Discussion

The administration of T.E.A.B. leads to a slight fall in gastric acidity as estimated by the alcohol test meal. After T.E.A.B. the induction of insulin hypoglycaemia fails to stimulate a rise in gastric acidity. This indicates the presence of vagal blockade and is in keeping with the known action of the drug. It can be assumed that such secretion as occurs after T.E.A.B. is due to the chemical mechanism of gastric secretion. It is interesting to note that after T.E.A.B. the injection of histamine does stimulate gastric secretion, albeit less than normally. This is interesting on account of the fact that histamine acts directly on the oxyntic cells, and so the reduction in acidity in this case cannot be due to an autonomic blockade. Hollander (1944) asserts that the oxyntic cells secrete acid of a constant strength; but if on histamine stimulation they secrete into a stomach which is comparatively amotile there will result a fair degree of buffering and dilution by alkaline and mucoid elements. This fall in acidity may therefore be attributed to retention, to which Johnson ascribes the same effect following vagotomy. He points out that in the amotile stomach there is difficulty in evacuating serial specimens completely, so that dilution of secretion occurs.

The reduction in night secretion is interesting. Because of the motility effect, it could be held that it was in part due to regurgitation of duodenal contents through a relaxed pylorus. A few experiments were abandoned because of bile-staining of the juices drained off; on the other hand, the 10 cases reported were free from bile in the suction specimen, and the volume in the 12-hour specimen after T.E.A.B. was less than that taken off the previous evening.

The average reduction in milli-equivalents per hour was 80%, comparing not unfavourably with 90% following anatomical section of the vagus.

The motility effect has been shown to be similar to that following vagotomy; but T.E.A.B., as well as inhibiting the parasympathetic supply of the stomach, might be expected to effect gastric function in some way by its action on the sympathetic. There are several records of the effect of splanchnic section on gastric secretion in man and animals. Brown (1933) could find no demonstrable change in free or combined acidity following complete removal of the sympathetic chain or coeliac ganglia in cats, and Ray (1942) investigated and found no change in gastric acidity after bilateral sympathectomy.

It has been claimed by Little *et al.* (1947) that T.E.A.B. is effective in preventing or modifying the course of peptic ulcer produced experimentally in animals. In view of its effects on the gastric secretion and motility, and particularly on the volume and acidity of the nocturnal juice, the hope was raised that it might be of value in the treatment of peptic ulcer in man. It is perhaps worthy of note that all 10 patients submitted to repeated injections of T.E.A.B. were free from pain during the progress of the experiment, whereas previously they had had incapacitating symptoms. T.E.A.B. has, however, certain practical disadvantages, especially in requiring to be given by injection and in giving rise to unpleasant subjective symptoms. It remains for future research to find a means of prolonging its action and minimizing its side-effects.

Summary

The chemistry and pharmacology of T.E.A.B. are described. T.E.A.B. produced a slight fall in gastric acidity in the secretory response to an alcohol test meal.
It negated the secretory response to hypoglycaemia.
It reduced the response to histamine.

It reduced the volume and acidity of the 12-hour spontaneous night secretion.

It produced a vagotomy-like effect on gastric motility.

Its effect on the cephalic and humoral phases of secretion is discussed after its use in 10 patients submitted to insulin and histamine stimulations respectively. The changes in the concentration of the night secretion in 10 ulcer patients and the effects on motility in five ulcer patients are discussed; a comparison is drawn with that following vagotomy. Its disadvantages are enumerated. Experimental use in peptic ulceration in animals is mentioned and suggestions are made for further use.

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NITROGEN MUSTARD THERAPY WITH SPECIAL REFERENCE TO HODGKIN'S DISEASE

BY

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Therapeutic trials with the nitrogen mustards in cases of neoplastic disease were started in the United States in 1942. Rhoads (1946) published the first analysis of results obtained, and many further reports have appeared since. Experiences in this country have been given by ApThomas and Cullumbine (1947), Wilkinson and Fletcher (1947), ApThomas (1948), Boyland *et al.* (1948), and Watson and Pemberton (1948). These reports make no claim that the treatment is any more than palliative. The best results have been obtained in cases of Hodgkin's disease, and moderate but variable remissions in other lymphomata and lymphosarcoma, chronic leukaemia, polycythaemia vera, and mycosis fungoides. In carcinomatous conditions the results have been disappointing except in bronchial growths, where in some cases transient benefit has followed treatment. In April, 1946, a trial supply of the "bis" compound was received. As it is now generally available, this interim report summarizing the benefits and dangers attending its use is being published.

