which was possible after about four minutes of the inhalation of 3% halothane. Induction of anaesthesia to a depth sufficient for skin incision required about eight minutes. This time could no doubt be reduced by using 4% halothane, but it appeared a useful safeguard for the apparatus to be unable to deliver a concentration in excess of 3%.

Recovery of reflexes at the end of operation was considerably slower than with nitrous oxide, but much depended upon the ability of the anaesthetist to anticipate the termination of the operation and discontinue the halothane.

There was, in general, no difficulty in obtaining sufficient relaxation for laparotomy. Many surgeons have now come to expect total paralysis for all surgical intervention in the abdomen, but, nevertheless, there would seem to be little doubt that 3% halothane would provide sufficient relaxation for appendicectomy or the suture of a perforated peptic ulcer. On an expedition a long induction and long recovery would be of less moment than in a general hospital with a busy operating schedule.

The most disquieting feature of halothane anaesthesia is the hypotension which is often seen, particularly in the deeper planes of anaesthesia. Systolic pressures down to 75 mm. Hg were encountered in the present study. Sequelae of hypotension due to halothane were not observed in this study nor when those participating have used halothane on other occasions. There is little experience of the use of halothane in the presence of surgical shock, but there is, as yet, no evidence to suggest that it is any more harmful than any other general anaesthetic agents. Wyman (1953) and Johnstone (1958) consider that vasodilatation is, in fact, beneficial—a view shared by many anaesthetists.

On a number of occasions the oxygen cylinder was removed during administration of an anaesthetic. The anaesthetist had no difficulty in converting the circuit to draw-through without interrupting the conduct of the anaesthetic, the use of air as carrier gas causing no visible change in the condition of the patient. A small number of patients were successfully ventilated artificially by manual compression of the reservoir bag. However, it is stressed that mouth-to-mouth respiration is preferable to this technique. Not only is the former technique difficult for the inexperienced, but, with the present apparatus, the fresh gas flow is interrupted during inspiration and thereby reduced to some 4–5 litres per minute.

At the present time medical officers appointed to the Falkland Islands Dependencies attend the Research Department of Anaesthetics of the Royal College of Surgeons for instruction in the maintenance of the apparatus. Thereafter they receive clinical instruction in its use at Hammersmith Hospital.

ADDENDUM.—Since this work was completed the author has made some use of the azeotropic mixture of halothane and ether as a general anaesthetic (Hudon, Jaques, and Boivin, 1958). Full evaluation of the mixture is not yet complete, but first impressions suggest that it might be more suitable than pure halothane under the conditions of an expedition. An equal depth of narcosis is obtained with a lower absolute concentration of halothane, and therefore the likelihood of hypotension is probably diminished. A calibrated and compensated vaporizer is available from Messrs. Cyprane for use with the azeotropic mixture.

I am grateful to Sir Vivian Fuchs and Dr. O. G. Edholm for their support in carrying out this work. We are indebted to the British Oxygen Gases development team at Harlow for the solution, at short notice, of the mechanical problems of the apparatus.

A production version of the apparatus (the "protothane") is under development by British Oxygen Gases Ltd.

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NITROGEN MUSTARD IN PALLIATION OF MALIGNANT EFFUSIONS

BY

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A frequent and distressing complication of the late stages of disseminated malignant disease involving the serosa is the effusion of fluid into the pleural, pericardial, and peritoneal cavities. Little success attended the treatment of this until the introduction by Müller (1945) of the direct intracavitary injection of radioactive zinc (Zn-63) and subsequently radioactive colloidal gold (Au-198) (Müller, 1950). Treatment with Au-198 has certain inherent disadvantages, including the difficulty of handling it, but perhaps the most important of these is the radiation hazard involved to the medical and nursing personnel administering the treatment.

More recently attempts have been made to treat malignant effusions with chemotherapeutic agents, thus avoiding the radiation risk, using nitrogen mustard (HN2), thiotepea (Bateman, 1955), and mannomustine dihydrochloride ("degranol") (Sellei and Eckhardt, 1958). The series of cases described here were treated to assess the value of intracavity HN2 in the control of recurrent malignant effusions.

Present Investigation

Selection of Patients.—Initially all patients referred with recurrent effusions were accepted for treatment. Two patients (Cases 11 and 19) lived only a short time after the treatment, which may in fact have accelerated their death. Now only patients with a reasonable expectation of life and in fair general condition are accepted. Histological confirmation of the diagnosis was sought in all patients, but the pathology of the tumour was not considered as a basis for the acceptance or refusal of treatment.

