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NITROGEN MUSTARD IN THE PALLIATION OF LUNG CANCER

BY

B. H. BASS, M.D., M.R.C.P.

Senior Medical Registrar, the London Hospital

Nitrogen mustard (methyl bis(β -chloroethyl)amine), or HN2, has been in use clinically since 1943. Either mustard or its derivatives have been used in the treatment of a variety of malignant diseases. Of these, bronchial carcinoma would seem to be a growth that by virtue of its anatomical site in the lungs would be susceptible to an intravenous cytotoxic agent. Unfortunately the neoplasm does not derive its arterial supply from the pulmonary arteries, but from the bronchial arteries. This means that an intravenous dose of HN2 does not in fact truly perfuse the growth until it has been diluted in the systemic circulation. Nevertheless, the mustard reaching the lung via the pulmonary arteries may be said to bathe the tumour, if only for a very short time.

While all agree that mustard is never curative, there is evidence that a fair proportion of patients do in fact get some alleviation of distress. Thus, Hatch, Bradford, and Ochsner (1956) found in their series of 198 patients that improvement occurred in 46% and that symptomatic relief resulted in more than half the group.

Lynch, Ware, and Gaensler (1950) described the response to HN2 in relation to the histology of the growth: 83% of anaplastic growths, 50% of squamous carcinoma, and 33% of adenocarcinoma were improved.

In a disease problem of the magnitude of lung cancer, which is reaching epidemic proportions, any agent which will produce symptomatic relief in such percentages of patients is worthy of consideration. It is because of the discrepancy between published results and the reluctance of clinicians to use nitrogen mustard that the present series is described.

Present Series

Twenty-five patients were treated with HN2 at three hospitals during the period of 1955–9. All the patients

had been rejected for surgery and were also considered unsuitable for radiotherapy. In a sense, therefore, these patients are a selected series in that they were all "poor-risk" cases with advanced disease.

Because of the evil reputation attached to nitrogen mustard for causing many unpleasant side-effects a standard regime was devised to minimize these. Nausea and vomiting are the most constant, and because of this the mustard was always given at night after a light evening meal. The drug was given as an intravenous injection into the rubber of a running normal saline drip. The drip was run very fast for one minute, immediately after the injection, in order to flush the mustard out of the vein. It was allowed to run normally for a further 10 minutes and then taken down.

Two hours prior to treatment sodium amylobarbitone, 3 gr. (0.2 g.), was given and this was repeated one hour before, and again at the time of the injection. If the patient awoke during the night a further 3 gr. (0.2 g.) was given. This 9-gr. (0.6-g.) dose of sodium amylobarbitone was usually adequate to ensure deep sleep until next morning. Occasionally, patients required 12 gr. (0.8 g.), especially if they had been taking barbiturates regularly before admission to hospital.

I have used a number of different drugs, including chlorpromazine, opiates, and cortisone, to determine whether alone or in combination they would prove superior to sodium amylobarbitone. They have not done so, and morphine is particularly noteworthy for its tendency to provoke nausea and vomiting when given after nitrogen mustard.

Initially a dose of 0.1 mg./kg. body weight was given on four successive nights. However, this regime was soon abandoned for a single treatment using 0.4 mg./kg. Quadrupling the dose did not make any significant change in the side-effects observed, and patients appreciated one infusion in place of the four. The patients were admitted for one night, and were then followed in the out-patient department. The treatment was repeated every eighth week.

Malignant pleural effusions resulting from bronchial carcinoma have been treated with local instillations of mustard into the pleural cavity. The procedure is a modification of Weisberger's (1958) method. The effusion is aspirated as completely as possible, and a standard dose of 15 mg. of HN2 diluted in 100 ml. of normal saline is instilled. This is sometimes painful, and, because of this, pethidine, 100 mg. intramuscularly, may be given half an hour before the procedure.

A reactionary effusion may form within 48 hours, and, though it usually reabsorbs, if large, requires aspiration. If fluid is still re-forming, the whole procedure is repeated after one week. Because little HN2 gets out into the general circulation after an intrapleural injection, the dose may be repeated at weekly intervals, or in combination with intravenous mustard without fear of producing bone-marrow depression.

The ages of the 25 patients (4 women and 21 men) ranged between 52 and 72 years (see Table). All were seen as in-patients, and after physical examination had standard chest x-ray films taken. Wherever possible, bronchoscopy was performed and a biopsy of the growth taken.

The 25 patients reported here came from a larger group, some of whom have been excluded because an exact histological diagnosis could not be made.