Dosage and Method of Administration

The amount of the drug that can be given is limited by the action on the bone marrow, and the American workers recommended that in a standard course the total dose of the "bis" derivative hydrochloride should be 0.4 mg. per kg. of body weight. This was divided into four doses of 0.1 mg. per kg. given intravenously on consecutive days. The vein used for the injection often becomes thrombosed, and to reduce the demand for veins trials were made with fewer but larger injections. This also

had the advantage that the vomiting which followed most injections was repeated on fewer occasions and the course was completed more quickly. When a patient is being treated for the first time it is advisable to start with a small dose—0.1 mg. per kg. or even less in debilitated subjects—and if the response is satisfactory the course may be completed by two further injections of 0.15 mg. per kg. In subsequent courses two injections of 0.2 mg. per kg. are given, or, if it is decided to give maintenance injections at regular intervals, 0.2 mg. per kg. once only, every four to eight weeks. The maximum single dose given to any patient was 12.5 mg. It was found that the best time to give the injections was in the morning after a light breakfast. The question of the time interval that must be allowed before a course is repeated will be discussed later in relation to toxic effects on the bone marrow.

The white crystalline salt is dissolved in about 10 ml. of sterile saline immediately before injection. It must not be allowed to stand after being dissolved, as it undergoes hydrolysis and becomes inactive. All-glass eccentric-nozzle syringes have been used with a size 17 needle; the injection may be given as quickly as the size of the needle permits. It was found that when the injection was made direct into the vein thrombosis occurred in about half the cases. This may lead to considerable difficulty if repeated courses are needed, and it is also advisable to retain one large vein in case blood transfusion is required later. An alternative technique of administration is to inject the drug into the tubing of a running saline drip, by which the incidence of thrombosis is much reduced. When a patient receives the drug for the first time, direct injection may be used, but if widespread thrombosis follows and further courses are likely to be indicated it is wiser to change to the drip-tube method. Veins partly occluded by tumour masses should be avoided. If any of the solution escapes into the subcutaneous tissue, oedema, redness, and discomfort appear in about 24 hours and may last several weeks.

Results

In many of the published reports success has been claimed if any regression of the tumour masses occurred after treatment. The regression may, however, be so slight or so transient as to be of no practical value, and may be unaccompanied by any improvement in the general condition. Stricter criteria have therefore been adopted in assessing this series. The results have been described as conspicuous benefit, moderate benefit, or failure. Conspicuous benefit is considered to have been obtained if a previously incapacitated patient is able to leave hospital and return to and continue in his normal occupation for at least three months; moderate benefit—a remission of similar duration in which the patient is able to leave hos-

TABLE II.—Duration of Remission in Cases showing Benefit

Case No.	Nature of Case	Course No.	Duration of Remission	Classification	Remarks
3	Hodgkin's disease	N.M.1	5 months	Conspicuous benefit	On maintenance therapy for six months subsequently
5	Hodgkin's disease	N.M.2	3 "		
		N.M.1-2	12 "		
		N.M.3	4 "		
6	Hodgkin's disease. Surgical excision	N.M.4	1 + "	" "	
		N.M.1	21 "	" "	
9	Hodgkin's disease. Previous x rays	N.M.1	6 "	" "	
		N.M.2	3 "		
		N.M.3	3 "		
		N.M.4	Nil		
19	Hodgkin's disease	N.M.1	4 months	Moderate benefit	Three subsequent maintenance injections. Total remission 7 months
24	Hodgkin's disease. Previous x rays	N.M.2	1 month		
		N.M.1	3 months	Conspicuous benefit	
25	Malignant lymphoma	N.M.1	5 "	Moderate benefit	
10	Mycosis fungoides	N.M.2	1 month		
		N.M.1	8 months	" "	
		N.M.2-3	3 "		

N.M. = Nitrogen mustard—the "bis" compound

pital and be about his home; and anything less than this—a failure. Thirty-eight patients have been treated and a total of 61 courses and a number of maintenance injections have been given. The cases treated and the results obtained are shown in Tables I and II.

Cases of Hodgkin's Disease that had not received Previous X-Ray Therapy.—In a group of six cases there were two in which conspicuous benefit was obtained. Both had visceral deposits, and one of them (Case 3) had fever and anaemia and the other (Case 5) amyloidosis and hypoproteinaemia. Case 19, with lymphadenopathy, fever, and anaemia, had a remission after the first course of four months during which she was able to leave hospital and do some of her housework; a second course, however, produced less improvement and deep x-ray therapy was given. The three failures included one with anaemia, fever, and hepatosplenomegaly, which showed no response at all; one with axillary lymphadenopathy, which rapidly recurred; and one in which enlarged mediastinal glands showed slight regression only. The last two cases were examples of the commonest type of Hodgkin's disease, which presents with localized glandular masses, and on account of the poor results obtained here, and reported by others, no further cases of this type were given nitrogen mustard as the initial treatment. A further case (No. 6) had a large mass of glands excised from the side of the neck. Microscopical examination showed Hodgkin's disease, and a course of nitrogen mustard was given. The patient has remained well and been gaining weight since (21 months).

