gr. 1/100 3 times a day in an attempt to augment the effect of nitrogen mustard on the nuclear disintegration. The colchicine was discontinued after one week due to severe nausea, vomiting and diarrhea. On April 16, the white count dropped to 600 with P. 38 per cent, E. 4 per cent, L. 18 per cent, and M. 10 per cent. The platelet count was 160,000. X-ray treatment at this time was discontinued. He began to show a septic temperature curve. Penicillin, 800,000 units daily, was given. Blood cultures prior to the administration of the penicillin showed no growth. Ulceration of the skin lesions extended rapidly. His general condition deteriorated and on May 22 signs of broncho-pneumonia appeared. His W.b.c. on May 18 was 1,600 with P. 54 per cent, E. 3 per cent, L. 32 per cent and M. 10 per cent. On May 30, he appeared moribund with a temperature of 104 degrees and very extensive skin involvement with ulceration. Death occurred on June 4.

Comment. This 50 year old male gave a history of mycosis fungoides of only 2½ years duration, with early radio-insensitivity. His skin lesions were unusual in that they started as bullae and vesicles and rapidly reached the tumor stage with extensive ulceration. One hundred and thirty-two mg. of nitrogen mustard were given in 3 courses over a period of 3 months. The last course was combined with extensive skin involvement with ulceration. One hundred and thirty-two mg. of nitrogen mustard were given in 3 courses over a period of 3 months. The last course was combined with extensive skin involvement with ulceration. One hundred and thirty-two mg. of nitrogen mustard were given in 3 courses over a period of 3 months. The last course was combined with extensive skin involvement with ulceration.

Case 6. Mr. C. A., age 54, was admitted to the Los Angeles County General Hospital October 21, 1946, because of a generalized itching eruption and painful ulcers on the lower abdomen and genitals. His present illness began fifteen months earlier with an itching rash on the back, spreading to the extremities. Six months later a similar eruption appeared on the lower abdomen, pubis and genitals. Two months later the genital lesions ulcerated.

Physical examination. Upon examination, he presented a generalized eruption consisting of large erythematous patches and plaques. Some of the patches were elevated and infiltrated, others were eczematous and those over the suprapubic areas and scrotum were covered with multiple ulcerated nodules (figure 7), the remainder of the examination was normal.

Laboratory examination. The hemogram showed: R.b.c. 3,940,000, Hgb. 33.4 Gm., W.b.c. 6,400, P. 61 per cent, L. 18 per cent, M. 13 per cent, E. 1 per cent, B. 2 per cent, promyelocytes 1 per cent, unclassified (young) 3 per cent, and platelets, normal. Biopsy from a nodule on the abdomen was reported as typical of mycosis fungoides and was characterized chiefly by an infiltration of lymphocytes. The Wassermann and Frei tests were negative.

Therapy and course. During the first week of November 1946, he received a total of 115R units of x-radiation to the eczematoid weeping plaques on the neck, and to the suprapubic area. No change was noted
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during the following 3 weeks. On December 11, 13 and 15, he received 4.5 mg. nitrogen mustard, intravenously for a total of 13.5 mg. Daily blood counts showed no appreciable change. On December 16, the day after the last injection, he developed an acute inflammatory dermatitis of the right cheek and around some small infiltrated nodules. This was thought to be a cellulitis although there was no elevation of temperature, white count, or acute adenitis. Penicillin, 310,000 units daily, was administered for 6 days. Ten days following the last injection of nitrogen mustard, all the ulcers were completely healed, the raised infiltrated plaques were flattened and dull brown in color, many of the flat eczematous patches had completely disappeared and the patient was greatly relieved of his pruritis (figure 8). However, the cellulitis-like eruption of the cheek was still present but not as acutely.

By January 10, the acute dermatitis of the cheek had subsided. However, the infiltrated plaques on the right elbow and forearm had become nodular and eczematous, and several new ulcers had appeared in the scrotum and in the groin. Three more intravenous injections of nitrogen mustard, 6 mg. each, were administered on January 11, 12, and 13, 1947. There was an immediate recurrence of the cellulitis-like dermatitis of the right cheek, with a similar acute eczematous dermatitis of the left side of the neck. Therapy was discontinued. One week later the ulcers were completely healed, and the infiltrated and eczematous plaques of the body greatly improved. The patient remained improved for the next 2 months. During this period the acute lesion on the cheek became infiltrated, thickened and nodular. A second biopsy showed the same characteristic infiltration of mycosis fungoides. By the end of the second month infiltrated nodules and new ulcers had appeared. He was given a third course of nitrogen mustard totaling 14 mg. Simultaneously, he was also given colchicine 1/100 gr. (0.6 mg.) 3 times a day increasing to 1/50 gr. (1.2 mg.) 3 times a day, on the theory that there might be an additional effect on nuclear disintegration. One week after the course of nitrogen mustard therapy, the ulcers were again completely healed; the larger nodules had shrunk considerably in size, but the lesion on the cheek remained unchanged. This time improvement persisted for only 3 weeks. At the date of report he has begun to show early signs of recurrence.

