NITROGEN MUSTARD IN TREATMENT OF BRONCHIAL CARCINOMA

BY

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In our present state of knowledge surgical treatment offers the only hope of cure for patients with bronchial carcinoma. When the condition is inoperable it is generally agreed that treatment should be directed to the relief of symptoms, and that when the lesion is of limited extent radiotherapy is the best palliative measure. As an alternative to radiotherapy in the inoperable cases, nitrogen mustard has some claims for consideration, and in this unit an attempt has been made during the past eight years to assess its value. Oswald (1956), quoting Smithers (1951), stated that none of the chemotherapeutic agents "seems to have the slightest beneficial effect upon bronchial carcinomata." This statement has prompted the present attempt to review the value of nitrogen mustard in this field.

Patients Treated and Results

In the past eight years 46 patients with bronchial carcinoma have been treated with nitrogen mustard. The first 16 of these patients have been previously reported (Brown and Davis, 1949). The majority of patients received nitrogen mustard (methyl-bis (β -chloroethyl) amine hydrochloride) on each of four consecutive days, the dosage varying from 7 to 10 mg. a day. A few patients who were desperately ill received a single dose of 10 mg.

The results of treatment are summarized in the Table. Twenty-one patients (46%) obtained no help from nitrogen mustard therapy. Fourteen (30%) had subjective improve-

Effect of Nitrogen Mustard on 46 Patients with Bronchial Carcinoma

No improvement		21 (46%)
Symptomatic improvement		14 (30%)
Symptomatic and objective improvement		10 (22%)
Unable to assess (patient went abroad)		1 (2%)

ment but no objective change was observed. Half of these patients stated that pain had been eased and three had relief from breathlessness. All 14 experienced a general improvement in their health. Ten patients (22%) had both symptomatic and objective benefit from nitrogen mustard therapy.

In an uncontrolled trial the assessment of the effect of a drug in causing symptomatic improvement is always difficult, but some support for the belief that nitrogen mustard is truly effective is obtained from the 10 patients who showed objective improvement. The following are brief details of these 10 cases.

Four patients had clinical and radiological evidence of re-expansion of collapsed lung and/or reduction in size of the tumour mass. In one of these patients cervical gland metastases disappeared, and in another temporary improvement in paraplegia occurred.

Two patients had reduction in the size of cervical gland enlargement; in a third patient a considerably enlarged liver became palpable; and in a fourth there was radiological evidence of decrease in size of mediastinal glands.

One patient with mediastinal obstruction obtained great relief. Facial and jugular venous engorgement disappeared and breathlessness was relieved. The patient was able to return home.

One patient who had a paraplegia with metastases in the vertebral bodies regained leg movement and control of bowel and bladder function for 10 days before relapsing.

It should be stressed that objective improvement was of short duration and seldom exceeded one month. Similarly, symptomatic benefit could generally be measured in weeks before relapse occurred. Almost half of those who failed

to benefit were desperately ill when treatment was given, and many died within a few weeks of completion of therapy.

When nitrogen mustard is given with adequate premedication, using pentobarbitone sodium and chlorpromazine (Wintrobe *et al.*, 1954) very little systemic upset is experienced by the patient. Four hours before the administration of nitrogen mustard 25 mg. of chlorpromazine is given orally. This dose is repeated with 3 gr. (0.2 g.) of pentobarbitone sodium at the time of administration of the mustard. If the patient complains of nausea after treatment chlorpromazine is again given either orally or parenterally. We have used this regime for the past year and have been very favourably impressed with the results obtained.

Discussion

Nitrogen mustard may exert a palliative effect in about half the patients with inoperable bronchial carcinoma to whom it is given. Brown and Davis (1949) published the results of 16 cases treated with nitrogen mustard: four had both subjective and objective improvement, four subjective improvement only, and in eight no response was observed. This series has been extended by a further 30 consecutive cases and very similar results have been observed. In the combined series 52% of patients received benefit, of whom 22% had subjective and objective improvement and 30% subjective improvement alone. These results are in close agreement with those reported by Davidson *et al.* (1951), who stated that approximately 50% of 54 patients treated by chemotherapy alone obtained some symptomatic benefit, generally of less than one month's duration.

Although nitrogen mustard has a beneficial effect in a proportion of patients with inoperable bronchial carcinoma, the results obtained are seldom dramatic and are usually short-lived. When the disease is only of local extent, radiotherapy will usually give better results in that the benefit may be of considerable duration. The question then arises whether treatment with nitrogen mustard is worth while. There are three main reasons why we believe that it has some place in the treatment of bronchial carcinoma.

1. In our experience harm has never resulted from the careful administration of nitrogen mustard, and sometimes it has done good. Occasionally two or even three courses have been given at intervals of not less than six weeks without ill effect.

2. Radiotherapy centres are confined to large towns and cities. Often it is problematical whether it is worth while to transfer an ill patient from a peripheral hospital to a busy radiotherapy centre, particularly if the journey is likely to be distressing to the patient. Nitrogen mustard, on the other hand, can be given in any hospital, no special equipment is required, and the expense is much less.

3. In the past a justifiable criticism of nitrogen mustard therapy was that the side-effects of treatment were more unpleasant than the symptoms of the disease. This criticism is now seldom applicable if a proper sedative and anti-emetic regime is carried out. Most patients are pleasantly sleepy throughout the treatment period, and the side-effects from nitrogen mustard are often much less than those from x-ray therapy.

