

Nitrogen Mustard Therapy in Hodgkin's Disease

A. LANFRANCO B.Sc., M.D.

(Demonstrator in Medicine,)

Asst. Physician, St. Luke's Hospital.

As far back as the first World War it was observed that mustard gas had a cytotoxic effect on the haemopoietic tissues. In 1931, attempts were initiated to test its value in the treatment of neoplastic diseases, and at the beginning of the last war, experiments with its nitrogen derivatives were again renewed in England. It was in America, however, that reports of clinical trials were first published.

The nitrogen mustards in common use are the two aliphatic compounds methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride. The first has been more universally used so far, but there is no therapeutic difference between the two. An aromatic nitrogen mustard, bis (beta-chloroethyl) naphthylamine, which is given orally and is less toxic, has been tested recently in the treatment of Hodgkin's disease and other conditions, (1) but extensive clinical trials are still forthcoming. Both the aliphatic compounds are readily soluble in water, when they undergo rapid chemical rearrangement, forming first cyclic ethylene-imonium derivatives, and later other relatively inactive compounds. Their therapeutic activity is due to the derivatives first formed in solution, which have a powerful effect on mitosis and on the intra-cellular enzyme system, causing mitotic arrest and nuclear fragmentation, an action which is similar to that of irradiation. Because of

this effect, nitrogen mustard hydrochloride has been tried in the proliferative and in the neoplastic diseases of the haemopoietic tissues, such as Hodgkin's disease, chronic myeloid leukaemia, the reticulosarcomas, reticulosarcoma, multiple myeloma and polycythaemia vera, as well as in mycosis fungoides and carcinoma of the lung. Hodgkin's disease and mycosis fungoides, however, responded best. In both diseases long remissions were reported by different workers, and in mycosis it was observed further, that the drug was most effective in those cases where the reticulum cells dominated the cutaneous infiltrations, leading to the conclusion that nitrogen mustard might have a selective action on this type of cell. (2)

Nitrogen mustard hydrochloride is supplied in a dry form in 10mg. doses. It must be dissolved in normal saline solution and is to be used immediately, otherwise hydrolysis will render the compound inactive. The usual dose is 0.1mg. per kilogram of body-weight, injected intravenously daily or on alternate days for a total of three to six doses, depending on the response and on the type of case. No further course of treatment should be undertaken within an interval of at least six to eight weeks. Lower or higher doses have been recommended in selective cases, but no single dose should exceed 8mg. The injection is best given early in the morning after a light breakfast.

(1) B.M.J. — 1949-2-641.

Annual report of the Empire Cancer Campaign — 1948 p.59.

(2) B.M.J. — 1948-2-304.

Blood — 1947-2-564.

Since nitrogen mustard derivatives retain the vesicant properties of mustard gas, their administration requires expert intravenous technique, because undue damage to the endothelium of the vein will inevitably result in thrombosis, thus rendering subsequent treatment difficult or impossible. Leakage in the subcutaneous tissues should be scrupulously avoided, as it will cause a severe local reaction which may go on to tissue necrosis. Nausea and/or vomiting nearly always occur three to four hours after the injection,

doses, while in England (2) this drug did not stop the nausea or allay the vomiting. Phenobarbitone was equally disappointing. However, the action of nitrogen mustard hydrochloride on the haemopoietic tissues is double edged, and haematological control should be maintained in all cases, ideally by means of bone-marrow smears. The effect on haemopoiesis is apparent within two to five days and is greatest by the eighteenth day after the last injection, and may be prolonged as far as the thirtieth day. At first, there is

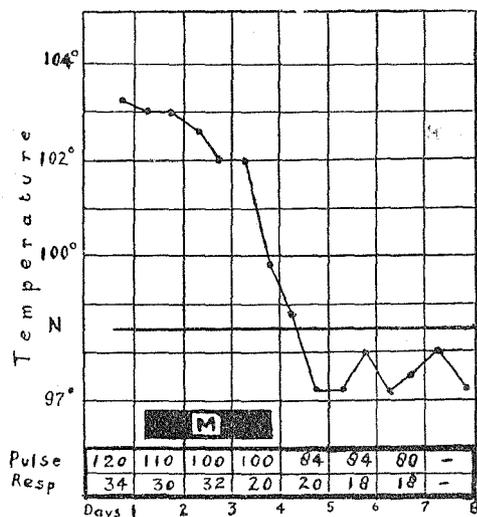


FIG. 1.

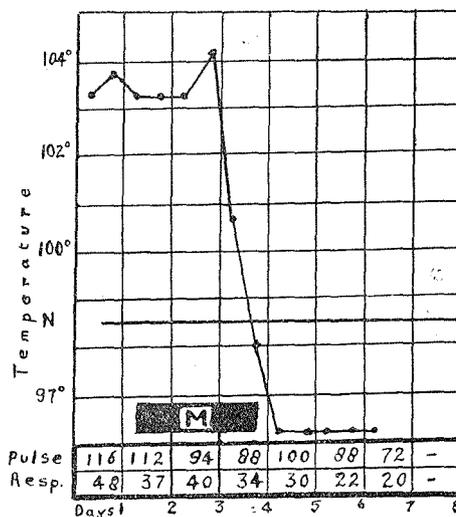


FIG. 2.

