present series had sphygmomanometer cuffs inflated around the upper thighs in an attempt to protect the bone-marrow of the lower limbs during the short period of mustine activity. This method failed, but successful bone-marrow protection has apparently been achieved by more complex means such as occlusion of the abdominal aorta with an intra-aortic balloon catheter (Miller and Lawrence, 1961) or external abdominal compression (Duff *et al.*, 1961) or by differential perfusion hypothermia of the lower limbs and pelvis (Lee *et al.*, 1962). Yet even with successful bone-marrow protection the dose of drug is still limited by damage to other vital tissues. Thus mustine in high concentrations may cause serious harm to the central nervous system and intestinal mucosa.

Satisfactory results in lung cancer chemotherapy will probably have to await the discovery of new drugs which are less damaging to normally dividing tissues. Meanwhile in carefully selected cases the best palliation can be achieved with the drugs at present available if they are given in maximal doses.

Summary

Thirty-two patients with advanced bronchial carcinoma were treated with a maximal sublethal dose of mustine (nitrogen mustard). The therapeutic and toxic effects are described and the method is discussed in relation to other chemotherapeutic techniques. In

view of the striking powers of recovery of bone-marrow after damage by mustine, it is suggested that the currently accepted therapeutic dose is unduly small.

I wish to thank Dr. L. R. West, under whose care these patients were admitted, for his interest and advice.

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Preliminary Communications

Combined Nitrogen Mustard and Hyperbaric Oxygen Therapy in Advanced Malignant Disease

The belief that tumour cells are more susceptible to damage by ionizing irradiation and certain chemicals when the oxygen tension of tissues is increased led us to study the effects of a cytotoxic drug given to patients with advanced malignant disease under conditions in which the oxygen tension of all body tissues is greatly increased.

Methods.—The patients, who were not premedicated, were taken into a specially designed pressure-chamber, details of which have already been published (Illingworth *et al.*, 1961). While the patient inhaled oxygen continuously the pressure was increased to and maintained at two atmospheres (absolute). After 15 minutes at full pressure a single dose of nitrogen mustard, 0.5 or 0.6 mg./kg. body weight, was given into a fast-running intravenous saline infusion; 20 to 30 minutes later the pressure was reduced to atmospheric, the oxygen inhalation was discontinued, and the patient was returned to the wards.

CASE REPORTS

Case 1.—A man aged 50 had had a total gastrectomy with oesophago-jejunal anastomosis, splenectomy, and partial pancreatectomy for carcinoma of the stomach in 1955. He remained well on vitamin-B₁₂ therapy until 1960, when he had a myocardial infarct. Although symptom-free, secondary deposits were seen on chest x-ray films at this time. He was readmitted because of pleuritic chest pain and general deterioration nine months later. Treatment with 26 mg. of nitrogen mustard (0.6 mg./kg. body weight) in the pressure-chamber did not give any subjective benefit

and there was no change in the radiological appearances of the chest lesions on the 3rd, 9th, and 18th days after treatment. Marrow damage was manifest by a fall of previously normal peripheral blood values to Hb 55% and W.B.C. 500/c.mm. on the 10th day after treatment, but there was spontaneous and complete restoration to normal before death 23 days after treatment. Microscopical examination of the pulmonary lesions obtained at necropsy showed a well-differentiated mucin-secreting adenocarcinoma of the stomach morphologically identical to the primary tumour: there was no evidence of damage to the specimens of tumour examined.

Case 2.—A man aged 39 had had a total gastrectomy with oesophago-jejunal anastomosis for carcinoma of the stomach in 1959. Dysphagia began one year after operation, and although no abnormality was seen on oesophagoscopy there was radiological evidence of obstruction at the anastomosis. Bouginage afforded temporary relief. A nodule appeared in the abdominal wound and part was excised: microscopy showed secondary tumour. Treatment with 27 mg. of nitrogen mustard (0.5 mg./kg. body weight) in the pressure-chamber gave marked subjective relief from dysphagia, but there was no histological evidence of damage to the remainder of the tumour nodule, which was excised on the 7th day after treatment. Dysphagia recurred, and a second treatment with 27 mg. of nitrogen mustard (0.5 mg./kg. body weight) was given in the pressure-chamber 31 days after the first treatment. Again there was brief subjective benefit but no objective evidence of improvement, and he continued to deteriorate slowly, dying four months after the initial treatment. The peripheral blood values did not fall after either treatment. Microscopical examination of the primary tumour, the secondary lesions in the abdominal wound, and tumour tissue within the abdomen obtained at necropsy did not reveal any differences between the samples, all of which were those of a poorly differentiated mucin-secreting adenocarcinoma of the stomach.

Case 3.—A woman aged 52 was admitted to hospital in a confused state as an emergency case. The main features on examination were dysphasia, right facial weakness, papilloedema, hyperreflexia, and extensor plantar responses. X-ray examination of the skull showed no abnormality, but a right-sided hilar mass was seen on the chest film. E.E.G.

showed gross bilateral delta activity. She was treated with 34 mg. of nitrogen mustard (0.6 mg./kg. body weight) in the pressure-chamber. On the following day she was comatose, but five days later there was marked subjective and objective improvement: speech was normal, the papilloedema had regressed, the E.E.G. pattern had improved, and the hilar mass was smaller. The benefit was brief and she deteriorated and died 14 days after treatment. There was evidence of marked marrow damage, the peripheral blood values before death being Hb 70%, W.B.C. 300/c.mm., platelets 20,000/c.mm. *Staphylococcus aureus* phage type 80/81 was isolated from throat swabs the day before death. At necropsy the primary growth, an oat-cell carcinoma of the bronchus, and the metastases in the brain contained considerable areas of necrosis, but much of the tumour tissue appeared viable.