It is concluded that if nitrogen mustard is used in the full realization that it is a purely palliative measure which will help only one-half of the patients to whom it is given, and if it is administered only to those in whom the disease has metastasized to mediastinal glands or beyond and whose symptoms require treatment, then it is believed that it still has a place in the treatment of inoperable bronchial carcinoma.

Summary

Nitrogen mustard has been administered to 46 patients with inoperable bronchial carcinoma. Twenty-four derived some benefit from treatment, but this was generally of short duration. It is concluded that the place of nitrogen mustard therapy is one of palliation when the tumour has spread to mediastinal glands or

beyond and symptoms urgently require treatment. It has the advantage over radiotherapy that it can be given in any hospital. Unpleasant side-effects of the treatment can be minimized by the use of pentobarbitone sodium and chlorpromazine.

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PERFORATION OF PEPTIC ULCER OF THE OESOPHAGUS INTO THE PERICARDIAL CAVITY

REPORT OF A CASE

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Chronic peptic ulcer of the oesophagus is a well-recognized complication of those types of diaphragmatic herniae which allow regurgitation of acid gastric contents into the oesophagus (Jackson, 1929; Dick and Hurst, 1942). Like peptic ulcers elsewhere, if untreated they may perforate. Because of the usual anatomical situation (on the postero-lateral aspect) perforation occurs most commonly into the mediastinum or into one or other pleural cavity (Friedenwald *et al.*, 1929; Coffey and Dravin, 1951; Gent, 1951). Very rarely the aorta (Christopherson, 1917) or the pulmonary veins (Barrett, 1950) are involved. We describe here a case in which the ulcer was situated on the anterior wall and perforation took place into the pericardial cavity.

Case Report

A sales representative first came under the care of one of us (K.S.) in 1943, when he had a duodenal ulcer, radiologically proved. In 1948, at the age of 58, he was found to have a "sliding" diaphragmatic hernia. In September, 1949, a small pocket of peptic ulceration was seen radiologically on the posterior wall of the lower end of the oesophagus. Oesophagoscopy confirmed the presence of the ulcer. In May, 1951, he was operated upon. An oesophageal ulcer and short oesophagus were found in association with a diaphragmatic hernia. The hernia was repaired and the stomach replaced in the abdomen. The diaphragm was fixed to the oesophagus at a higher level. Left phrenic crush and double vagotomy were also carried out.

After this the patient felt well and regained weight until, in October, 1951, he began to get more dyspepsia, associated with pain in the left shoulder. A further barium-meal examination showed that reflux was still occurring from stomach to oesophagus, although there had been no recurrence of the hernia.

In January, 1953, one of us (K.S.) was called to see him because of symptoms of general malaise and pain in the left shoulder. His temperature was 99.2° F. (37.3° C.), pulse

80 a minute and regular. He was thought to be suffering from a mild influenzal infection and was advised to remain in bed. At 2 a.m. the following day he woke up suddenly with severe retrosternal pain. When seen at 4.30 a.m. he presented the clinical picture of coronary thrombosis. An injection of $\frac{1}{2}$ gr. (22 mg.) of "omnupon" was given. Three hours later he was still deeply shocked and in great pain, and an unusual murmur was then heard throughout the precordial area. It could not be separated from the heart beat. One had the impression that liquid was rushing through a narrow opening, the sound being comparable to that of water passing through a narrow gorge. His blood pressure, previously about 170/110, was now 140/80.

An electrocardiogram taken sixteen hours after the onset of the pain showed no evidence of myocardial infarction. Nevertheless, the differential diagnosis was thought to lie between: (1) myocardial infarction, (2) dissecting aneurysm, and (3) perforation of a peptic ulcer of the oesophagus or perforation of an ulcer in a reformed hiatus hernia. The patient's general condition was such that open exploration or any other investigation could not be considered. The murmur persisted unchanged throughout the day until death occurred, about 21 hours after the onset of the severe pain.

Necropsy was performed sixty hours after death (D.D.G.). On opening the chest the pericardial sac was found to be distended, and 100 ml. of greenish-black liquid, containing semi-digested food particles, was removed. Two small perforations were found in the posterior part of the sac just to the left of the inferior vena cava (Fig. 1), through which more of the greenish-black liquid was seeping. The flow of this liquid (which was later seen to be identical in appearance with the stomach contents) could be increased by pressure on the stomach. At the lower end of the

oesophagus, on its anterior aspect, was found a pear-shaped ulcer (5 by 5 by 4.5 cm.) 2 cm. deep, four-fifths of which lay about the level of the attachment of the diaphragm (Fig. 2). The edges of the ulcer were thickened and overhanging. The central part of the floor was extremely thin and two perforations were seen (0.8 by 0.5 and 0.2 by 0.2 cm.). A probe passed through these emerged in the pericardial sac.

FIG. 1.—The heart has been lifted forward to show the perforations, through which a probe is lying.

FIG. 2.—The posterior wall of the oesophagus has been cut to show relationship of ulcer to cardia. A probe lies through one of the perforations. A piece of suture material appears in the inferior edge of the ulcer.