Results

The results have been assessed by the objective clinical improvement, changes in the x-ray films, and by the subjective relief of pain and dyspnoea. If before treatment a patient needed large doses of analgesics and afterwards needed little or none, this must count as improvement, even though the x-ray films remained unchanged.

Of the 25 patients, 17 (68%) were improved. The cytology seems to influence the response to mustard. Of the 17 benefited by HN2, 11 had anaplastic growths. The remaining six cases comprised squamous-cell carcinoma, adenocarcinoma, and alveolar-cell carcinoma. Apart from the anaplastic group, who are usually mustard-sensitive, there seems little point in further

differentiating the neoplasms cytologically. Of the cases responding well to mustard, 66% were anaplastic carcinomata; the remaining 34% constituted all other forms of growth.

The survival time of the group is poor, the longest survival after treatment being 10 months (Fig. 1). The patient with the alveolar-cell carcinoma is probably alive only by virtue of the slow progression of this neoplasm. It is emphasized that HN2 does not prolong life in these patients, and is given purely as a palliative measure.

Side-effects.—These may be divided into two groups—the immediate and the delayed. Of the former, local thrombophlebitis at the injection site,

headache, nausea and vomiting, and diarrhoea have been described. For practical purposes only nausea and vomiting are of any importance. By using the regime outlined, these unpleasant symptoms can be reduced to a minimum. Of the 25 patients, 12 awoke in the night, usually about four hours after the injection of HN2, and vomited once. They could not remember the experience the day after. Just over half the group slept uneventfully and awoke the next day without experiencing any unpleasant symptoms. This is such a common experience that it is difficult to appreciate the reluctance of many clinicians to use mustard on account of its "great toxicity." The delayed side-effects

FIG. 1.—Survival time in months of 25 cases of lung cancer treated with nitrogen mustard.

Case No.	Age and Sex	Condition Before Mustard	Total Dose and No. of Courses	Response
1	M 56	Collapse of R.L.L.	28 mg. I.V. 1 course	Re-expansion of R.L.L. Died of metastases after 3 months
2	F 69	Right pleural effusion. Mediastinal obstruction (Fig. 4)	5 mg. into pleura. 1 course D.X.T. to mediastinum	Well, with no effusion, 4 months after HN2. (Fluid uninfluenced by D.X.T.) (Fig. 5)
3	M 71	Massive left effusion. Mediastinal mass	22 mg. I.V. 1 course	Died 10 days after treatment
4	M 54	Collapsed L.L.L. with effusion	30 mg. I.P. 2 courses	Pain-free with no effusion 8 months after HN2
5	M 68	Collapsed L.U.L.	46 mg. I.V. 2 courses	Well after 6 months. No re-expansion of L.U.L.
6	M 52	Left pleural effusion. Mass in R.U.L.	42 mg. I.V. 2 courses	Chest pain relieved, but died 4 months after HN2
7	M 55	Bony metastases. Mass in L. main bronchus	25 mg. I.V. 1 course	Bone pain relieved. Died 1 month after HN2
8	M 66	Haemoptysis + + +. Collapsed R.U.L.	100 mg. I.V. 4 courses	Haemoptysis dramatically eased. Clearing in R.U.L. Died 10 months after first course
9	M 66	Collapsed R.M.L. and R.L.L. with effusion (Fig. 1)	69 mg. I.V. 3 courses	Effusion cleared. Died after 7 months with carcinomatosis (Fig. 2)
10	M 58	Pul. tub. and neoplasm. Collapsed L.U.L. Bony metastases	48 mg. I.V. 2 courses	Bone pain greatly diminished. Died 3 months after HN2
11	M 64	Collapsed R.U.L. S.V.C. obstruction	46 mg. I.V. 2 courses	R.U.L. re-expanded. Jugular venous pulse lowered. Died 9 weeks after HN2
12	M 70	Collapsed L.L.L.	24 mg. I.V. 1 course	No response. Died 2 months later
13	M 53	S.V.C. obstruction	48 mg. I.V. 2 courses	J.V.P. lowered. But recurred after 5 weeks. Died
14	M 53	Collapsed R.U.L. Chest pain + + +	66 mg. I.V. 3 courses	Partial re-expansion of R.U.L. Pain less. Died 6 months after HN2
15	M 72	Right pleural effusion	48 mg. I.V. 30 mg. I.P. 2 courses each	Effusion absorbed. Lung unchanged. Died 8 months after HN2
16	F 68	S.V.C. obstruction	60 mg. I.V. 2 courses	Dramatic response initially, but died 4 months after first course
17	M 70	L. phrenic paralysis. Mass at left hilum	75 mg. I.V. 3 courses	No change. Died 6 months after HN2
18	F 67	Lymphangitis carcinomatosa	25 mg. I.V. 1 course	No change. Died 3 weeks later
19	M 62	Right pleural effusion N.G. R. main bronchus	45 mg. I.P. 3 courses	Effusion cleared. Died of metastases 4 months after HN2
20	M 66	Collapsed R.M.L. and R.L.L.	46 mg. I.V. 2 courses	Less dyspnoeic. Died 3 months after HN2
21	M 72	Total collapse of L.U.L.	28 mg. I.V. 1 course	No change. Died 6 weeks later
22	M 63	Recurrent laryngeal and L. phrenic paralysis	30 mg. I.V. 1 course	No change. Died 3 weeks later
23	M 60	Mediastinal obstruction. Right effusion	32 mg. I.V. 15 mg. I.P. 1 course	Partial clearing of effusion. Died 8 weeks after HN2
24	M 58	Hemiplegia. Pneumonectomy 18/12 before	28 mg. I.V. 1 course	Bone pain dramatically improved. Died 1 month after HN2
25	F 64	"Alveolar-cell" carcinoma	69 mg. I.V. 3 courses	Less dyspnoea but x-ray unchanged. Alive 6 months after HN2