M — Nitrogen Mustard Hydrochloride.

tion, and loss of appetite and headache are frequently present during the course of treatment, but these side effects are of no consequence and can be disregarded. Opinions about the prevention and allay of these symptoms have been conflicting. American workers (1) claimed good results with pyridoxin hydrochloride injected intravenously in 200 mg.

a fall in the total leucocyte count — a transient lymphopenia with a temporary increase in the neutrophils — rapidly followed by a decrease in granulocytes, which may take up to a month to return to the normal level (3). However, with the doses mentioned, the whites rarely fall below 2,000 per c.mm., and agranulocytosis has only been reported in less than one per

(1) Shullenberger, Watkins, Kierland — 1949 — J.A.M.A. — Vol. 139. No. 12. p.773.
 (2) Nabarro, J.D.N. — 1949. B.M.J. 2. p.624.
 (3) Ibid.

cent of cases. The effect on the erythrocyte count is variable and usually insignificant. A fall in the platelets may occur, but is less frequent and the count seldom falls below 60,000 per c.mm. Purpura, however, has been observed in a number of cases, but, when it occurred, was transient and did not require any special treatment (1).

During the last year, the opportunity occurred to treat three cases of Hodgkin's disease with the 'bis' compound of nitrogen mustard hydrochloride. These did not belong to a selected group, but were the only cases available for treatment during that period. The daily dose given in each case was 0.1mg. per kilogram of body-weight. The intervals between repeated courses ranged from four to six weeks. The secondary anaemia was treated in each patient with iron and crude liver extract.

Case 1. A young man, aged 19 years. In September 1946, he had fever, anaemia and splenomegaly. For the last three years he had bouts of fever, with spontaneous remissions of not more than fifteen days duration. He was admitted to hospital on 23rd February 1949, complaining of abdominal colicky pains and shortness of breath. He looked very ill, anxious and dyspnoeic (respirations 36 per minute). The temperature was 103°F. and the pulse 120 per minute. The cervical and inguinal glands were enlarged. The spleen was 5ins and the liver 2ins below the costal margin. The red blood corpuscles numbered 3,250,000 per c.mm. and the white corpuscles 5,300 per c.mm. (polymorphs 50, lympho. 32 and mono. 18 per cent), the haemoglobin being 50 per cent (Sahli). A skiagram of the chest showed enlargement of the mediastinal glands and glandular biopsy revealed Dorothy Reed cells. The temperature ranged from 100° to 103°F. up to 25th March, when nitrogen mustard was given for three consecutive days. Except for nausea and vomiting for three hours after the injection, no untoward results were observed. On the second day of treatment, the temperature dropped down to 96°F., the respiratory rate returned to within normal and the glands disappeared almost completely. The spleen decreased by an inch, but there was no change in the size of the liver. The

improvement in the general condition was remarkable, appetite increased, and there was progressive gain in weight. He was discharged from hospital on 13th May.

On 27th June, three months after the first course, a relapse was again treated with similar doses of nitrogen mustard and again there was a marked response (Fig.1), the patient being sent home three weeks after admission.

However, a week later, he was readmitted to hospital, and this time he looked extremely ill. The face was bloated and of a greenish pallor. The cervical glands were considerably enlarged and the spleen reached almost to the pelvic brim. He was very dyspnoeic and was running a temperature of 103°F. The red blood corpuscles were 2,850,000 per c.mm. and the white corpuscles 6,400 per c.mm. (polymorphs 60, lympho. 33, and mono. 7 per cent), the haemoglobin being 45 per cent. A third course of mustard gas was again following by a remission, which was of five days duration. From then on, his condition deteriorated rapidly and he died in October 1949.

Case 2. The next patient, a young man of seventeen, noticed, in January 1949, a painful swelling in the left arm-pit; he had no fever and no other complaint, and the swelling subsided spontaneously after a few days.

In March 1949, he was remitted to hospital for 'Fever — unknown origin'. He looked ill, was pale and short of breath. The temperature was 104°F., the pulse 120 and the respiration 42 per minute. The cervical, the left axillary and the mediastinal glands were enlarged, while the liver was 1in. and the spleen 2ins below the costal margin. There was a moderately severe anaemia (red blood corpuscles 3,500,000 per c.mm., haemoglobin 50 per cent) and a leucocytosis of 23,000 per c.mm. (polymorphs 78, lympho. 12, and mono. 10 per cent).

On 19th March, nitrogen mustard hydrochloride was given for three consecutive days. On the third day, the general condition improved greatly, and the temperature went down to below normal (Fig.2). The glands vanished, but the liver and spleen did not decrease in size. Improvement was maintained and he was discharged at the beginning of April.