Cases of Hodgkin's Disease Treated Initially with X Rays.—The 14 patients who were treated initially with deep x rays and subsequently given nitrogen mustard fall broadly into two groups. The first (four cases, one conspicuous benefit (No. 24), three failures) had had repeated recurrences in one group of glands and the condition of the skin precluded further irradiation. The disease in patients of the second group had, after a slow or rapid evolution, apparently reached the terminal stage. In some, numerous deposits of Hodgkin's tissue were rapidly appearing in different sites; in others, despite such evidence of activity as fever or anaemia, there were no deposits suitable for local x-ray treatment. (Ten cases, one conspicuous benefit (No. 9), nine failures.) In two cases of the more acute type in which the remissions produced by irradiation were of brief duration, those following nitrogen mustard were equally disappointing.

TABLE I.—Summary of Cases Treated and Results

Nature of Case	Number of Cases	Result		
		Conspicuous Benefit	Moderate Benefit	Failure
Hodgkin's disease:				
Previously untreated	6	2	1	3
Previously treated by surgery	1	1	0	0
Previously treated by x rays	14	2	0	12
Malignant lymphoma	3	0	1	2
Acute lymphatic leukaemia	1	0	0	1
Chronic lymphatic leukaemia	1	0	0	1
Lymphatic leukaemia with lymphoblastic lymphoma	1	0	0	1
Multiple myeloma	1	0	0	1
Carcinoma of bronchus	5	0	0	5
Carcinoma of rectum	1	0	0	1
Mycosis fungoides	3	0	1	2
Lipomelanotic reticulosis	1	0	0	1

Results in Other Conditions.—There were three cases of malignant lymphomata of other types: a reticulosarcoma which showed no response, a very primitive lymphoma in which dramatic but incomplete and transient regression occurred, and a slow-growing lymphoblastic lymphoma in which there was moderate benefit (Case 25). In the cases of carcinoma of the bronchus treatment failed to relieve either chest or nerve-root pains. The three cases of mycosis fungoides were all of long standing, and although an incomplete remission of reasonable duration was obtained in one the results were disappointing.

Complications and Side-effects of Nitrogen Mustard Therapy

The three most important of these are: changes in the blood, vomiting, and venous thrombosis at the site of injection. The last-named has already been discussed.

The white cell levels changed in nearly all cases. In the first few days a transient increase of neutrophils and reduction of lymphocytes was usually found; much more important, however, was the granulopenia which followed—maximal at the beginning of the second week and returning to normal levels about the fourth. Complete absence of polymorphs from the peripheral blood occurred in two patients. The first had an acute malignant lymphoma, which showed partial regression after a course of treatment. As a desperate remedy this was repeated after two weeks, but the patient died one week later and the agranulocytosis which had developed was probably a contributory factor. The second patient had Hodgkin's disease, and derived some benefit from a course of nitrogen mustard, which was repeated after two months. Typical agranulocytic angina followed, but intensive penicillin therapy controlled the infection and white cells reappeared in the peripheral blood. He was later given a blood transfusion and was able to leave hospital, but he died at home shortly afterwards. In neither of these patients was the haematological response to the first course suggestive of unusual sensitivity, and the pre-treatment levels of polymorphs and lymphocytes were within normal limits in the first case and in the second were 3,900 and 260 per c.mm. respectively.

The depression of the white cell count is the limiting factor when the repetition of courses after a short interval is being considered. In the case mentioned above a second course was given as a desperate remedy after two weeks; on five other occasions a second course was given after four weeks without untoward result. With further experience this procedure was rarely adopted. If the clinical response to the first course is transient or incomplete little benefit may be expected from re-treatment at so short an interval; and if the patient is still in remission it is better to await evidence of renewed activity before undertaking a further course or starting maintenance therapy.

The use of nitrogen mustard therapy in cases of Hodgkin's disease with severe leucopenia has been discussed by Rosenthal (1948), who recommended splenectomy prior to treatment. The following case is of interest in this respect.