FIG. 2.—Case 9. Right pleural effusion with collapse-consolidation of right middle and lower lobes, before treatment with intravenous nitrogen mustard.

of HN2 are related to its activity as a depressant of bone-marrow activity. If the total white-cell count in the peripheral blood is below 5,000 cells per c.mm. the drug is withheld. Blood counts have been taken at regular weekly intervals after treatment, but no significant leucopenia has been found.

Discussion

The present results agree well with the experiences of Lynch *et al.* (1950). These authors studied 60 patients, and used dosages of mustard varying from 0.1 to 3 mg./kg. They gave the mustard until depression of the leucocyte count in the peripheral blood was engendered. They advise continuing the drug until the percentage of lymphocytes in the circulating blood begins to fall. They maintain that certain patients show regression of the neoplasm only when this stage of lymphopenia is induced. To minimize nausea and vomiting, 100 mg. of pentobarbitone was given. This is a small dose as compared with the sodium amylobarbitone which I usually give. Nevertheless, 17 of the patients of Lynch *et al.* had no nausea or vomiting. They found that the anaplastic growths were the most mustard-sensitive (83% improved); only 50% of squamous-cell neoplasms and 33% of adenocarcinoma responded. This sensitivity of anaplastic growths to HN2 is a constant finding.

Kent and Reh (1950), in a series of 19 cases of lung cancer, found that the anaplastic growths responded best to mustard. Levine and Weisberger (1955) went further, and stated that, of the anaplastic carcinomata, only the "small-cell carcinoma" is truly mustard-sensitive. They claim that HN2 has no significant effect on squamous-cell carcinoma, adenocarcinoma, or "anaplastic" carcinoma. For this reason they split off the "small-cell carcinoma" as a distinct entity away from the

anaplastic group. They gave doses of HN2 varying from 0.4 to 1.5 mg./kg., but no benefit was observed in increasing the dose above 0.4 mg./kg.

Hatch *et al.* (1956), in their study of 198 patients, summed up their results when they stated that there was good subjective improvement but no prolongation of life. 46% of this group were improved by HN2.

The present series of 25 patients fits into the pattern observed by previous authors (see above). HN2 does not prolong life in patients suffering from carcinoma of the bronchus; neither does it compete with thoracic surgery or radiotherapy as the elective treatment for such cases. What does emerge after 16 years' collective experience is that HN2 has a useful, albeit limited, role in the management of lung cancer. It is essentially

FIG. 3.—Case 9. After nitrogen mustard. The right side shows clearing of the effusion and re-expansion of the collapsed lobes. The lesion in the left upper lobe is unchanged.

FIG. 4.—Case 2. Malignant right pleural effusion which persisted despite deep x-ray therapy to the mediastinum.

FIG. 5.—Case 2. After 5 mg. of nitrogen mustard intrapleurally. The effusion did not recur.

palliative, but any therapy capable of affording symptomatic relief to over two-thirds of otherwise untreatable patients should not remain neglected.

Summary

25 patients with advanced lung cancer were treated with HN2. The results are described, and some correlation with the tumour cytology is made.

A regime for minimizing the side-effects of HN2 is described in detail.

