

possibility in advance, but it was never felt to contraindicate treatment, as the hair regrows during maintenance therapy.

Nausea and vomiting may occur, but this depends on the dosage and susceptibility of the patient. The severity and incidence of this side-effect is, in our opinion, less than that seen using comparable doses of mustine (HN2) or thiotepa.

Cyclophosphamide has been used by other workers as a prophylactic measure in conjunction with surgery. Denk *et al.* (1961) report a series of 282 cases of carcinoma of the bronchus which have been treated chemotherapeutically for two years after radical operation, and claim that at 18 months the survival rate was 81% compared with 42% without the drug. This form of treatment has not been used in this series.

The long-term results are not encouraging in the present series despite continued treatment. Only two patients, both with carcinoma of the breast, responded for more than one year and only one of these remained symptom-free after 18 months.

Summary

A series of 76 cases of disseminated malignant disease have been treated with cyclophosphamide (a cyclic nitrogen mustard phosphamide ester). Twenty-three of these cases showed an objective response. Long-term results are not encouraging. Complications and side-effects are discussed. It is suggested that treatment with cyclophosphamide is worth while in patients with advanced malignant disease, although response is often short-lived.

We are grateful to Mr. Victor Riddell, who was the first person to draw our attention to the potentialities of cyclophosphamide. We are indebted to Dr. J. L. Stafford for much helpful advice, and to other members of the consultant staff of St. George's Hospital who have allowed their patients to be included in this series. We thank the photographic department of St. George's Hospital for the illustrations, and Dr. J. M. Simister, of Ward, Blenkinsop & Co. Ltd., for supplies of the drug. One of us (N. H. K.) acknowledges his gratitude to the British Empire Cancer Campaign for a full research grant during the tenure of which much of this work was carried out.

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"Science is rarely advanced by what is known in current jargon as a 'break-through.' Rather does our increasing knowledge depend on the activity of thousands of our colleagues throughout the world who add small points to what will eventually become a splendid picture, much in the way that the Pointillistes built up their extremely beautiful canvases." (Anniversary address to the Royal Society by Sir HOWARD FLOREY, P.R.S.)

HIGH-DOSE NITROGEN MUSTARD THERAPY WITH INTERMITTENT AORTIC OCCLUSION

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Nitrogen mustard (methyl-bis (β -chloroethyl) amine, HN2) is an alkylating agent widely used in the treatment of malignant disease (Rhoads, 1946). Alkylating agents are believed to interfere with tissue growth by reacting with the cellular nucleic acids (Zamenhof *et al.*, 1956; Stacey *et al.*, 1958). This effect is not tumour-specific, and the highest degree of inhibition appears to be achieved with tissues undergoing the most rapid replacement. Apart from tumour tissue, these include bone-marrow, lymph nodes, and intestinal epithelium.

HN2 produces cellular damage in these tissues which can readily be observed histologically as early as one day after administration (Sternberg *et al.*, 1958). Biological evidence of its cytotoxic effect *in vivo* can be obtained as early as 10 minutes after administration (Burchenal *et al.*, 1951). The kinetics of the affected cell type determine the timing of the clinical symptoms. Lymphocyte depression may become apparent within hours, intestinal disturbances—rarely at conventional doses—within days. Three weeks may elapse before the depression of the white-cell precursors is fully reflected as leucopenia in the peripheral blood. For all practical purposes, the effects of several doses of HN2 given within a short period of time appear to be cumulative for the proliferating tissues.

In addition, there are effects of HN2 which are not related to cell reproduction but concern the nervous system and produce symptoms immediately. While nausea and vomiting are often observed with conventional doses, fatal convulsions, like those occurring in cats after high doses (Sternberg *et al.*, 1958), have not been observed in man after systemic administration of tolerated mustard doses. There is no conclusive evidence that effects on the nervous system are cumulative if HN2 is administered in fractionated doses.

Clinically, the most important manifestation of mustard toxicity after systemic administration is bone-marrow depression. The dose which can be tolerated by the patient is the dose from which his bone-marrow can recover before fatal complications occur. Therefore attempts have been made to raise the concentration of

HN2 in the tumour tissue without increasing the amount of drug affecting all or parts of the bone-marrow. They can be classified as follows: (1) Local administration into malignant effusions (Karnofsky *et al.*, 1948). (2) Administration into the artery supplying the tumour area (Klopp *et al.*, 1950; Cook, 1959). (3) Regional perfusion by temporary exclusion of the tumour-bearing area from the general circulation (Creech *et al.*, 1958). (4) Systemic administration with protection of parts of the bone-marrow by (a) removal and storage of bone-marrow before drug administration (Clifford *et al.*, 1961), or (b) temporary occlusion of the abdominal aorta and collateral arteries during and shortly after drug administration (Miller and Lawrence, 1961). Essential for the procedures outlined under Nos. 3 and 4b is the fact that HN2 is active in the circulating blood for less than 10 minutes (Ryan *et al.*, 1958).