Method of Treatment.—Most of the patients were admitted to hospital for three or four days. Two refused

admission and were treated, with some misgiving though without difficulty, at home. Paracentesis was carried out in the ward, as much fluid as possible being removed. Half an hour before the injection of the HN2, 50 mg. of chlorpromazine was given intramuscularly. The HN2, freshly made up in 20 ml. of sterile saline, was injected through the cannula, using a two-way tap for the pleural effusions, and directly through the rubber tubing after abdominal paracentesis, this being followed by 50 ml. of normal saline. In spite of great care being taken to ensure that the needle tip was within the cavity and that the fluid was draining freely, leakage of HN2 occurred into the abdominal wall in Case 2, producing an area of induration 6 cm. across. This broke down 10 weeks later and took some time to heal. After the injection of the HN2 the patient's position is frequently changed over the next two hours to distribute it as evenly as possible. Bonte *et al.* (1956) reaspirate the effusion on the following day. This was done only in Case 2, when no more fluid could be obtained. No further paracentesis was carried out in this series until more symptoms developed.

Dosage.—The recommended dose of HN2 for intravenous use is 0.4 mg./kg. body weight, but no attempt was made to follow this, most patients being given 20 mg. in a single dose. Weisberger (1959, personal communication) is now using doses of 0.6 mg./kg. body weight, which would mean giving a dose of 38 mg. to a 10-stone (63.5-kg.) patient, and those patients of ours who did not respond to treatment might have done so had this higher dose been used.

Complications.—Many patients had nausea and sickness, mostly transient, but persisting for 48 hours in two patients and for 72 hours in one patient in spite of the chlorpromazine. Two patients had a short febrile reaction. One patient (Case 14) complained of a local burning sensation with soreness at the site of injection, possibly due to a small localized leak of the mustard. Blood counts after treatment were normal, and no leucopenia was seen.

Results

During the past three years 19 patients with malignant effusions have been treated with intracavitary HN2 (see Table). No case of malignant pericardial effusion was seen.

Eight (42%) patients showed no improvement, the fluid continuing to accumulate at the same rate as before treatment. Three (16%) showed moderate improvement, the fluid formation continuing but in decreasing amounts, and the necessity for frequent paracentesis was reduced. The remaining eight (42%) responded satisfactorily to treatment. No further paracentesis was necessary up to the time of death in six patients, and the survival ranged from 2 to 15 months, with an average of 6.6 months. Of the other two patients who responded satisfactorily, one lived nine months, requiring paracentesis twice, and the other lived 27 months and required tapping once in this time.

Discussion

Eleven (58%) of the 19 patients treated showed improvement of their symptoms. Four cases of ovarian adenocarcinoma responded satisfactorily, and two failed to do so, one of which was an anaplastic tumour. Four patients with bronchial carcinoma responded to treat-

ment and two did not. Both patients with a malignant effusion due to a carcinoma of the breast responded, as did one patient with a gastric carcinoma who lived nine

Details of Cases

Case No.	Sex and Age	Diagnosis	Dose of HN2 Injected (mg.)	Reaction	No. of Tappings After Injection to Time of Death	Survival from Time of Treatment	Result
1	M 47	Carcinoma of bronchus with pleural effusion (no pathology)	20	Vomited once	7	1 mth.	No improvement
2	F 59	Adenocarcinoma of stomach with ascites	25	Infection and ulceration at site of paracentesis	2	9½ mths.	Satisfactory—no paracentesis for six months after injection
3	F 72	Adenocarcinoma of ovary with ascites	30	Nausea for 48 hours	None	4½ "	Satisfactory
4	M 61	Anaplastic carcinoma of bronchus with pleural effusion	20	Transient pyrexia	None	2½ "	"
5	F 57	Papillary adenocarcinoma of ovary with ascites	10		1	27 "	"
6	F 65	Carcinoma of breast with pleural effusion (malignant cells in fluid)	20	Transient pyrexia	None	15 "	"
7	F 61	Adenocarcinoma of ovary with ascites	30	Nausea	4	5 "	No improvement
8	M 63	Carcinoma of bronchus with pleural effusion (no histology)	20		2	2½ "	"
9	F 76	Carcinoma of breast with pleural effusion	20	Nausea and pyrexia for 48 hours	None	4 "	Satisfactory
10	F 55	Carcinoma of uterine body with pleural effusions and ascites	25 into right pleural cavity	Vomited once	Many	5 "	No improvement
11	F 54	Carcinoma of stomach with ascites (no histology)	20	Transient nausea and sickness	None	10 days	"
12	F 56	Pleomorphic carcinoma of bronchus with pleural effusion	20	Transient nausea	4	5½ mths.	Satisfactory. Fluid formation slowed down
13	M 76	Carcinoma of bronchus with pleural effusion (malignant cells in fluid)	25	"	None	4 "	Satisfactory
14	M 61	Carcinoma of bronchus with pleural effusion (negative biopsy)	20	Vomited once, transient malaise. Local burning	None	8 "	"
15	F 48	Carcinoma of ovary with ascites (malignant cells in fluid)	20		2	6 "	Satisfactory. Fluid formation slowed down
16	F 40	Cystadenocarcinoma of ovary with ascites	20		2	5½ "	"
17	F 57	Anaplastic carcinoma of ovary with ascites	20	Sickness for 3 days	6	4 "	No improvement
18	F 71	Carcinoma of stomach with ascites	10		3	4 "	"
19	F 75	Carcinoma of colon with ascites	20		None	1 week	"

months and required paracentesis only twice. Three effusions due to metastases from gastro-intestinal carcinoma showed no response.