Eight days later he had a relapse (period of remission twenty one days). His condition had deteriorated considerably and he looked ill. He was very dyspnoeic and was running a temperature of 103°F. All accessible glands were enlarged

and he complained of severe abdominal colicky pains with loose stools. The haemoglobin went down to 35 per cent, and the white corpuscles were 8,800 per c.mm.

A second course of mustard gas was again followed by some improvement, the temperature going down to below normal. After five days the temperature again shot up to 104°F. and he died four days later.

Case 3. The last patient to be treated, a man 27 years old, had both nitrogen mustard hydrochloride and deep X-Ray therapy. For twelve months before admission, he had girdle pains. For the last three months, he ran a temperature of 100° to 102°F., at the same time noticing lumps at the side of the neck and in the left groin. He was admitted to hospital at the end of August 1949, looking thin and very pale. The temperature was 102°F., the pulse 120, and the respiration 28 per minute. There was splenomegaly and multiple glandular enlargement, but the liver was not palpable. The red blood corpuscles numbered 3,000,000 per c.mm. and the white corpuscles 10,500 per c.mm. (polymorphs 80, lympho. 28 and mono. 2 per cent), the haemoglobin being 50 per cent.

Nitrogen mustard hydrochloride was started on 8th September. The temperature dropped down to below normal after the first dose, but because of a rise the next day to 99°F., which persisted, six consecutive injections were given. Dramatic improvement followed. The glands decreased in size, the temperature settled to below normal and the patient felt so well that he was discharged as out-patient on 21st September.

A relapse occurred a month later (period of remission thirty seven days), but this time he did not look so ill as when first admitted. The temperature was only 99°F., the glands had not increased in size since his discharge from hospital, but moderately severe anaemia was still present, the white cell count, however, remaining within normal limits. This time he complained of severe pain in the chest and in both knee-joints, but no neurological signs were present. Skiagrams of the chest and of the spine showed mediastinal enlargement and lymphadenomatous involvement (D11, D12; L1, L2) respectively.

A second course of six injections of nitrogen mustard was again followed by a remission and patient was discharged on 1st November.

He had to be readmitted, however, twenty

days later with a temperature of 102°F. The glands were all enlarged, but there was no pain and he did not feel very ill. Because of the short remission and of the bone lesions, deep X-Ray therapy was tried, but three sittings of filed radiation at twenty four day intervals did not have any effect on the temperature and the general condition remained stationary throughout. On 10th February, a further course of three consecutive doses of mustard gas was followed by a sudden drop in the temperature and an improvement in the general condition. The temperature rose up again a month later, and in spite of another trial with X-Ray therapy, it persisted between 101°F. and 103°F. up to the end of March. Three doses of mustard gas at alternate days again brought on a remission, which has persisted so far.

The intensive treatment in this case was checked by frequent blood tests, which remained satisfactory throughout. Serial X-Rays showed that there was no progression or regression in the bone lesions, though pain did not recur.

It is readily admitted that the small number of cases described have no statistical significance, for they fall far short of the requisite data, yet in such a relatively rare condition as Hodgkin's disease every little helps. It is interesting, however, to point out that the results obtained in this small series compare well with those described in the literature to date.

The immediate objective response to treatment was, in all cases, a sudden drop of the temperature to below normal and an appreciable decrease in the size of the enlarged glands. The spleen was very little affected, and the liver not at all. Case 1 was a disseminated Hodgkin's. The better results obtained in this instance (immediate lowering of the fever, improvement in the general condition, longer remissions) agree with those reported by Nabarro in 1949 (1). He observed that nitrogen mustard therapy was encouraging in the chronic disseminated case, not very satisfactory in the acute type (case 2 in this report) and wholly disappointing when localised involvement predominated;

(1) Nabarro, J.D.N. — 1949, B.M.J. 2, p.625.

in such cases irradiation by roëntgen rays should be the treatment of choice. Case 3 was interesting because of the lymphadenomatous changes in the spine — an unusual site of metastasis in a disease which is itself uncommon — and because it proved beyond doubt that disseminated lymphadenoma fares better with mustard gas than with X-Ray treatment.

As regards side effects, none other than nausea and vomiting (case 1) were encountered in this series. Blood tests were carried out periodically, but did not show any of the complications described in the literature.

Up to the present, the nitrogen mustard derivatives far from solve the problem in the treatment of the lymphadenopathies and allied diseases, yet they have a right to claim a definite place as pal-

liative measures. Their availability and the comparative ease of administration are certainly an advantage. At least, remissions from disturbing symptoms, and therefore a more tolerable life for the patient, can be obtained in those cases which formerly did not respond to the only treatment then available — irradiation. Moreover, in the terminal stages of the disease, a dramatic remission may occur; this means prolonging life, and, where there is life there is always hope! For, although the importance of the nitrogen mustards lies not in their immediate therapeutic application, yet better understanding of their mode of action may prove the advent of a related compound which is more powerful and more specific.

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