Case 5.—Man aged 26. Onset in June, 1944, with fever and enlarged axillary glands. Biopsy in January, 1947, showed Hodgkin's disease with amyloidosis; there were hepatomegaly, ascites, and oedema of the legs; Congo-red test gave 100% absorption, and serum albumin was 2.1 g. %. Two courses of nitrogen mustard at a four-weeks interval (26 mg. and 32 mg.) gave a good remission of twelve months' duration. In March, 1948, a relapse was treated with a further course of 25 mg., again with good response. In July a further relapse occurred and the absolute polymorph count was 128 per c.mm.

Sternal puncture showed that 73% of cells were of the granulocyte series, and therefore a further course of 25 mg. was given, which led to a steady rise in polymorph counts. He received four maintenance injections of 12.5 mg. each and remained at work until December, 1948. He died in January, 1949.

The red cells were not usually affected when early cases of Hodgkin's disease were treated, unless the patient was anaemic, in which case a spontaneous rise to normal levels accompanied a good clinical response (Case 3). In terminal cases this treatment may produce extreme depression of the haemoglobin level, although it is difficult to decide to what extent this is due to the treatment rather than to the evolution of the disease. In the following case treatment was followed by an immediate improvement, but in the second week the patient became very anaemic, presumably as a result of the action of the drug on the bone marrow. The patient was, however, kept alive by blood transfusion and subsequently had a satisfactory remission.

Case 9.—Man aged 42. Onset August, 1944, with cervical lymphadenopathy; biopsy showed Hodgkin's disease, and a course of deep x-ray therapy was given. From April, 1946, to April, 1947, he had recurrent bouts of fever, for which he received further x-ray treatments and blood transfusions. He was then admitted to hospital, when examination showed him to be emaciated, febrile, and anaemic (Hb 60%), although there were no localized deposits of disease tissue. He was thought to be in the terminal stage of the disease. A course of nitrogen mustard (28 mg.) produced a dramatic fall of temperature and a great improvement in his condition and appetite. He left hospital a week later, but a fortnight after treatment he became very ill and had petechiae, and his haemoglobin was found to be 32%. A transfusion of 1 pint (570 ml.) of packed red cells was given and the level rose over a period of four months to 100%, and by then his general health was excellent. A further course of 25 mg. was given in November because his haemoglobin level had dropped to 86%; after the injections it fell to 60% but recovered spontaneously. Before this course his platelets were 300,000 per c.mm., but by the 15th day they had completely disappeared from the peripheral blood, and he had a few petechiae on his legs, although a capillary fragility test was negative. The pre-treatment level was not regained until eight weeks later. The remission after this course lasted until February, 1948, when a further 25 mg. was given. The haematological changes on this occasion were much less marked. He started getting severe pain in the neck in May, and local deep x-ray therapy brought considerable benefit. A further course was given in July; but this had no effect on the fever, which had recurred, and he died in September, 1948.

Platelet counts were not done in all cases, but in a few there was a pronounced fall during the third week after treatment, although purpura was seen in only one case (No. 9).

Nausea occurred in 80% of courses and vomiting in 70%. The latter started, often very suddenly, about three hours after the injection and lasted from two to six hours. It varied greatly in severity, and in three cases was so bad that the last injection of the course was omitted. It was worse after larger doses, but the increase was not marked. Pyridoxin and phenobarbitone were tried but had no significant influence. One patient in the terminal stages of Hodgkin's disease died 48 hours after an injection of 5 mg. She had rather severe vomiting, which probably hastened her death.

Discussion

There can be no doubt that malignant lymphomata, particularly the Hodgkin type, respond to nitrogen mustard therapy. This is shown clinically by regression of lymph nodes, spleen, and other deposits, remission of fever, and

improvement in strength, weight, and blood picture. It is nevertheless evident that this remedy is not curative; and to assess its value the length and completeness of the remissions which follow its use must be compared with those obtained by deep x-ray therapy—hitherto the only comparable form of treatment available. It is also necessary to take into account the particular difficulties of the therapy itself. In the case of the nitrogen mustards there are the dangers of the actions on the haematopoietic tissues and the discomforts of those on the gastro-intestinal tract. With deep x-ray therapy the duration of treatment is longer, the necessary apparatus must be available, and irradiation sickness and bone-marrow depression may occur.

The course of Hodgkin's disease is extremely variable. It may progress with all degrees of rapidity, and the prognosis cannot be correlated either with the histological appearances or with the clinical picture at any one time. Assessment of any therapy in this condition is therefore difficult, and can be attempted with confidence only on larger series of cases. It is possible to draw only the most tentative conclusions from a series as small as this.