These results are comparable with those reported by other authors. In a series of 43 patients treated by Weisberger *et al.* (1955) there was improvement in 28 (65%) and no reaccumulation of fluid in 20, the most favourable response being in patients with mammary or ovarian carcinoma. Bonte *et al.* (1956) treated 40 patients, with improvement in 25 (62%). A further 88 patients reported by Weisberger (1958) showed approximately the same percentage—64—to be improved, and again the most favourable response was obtained in patients with breast and ovarian tumours. In a series of 25 patients with bronchial carcinoma described by Bass (1960) five with malignant effusions were treated by the direct intrapleural injection of HN2, there being no reaccumulation of fluid up to the time of death in four.

Many authors agree (King *et al.*, 1952; Storaasli *et al.*, 1953; Kent *et al.*, 1954; Wheeler *et al.*, 1955) that Au-198 can produce slowing down or cessation of malignant effusions in about 50–60% of patients, and that the best response is obtained where the primary tumour arises in the breast or ovary. Hilton *et al.* (1957) reported the results of treatment with Au-198 of 94 patients at University College Hospital. 40 of these showed a good response with no further fluid formation, and eight a moderate response, the fluid forming less rapidly. 21 patients with bronchial carcinoma showed a good response, with an average duration of 6.6 months, one patient living 16 months without significant reaccumulation of fluid. The average duration of improvement in seven patients with ovarian carcinoma showing a good response was 7.2 months, one patient being alive after two years, at the time of writing, with no ascites. The average duration of improvement in 10 patients with carcinoma of the breast was 8.4 months, eight being alive at the time of writing. The results of 235 patients with malignant effusions who were treated at the Royal Marsden Hospital with Au-198 are reviewed by MacKay (1957). In his series 59 patients showed good inhibition and 16 showed some inhibition of fluid formation. 26 survived over one year, two with effusions due to breast carcinoma living six years.

Müller (1956) found that the general body dose was less than 10 milliroentgens (mr.) and the hand dose 20 to 50 mr. for the giving of a dose of 150 millicuries (mc.) of Au-198. These figures can be kept within such limits only if the operator is quick and skilled, and would certainly be exceeded if it were given by a slow and inexperienced person. Thus Au-198 for routine use involves little radiation exposure in experienced hands provided adequate facilities for protection and monitoring are available.

It would seem that the results of treating malignant effusions with Au-198 or with HN2 are virtually the same. The latter would appear to have definite advantages in that no radiation hazard is involved, no protective measures are required, and administration is consequently simple and can be done in a general hospital without a radiotherapy department. It is perhaps also pertinent to point out that 20 mg. of HN2 costs 5s. and the average dose of Au-198 (100 mc.) costs £6 15s.

The series of patients reported here is small, but there is no clear pattern of response to the HN2, and, subject

to the patient being in reasonable general condition, treatment should be attempted in all cases of increasing malignant effusions causing symptoms and requiring tapping. It is not possible, from the histology, to forecast which patients will respond satisfactorily.

Summary

Nineteen patients with malignant effusions were treated with the direct intracavitary injection of nitrogen mustard. Eleven showed improvement, and in six no further paracentesis was required up to the time of death.

The literature on the treatment of malignant effusions with radioactive colloidal gold and with nitrogen mustard is briefly reviewed, and about 60% of patients can be expected to respond satisfactorily to either method. The latter has the advantage that no radiation hazard is involved.

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ROLE OF CYTOTOXIC AGENTS IN PRODUCTION OF AMYLOIDOSIS IN HODGKIN'S DISEASE

BY

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That amyloidosis may occur in Hodgkin's disease is fairly well recognized, though it is mentioned in only 6 out of 20 standard textbooks of pathology or monographs on Hodgkin's disease that have been consulted. The frequency of this association has been described by these authorities as "rare" or "occasional."

It was rather a surprise, therefore, to find that of 20 cases of amyloidosis occurring in a series of 3,192 consecutive necropsies performed in a general hospital between 1947 and 1959 Hodgkin's disease was the commonest concomitant of secondary amyloidosis. Of these 20 cases, six had primary amyloidosis; and the associated diseases with secondary cases were Hodgkin's disease four, multiple myelomatosis three, pulmonary tuberculosis three, rheumatoid arthritis two, osteomyelitis one, and empyema one. Furthermore, all four cases of Hodgkin's disease with amyloidosis had been treated with either nitrogen mustard or tretamine (triethylene melamine).