Case 4.—A man aged 48 was admitted to hospital as an emergency with marked cachexia. Chest x-ray examination showed an encysted pleural effusion and collapse of the posterior apical segment on the right side. A supraclavicular gland was excised and microscopy showed a mucin-secreting adenocarcinoma of the bronchus. Treatment with 42 mg. of nitrogen mustard (0.6 mg./kg. body weight) in the pressure-chamber did not confer any benefit, and he died seven days later with evidence of marrow damage. Hb was 64%, W.B.C. 2,500/c.mm., platelets 30,000/c.mm. Necropsy showed a primary adenocarcinoma of the right bronchus with metastases in the pericardium, liver, pancreas, spleen, vertebrae, and para-aortic and cervical lymph nodes. There was no microscopical evidence of inhibition of tumour growth.

Case 5.—The patient was a man aged 30. Biopsy of a mass in the neck showed a lymphosarcoma of high mitotic activity. A few months later he developed a left-sided pleural effusion and evidence of superior vena caval obstruction. Radiotherapy was given with some relief, but within a short time there was widespread adenopathy, skin infiltration, and recurrence of the pleural effusion. Treatment with 33 mg. of nitrogen mustard (0.6 mg./kg. body weight) in the pressure-chamber afforded no objective or subjective benefit, and there was evidence of marrow damage persisting until death four weeks after treatment. Prior to death the peripheral blood values were Hb 55%, W.B.C. 350/c.mm., platelets 20,000/c.mm. At necropsy the lymph nodes, brain, spleen, and marrow were found to be extensively infiltrated by lymphosarcomatous tissue and the bone marrow was hypocellular. There was considerable damage to the neoplastic process, especially in the lymph nodes, where there were many areas of necrosis, but apparently viable tumour was still evident.

Case 6.—This patient was a man aged 53. After partial gastrectomy in 1957 the base of the gastric ulcer was found to be the seat of reticulosarcoma. He remained well for three years and then developed a mass in the neck, which was excised and found to be necrotic tissue and reticulosarcoma. Local radiotherapy was given with benefit. He then developed a megaloblastic anaemia which responded temporarily to vitamin B₁₂, although the serum-vitamin-B₁₂ level was normal. His condition deteriorated when folic acid had to be given to control the anaemia and he was treated with 20 mg. of nitrogen mustard (0.5 mg./kg. body weight) in the pressure-chamber. There was a dramatic subjective benefit after treatment but little objective improvement. The only evidence of marrow damage was a transient fall in W.B.C. to 1,200/c.mm. His condition deteriorated, and he died two months after treatment. Necropsy was not performed.

COMMENTS

There is good evidence that the radiosensitivity of at least some tumours is related to the oxygen tension within the neoplastic cells (see Cater *et al.*, 1962). It seemed logical to explore the value of hyperbaric oxygen with cytotoxic drugs, the action of some of which has some resemblance to the effects of radiotherapy. Of

these the most suitable seemed to be nitrogen mustard because it exerts its effect briefly and rapidly, cyclization of the two β -chloro-ethyl groups occurring probably within 15 minutes of injection; the full effect would therefore occur at a time when the tissues were as well oxygenated as was possible under the conditions available. While this study was in progress Krementz and Knudson (1961) presented evidence that the tumoricidal effect of nitrogen mustard on Ehrlich ascitic tumour and sarcoma 37 in mice is potentiated by increased oxygen tension.

The course and fate of these patients does not necessarily imply that nitrogen mustard is not more effective when combined with hyperbaric oxygen, but the results, which are frankly disappointing, suggest that, if there is any benefit from this method of therapy, it is of doubtful clinical value at least in the types of case studied. So far as can be judged by histological studies the treatment had no effect on the two gastric carcinomas and the one adenocarcinoma of the bronchus. The oat-cell carcinoma of the bronchus (Case 3) was obviously affected, but this type of tumour often responds temporarily to nitrogen mustard (Bass, 1960). The lymphoid tumours were also damaged, but these neoplasms are well known to be relatively susceptible to nitrogen mustard, and in the one case studied at necropsy large areas of tumour tissue were apparently unscathed and viable.

The clinical course, side-effects including marrow depression, and the histological findings seen in this small series differ little from our previous experience with patients with similar lesions treated with similar doses of mustard but without hyperbaric oxygen therapy. It may be that we biased the case against this form of therapy by treating only patients with advanced disease not amenable to therapy other than cytotoxic drugs, but we did not feel justified in treating patients with malignant disease at stages which were considered amenable to conventional radiotherapy or surgery. It is possible also that other cytotoxic drugs might give better results, although there do not appear to be any good reasons for such a belief.

SUMMARY

The effect of combined nitrogen mustard and hyperbaric oxygen therapy was observed in six patients with advanced malignant disease. There was no evidence that the addition of hyperbaric oxygen therapy was of significant clinical benefit in terms of potentiating the tumoricidal effects or of reducing the side-effects of nitrogen mustard therapy.

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