In cases which present with localized glandular masses, nitrogen mustard therapy has not been found satisfactory, because the remissions are much shorter than those following irradiation.

In other cases, however, the disease is more generalized from the onset, with visceral involvement, fever, and anaemia. The x-ray bath technique is usually employed in these patients. The present series includes four cases of this type treated initially with nitrogen mustard; two responded well, one moderately, and in one the treatment failed completely. There were neither histological nor clinical features in the last case to explain the disappointing result. The first indication that the condition is responding is a dramatic fall of temperature after the first injection, and absence of such a fall is an ominous sign. The remissions obtained have been of reasonable duration and comparable to those following x-ray therapy. Visceral enlargement is a common feature of these cases, and irradiation is often followed by troublesome nausea and prolonged anorexia. With nitrogen mustard the treatment is completed in four days or less, and, although there is a temporary gastric upset, it soon passes and a good appetite develops if the condition is sensitive. It is in this type of case that further trials of nitrogen mustard therapy are particularly required before it can be decided which form of treatment is the more satisfactory.

In the late cases of Hodgkin's disease the problem is more difficult. In those in which there has been repeated recurrence of enlargement of the same group of glands the skin condition may prevent further irradiation and nitrogen mustard should be tried. In terminal cases a dramatic remission is occasionally obtained, and if the case is a chronic one it may be of reasonable duration. In the acute type, however, in which the condition has progressed rapidly, any remission is likely to be disappointingly short. The bone marrow is very susceptible in some of these cases and blood transfusion may be required. The decision to use nitrogen mustard in the terminal stage of the disease should be made only after careful consideration. The chance of an adequate remission is small, although an extra period of useful life may be gained in occasional cases. The patient is liable to have distressing vomiting, which may precipitate a fatal outcome, and severe leucopenia or anaemia is easily produced.

In the management of the typical case of Hodgkin's disease, presenting first with lymphadenopathy and after a

slow evolution showing signs of generalization, both irradiation and nitrogen mustard may have their place. The glands should be treated initially with deep x-ray therapy, and after the first two or possibly three courses prolonged remissions may be expected. When the intervals get shorter or signs of generalization appear, the patient should be admitted to hospital and a full course of nitrogen mustard given. Complete blood and platelet counts are required at least once a week for four weeks to detect undue sensitivity of the bone marrow. If the response to this course is satisfactory, maintenance injections at four to eight weeks' interval may be used subsequently. These can be given to out-patients at the week-end without interfering with their work, but blood counts must be done before each one. If particularly troublesome local lesions appear at this stage, deep x-ray therapy should again be considered.

Summary

A preliminary report is made of the use of nitrogen mustard (the "bis" derivative) in a small series of cases over a period of three years. The dosage and administration of the drug are discussed. Serious haematological complications occurred in some cases, particularly those of advanced disease. Nausea and vomiting and venous thrombosis were troublesome side-effects.

Owing to the difficulty in assessing the degrees of response in such a variable condition as Hodgkin's disease the results have been classified as conspicuous benefit, moderate benefit, and failure. Benefit implies a three-months remission, with return to work in the first case and ability to return home and be about the house in the second.

Cases of Hodgkin's disease presenting with localized glandular masses respond better to radiotherapy than to nitrogen mustard.

Cases in which the disease from the beginning is widespread, involving the viscera, probably do better with nitrogen mustard than with irradiation.

Nitrogen mustard can be profitably used in some of the cases for which radiotherapy is no longer suitable. Surprisingly good results have been obtained at this stage in one or two patients whose disease had run a prolonged course.

I have to thank Professor H. P. Himsforth for guidance throughout this study, the staff of University College Hospital for allowing me to treat patients under their care, Dr. M. Maizels and his assistants for the extensive haematological investigations, and Mrs. E. L. G. Hilton, Director of the Radiotherapy Department at the hospital, who referred many of the patients for treatment and gave much useful advice. The original supply of nitrogen mustard was received through the Medical Research Council.

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As an introduction to the social welfare services in Britain the British Council arranged a two-weeks course in London during August for 17 holders of United Nations Social Affairs Fellowships from Argentina, Belgium, China, Egypt, India, and Sweden. The course included lectures by experts illustrated by visits in the London area. These enabled the students to see Queen Mary's Hospital, Roehampton, the Vauxhall Motor Works, Luton, and a housing estate at Bushey, Herts. At the end of the introductory course the fellowship holders followed individual programmes of study, planned by the British Council, on detailed aspects of social welfare such as the treatment and prevention of juvenile delinquency, the rehabilitation of the disabled, welfare among children and young people, and welfare in industry.