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Fig. 7
CASE 6 (C. A.) MYCOSIS FUNGOIDES NODULES AND ULCERS

Fig. 8
CASE 6 (C. A.) COMPLETE HEALING OF ULCERS, AND INvolution OF NODULES TEN
DAYS AFTER THERAPY
Comment. This patient presented a rapidly progressive mycosis fungoides of 15 months duration, with multiple, large, eczematous, infiltrated patches and plaques, infiltrated nodules, and multiple ulcerated nodules on the lower abdomen, pubis and scrotum. He was given 3 courses of nitrogen mustard totaling 55.5 mg. The immediate response to the nitrogen mustard was excellent, but each course was followed shortly by a recurrence. A fixed drug eruption resembling cellulitis followed the first 2 courses of the drug, but not the third. Two courses of x-radiation were also given without effect. Colchicine was given along with the third course, but did not seem to be of value. The inability to arrest the disease process for more than a few weeks at a time stamps this case as a therapeutic failure.

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<th>Case</th>
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<th>4 (A. C.)</th>
<th>5 (K. S.)</th>
<th>6 (C. A.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>67</td>
<td>72</td>
<td>62</td>
<td>58</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>Duration of disease (yrs.)</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>30</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Radio-insensitive Lesions</td>
<td>Several Eczematoid nodular infiltrative “massive”</td>
<td>Several Eczematoid infiltrative Moderate</td>
<td>1 Eczematoid infiltrative</td>
<td>Dense</td>
<td>Minor changes</td>
<td>Abundant polymorph. infiltrate</td>
</tr>
<tr>
<td>Biopsy findings</td>
<td>Large no. R-E cells</td>
<td>R-E cells</td>
<td>R-E cells</td>
<td>R-E cells</td>
<td>R-E cells</td>
<td>R-E cells</td>
</tr>
<tr>
<td>N-Mustard dosage (mg.)</td>
<td>3 x 5</td>
<td>4 x 6</td>
<td>4 x 6</td>
<td>3 x 6</td>
<td>3 x 6</td>
<td>3 x 4.5</td>
</tr>
<tr>
<td>Total (mg.)</td>
<td>33</td>
<td>24</td>
<td>48</td>
<td>3 x 5</td>
<td>3 x 6</td>
<td>3 x 6</td>
</tr>
<tr>
<td>Months observed</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Results</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Fair</td>
<td>Death</td>
<td>Poor</td>
</tr>
</tbody>
</table>

DISCUSSION

In each of the 6 cases studied, the mycotic lesions, irrespective of type or the stage of the disease, showed a marked immediate response to nitrogen mustard therapy. In each instance, the disease was radio-resistant. In 4 (cases 1, 2, 3, 4), the disease was of long duration (between 8 and 30 years), and had responded to x-radiation over an appreciable period of time. The radio-resistant phase of the disease had existed, at the time of study, for several years. In 2 instances (cases 5 and 6) the disease process was of short duration (1½ years and 15 months respectively). Here the disease was exceptionally acute, and radio-resistance existed almost from the onset. Hence, the response of the tumor cells to nitrogen mustard seems to bear no relationship to their resistance to x-radiation or the duration of the disease. In this the reaction of the lesions of mycosis fungoides parallel those of Hodgkin's disease.

The degree of response varied from case to case. By a strange twist of fate, the cases were seen (and numbered) in almost the exact order of their response to the drug. (See table above.) Cases 1, 2, 3 may be said to have had an excellent response.
In each instance the lesions more or less completely cleared and the itching was greatly relieved. Case 4, in which the disease has existed 30 years, has shown only partial improvement. Cases 5 and 6 must be classed as clinical failures. While there was a prompt response to the drug, each course was followed by a relapse within several weeks, and the duration of improvement became shorter and shorter. Case 5 died as a direct consequence of the disease; while case 6 is progressing steadily to the same end, his disease process having been unrestrained by any method at our command. These 2 cases are exceptional because of their short duration (2$\frac{1}{2}$ and 1$\frac{1}{2}$ years), the rapid spread of the disease, and the biopsy findings as noted below.