The literature is briefly reviewed.

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A FURTHER REPORT ON THE CHORDA TYMPANI SYNDROME

BY

A. GREVILLE YOUNG, F.R.C.S.Ed.

Consultant Surgeon, Lister and North Herts Hospitals, Hitchin

AND

G. E. STEIN, M.A., M.B., F.R.C.S.

Consultant E.N.T. Surgeon, Whittington Hospital, London, and lately Lister and North Herts Hospitals, Hitchin

In an article on unilateral sweating of the submental region after eating, including a case report, it was suggested that the symptom-complex be termed "the chorda tympani syndrome" (Young, 1956).

An operation has been performed, the chorda tympani nerve being sectioned on the affected side. This abolished the patient's symptoms completely for one year and partially for still longer. Bauer (1956) and Roland (1956) advocated sectioning of the chorda tympani nerve as it crossed the middle ear. If the theory was correct this seemed to be the right course to pursue, and one of us (G. E. S.) then saw the patient and agreed to carry out the operation. Unfortunately, about the same time the patient developed a middle-ear infection on the affected side, so nothing could be attempted for several months, until all the inflammation had abated.

Case Report

An operation was performed on April 29, 1957, but on reflecting the tympanic membrane by an endaural approach some free fluid was found in the middle ear and the anatomy was thus obscured. Nevertheless, it was believed that the chorda tympani was sectioned, and certainly all symptoms of abnormal sweating were relieved at once. Eating an apple or tasting sour ingredients no longer caused redness and beads of perspiration on the chin of the affected side.

It was decided to publish the result of the operation, but six months later symptoms began to recur. It was thought

that the nerve had regenerated, and it was deemed wise to repeat the operation, but, this time, to remove a portion of the nerve rather than just section it.

This was carried out (G. E. S.) on May 13, 1958. For almost a year after that the patient was completely free of her embarrassing symptoms and was delighted with the result.

However, on questioning and examining her on May 19, 1959, she stated that at breakfast-time one morning early that month she had again sustained a flushing of the right side of the face and a little sweating. She had not taken any unusual or stimulating food that morning. After trying out one or two tests with negative results it was decided to reassess her condition at a later date.

The next examination took place on October 8, 1959. The patient stated that since the first recurrence of trouble early in May she had had several recurrences of flushing and sweating, but all except one had occurred at breakfast-time, the exception being at lunch-time. The attacks occur about one to three times a week, but are not nearly so severe as they used to be and really cause very little trouble or embarrassment. They do not appear to be associated with any particular food. Curiously enough, she seems to know when the attack is likely to occur, because on the days concerned she is conscious of a flow of saliva into the mouth on getting up in the morning and before taking her breakfast. She has had no trouble later in the day (except on the one occasion at mid-day) or when having a meal away from home—for instance, if she goes out in the evening on a social occasion.

When given a sour apple to eat (May 19, 1959, and again on October 8) no reaction occurred. The skin of the chin and face did not show signs of flushing or sweating as it did pre-operatively. There is no loss of taste sensation on eating. Hearing is only very slightly diminished in the right ear (she can still hear a watch ticking), but this may not be due to the operation, because, as noted above, she suffered from middle-ear inflammation before the attempts were made to sever the chorda tympani nerve.

Discussion

The original case report and the discussion regarding causation of the condition excited a great deal of interest, and letters were received from many places, some as far away as Vancouver, Capetown, and Czechoslovakia. A number of letters and articles have also appeared in the *British Medical Journal* discussing the cause of abnormal sweating of the face, particularly in regard to the auriculo-temporal syndrome. It would seem that in these cases, whether they be auriculo-temporal or chorda tympani syndromes, abnormal nerve regeneration is regarded as being the explanation of the conditions, though the mechanism of the abnormal regeneration is still not clear. Whatever the actual cause, sectioning of the particular nerves concerned seems to be a rational procedure. Unfortunately, whether it be the auriculo-temporal nerve which is concerned or the chorda tympani as in the above case, regeneration seems likely. In this case, however, the recurrence of mild symptoms after one year is interesting in that they no longer seem to be brought on by sour or bitter ingredients but occur mostly at breakfast-time, and not every day, suggesting a possible emotional element rather than an anatomical one. At all events the patient, who is a fine-looking girl of 17½ years, is very pleased with the result.

No evidence can be found that the chorda tympani has ever before been sectioned in order to treat unilateral sweating of the submental region.

This particular case report would seem to show that the chorda tympani syndrome is a definite entity which