The first 4 cases which showed good clinical responses, were of a similar nature. Their lesions were characterized by a prolonged premycotic stage (eczema, psoriasis, parapsoriasis) and infiltrations and nodule formation. There was little tendency toward breakdown into ulcerations or denudations. In contrast, cases 5 and 6 showed a distinctly different type of clinical picture, characterized by early nodule formation and extensive ulceration. In addition, case 5 presented the unusual feature of the lesions developing with vesicles and bullae which rapidly became infiltrated.

From a study of the biopsies, one fact has emerged which may be of considerable significance if substantiated in other types of clinical material. In cases 1, 2 and 3, which showed the best response, the biopsy specimens showed a high incidence of reticulo-endothelial cells. In case 2 "a massive infiltration by reticulum cells" was commented upon. In case 1, there was a massive polymorphous infiltration including reticulo-endothelial cells. In case 3 there was moderate infiltration of lymphocytes and some reticulo-endothelial cells. These findings showed a direct correlation with the clinical improvement. Thus, of the 4 cases, case 2 has done the best, clinically, case 1 second best, case 3 third best and case 4 the poorest. In contrast, cases 5 and 6 showed, on biopsy study, different pictures. In these 2 patients the histological picture presented an infiltrate in which the distribution and polymorphism was characteristic of mycosis fungoides, but sparse in reticuloendothelial cells.

These observations conform with the recognized fact that Hodgkin's disease, presumed to be of reticulo-endothelial origin, responds better to the nitrogen mustards than do the lymphosarcomas or lymphatic leukemia which are more specifically diseases of the lymphoid apparatus. Of interest are the observations of one of us (H.H.H.) in 2 cases of monocytic leukemia and in one case of reticulum cell sarcoma. In the first case of monocytic leukemia, life was prolonged for several months beyond the expected date of exitus, and the blood monocytes were reduced at will by the nitrogen mustard. In the second case, the blood monocytes are reduced with great ease by the drug. In the case of the reticulum cell sarcoma a most remarkable effect was secured. The patient (E.F., aged 34, to be reported later) was semimoribund at the time of treatment. He presented generalized glandular enlargement of moderate degree and a splenomegaly. Nitrogen mustard therapy resulted in disappearance of all evidence of the disease process. At the date of writing, 6 months later, the only evidence of disease are a slight immaturity of the
blood lymphocytes and a somewhat greater than normal fatigue on exertion. These observations suggest that the point of attack of the nitrogen mustard is specifically on the reticulo-endothelial tissue. Considerable interest attaches to the effects of the nitrogen mustard in the reticulo-endothelioses and in other diseases in which this system is extensively involved. However, one case of widespread Kaposi's sarcoma (idiopathic, multiple, hemorrhagic sarcoma of Kaposi) which some investigators believe to be of reticulo-endothelial origin, was treated with nitrogen mustard by one of us (B.A.N.) without effect upon the disease.

SUMMARY AND CONCLUSIONS

1. Six patients with mycosis fungoides, resistant to x-radiation, have been treated with nitrogen mustard.
2. Each patient showed a striking immediate response to the drug.
3. The extent of the remissions of the disease process, during the period of study (from 4 to 7 months), varied with the nature of the lesions and the biopsy findings:
   (a) Three patients with histories of prolonged premycotic stages and reticulo-endothelial cell hyperplasia on biopsy showed an excellent response to the drug.
   (b) One patient with a history of prolonged premycotic stage and biopsy findings of a dense polymorphic infiltrate, but with sparse numbers of reticulo-endothelial cells showed a partial response to treatment.
   (c) Two patients whose disease was of short duration with early nodule formation and ulceration with biopsy findings of rather few endothelial cells among the infiltrate showed rapid recurrences and progression of the disease.
4. Nitrogen mustard is an effective agent in the palliative treatment of mycosis fungoides.
5. It is suggested that the point of attack of the nitrogen mustard is on the neoplastic cell arising from the reticulo-endothelial system.
6. The response of mycosis fungoides to nitrogen mustard presents additional evidence of the neoplastic nature of the disease.

REFERENCES

THE INFLUENCE OF NITROGEN MUSTARD ON MYCOSIS FUNGOIDES: OBSERVATIONS RELATING ITS EFFECT TO THE RETICULO-ENDOTHELIAL SYSTEM

HENRY H. HENSTELL, JEROME N. TOBER and BEN A. NEWMAN