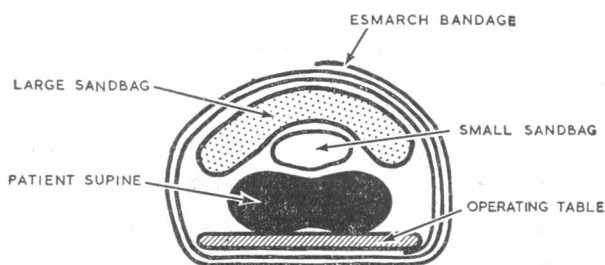
The lack of radiotherapy in Kenya and the high incidence of head and neck cancer (Clifford, 1960) have led to the use of HN2 in increasingly high doses. The impression was formed that the degree and duration of the anti-tumour effect was related to the quantity of the drug administered. With protection by autologous marrow, as a free graft (Clifford *et al.*, 1961), HN2 has been given in this department in doses of 2 mg./kg. with safety.

For cancer localized above the diaphragm, temporary occlusion of the abdominal aorta appeared to represent a possibility to protect parts of the haematopoietic tissue while obtaining a high concentration of the drug in the tumour area by intravenous administration. The observations of Miller and Lawrence (1961), that a single dose of 1.2 mg. of HN2 per kg. administered by this method produces eighth-nerve damage, suggested that effects on the nervous system limit the amount of drug which can be given as a single dose without serious complications. Since it was possible to give 2 mg. of HN2 per kg., divided into five doses, to patients protected by bone-marrow grafts (Clifford *et al.*, 1961) without producing symptoms attributable to damage to the central nervous system, it was thought that fractionation of the total dose might also be usefully combined with aortic occlusion.

The objective was to develop a technique which would make practicable repeated aortic occlusions within a period of a few days. This method is referred to as intermittent aortic occlusion (I.A.O.).

Technique

The patient, under full relaxant anaesthesia, is placed supine on a firm-topped operating-table. A small sandbag, 6 by 6 in. (15 by 15 cm.), is placed in the space bounded by the rib cage and the iliac crests, and a large sandbag 9 by 18 in. (23 by 45 cm.) is laid across this. An Esmarch bandage binds the bags firmly into the



Position of sandbags and Esmarch's bandage around patient and table.

abdomen by passing tightly around sandbags, patient, and table (see Diagram). The aorta is thus compressed against the lumbar spine, and most collateral vessels are also occluded. Cessation of the femoral arterial pulse indicates a satisfactory occlusion. The occlusion is maintained for 20 minutes, and is repeated during the next 48 hours. The total dose of HN2 is calculated on an mg./kg. body-weight basis. HN2 in a concentration of 1 mg./ml. of 0.9% saline is freshly prepared. On cessation of the femoral pulse, one-quarter of the total dose is injected into an arm vein over a period of two minutes. After 10 minutes the second quarter dose is given. After a further 10 minutes the tourniquet is released and the patient returned to the ward. The second half of the dose is given within 48 hours in a similar manner.

The plasma volume was determined using Evans blue, T-1824, and a method based on that of Mollison *et al.* (1950). The total blood volume was calculated from the plasma volume and the venous haematocrit. These studies indicated that aortic occlusion reduced the circulating blood volume to approximately one-half. Evans blue was injected into the cephalic vein immediately after occlusion. After an interval of 15 minutes, while the aorta was still occluded, blood was removed from the femoral vein. No dye could be demonstrated, indicating the effectiveness of the occlusion.

Intravenous pyelograms, taken during an aortic occlusion, demonstrated normal excretion of the dye through both kidneys. Thus, despite the width of the occluding bags, the occlusion appears to be effective distal to the renal arteries.

Sternal and iliac bone-marrow aspirations were performed in eight cases under anaesthesia prior to the first occlusion. Leucocyte and platelet counts were also taken at this time and at regular intervals thereafter on all patients. Sternal and iliac bone-marrow aspirations were performed 10 days after occlusion and sternal marrow aspirations six weeks after occlusion in eight and six patients respectively.

Results

Ten patients with advanced neoplastic disease have been treated with I.A.O., using doses from 1.5 to 3 mg. of HN2 per kg. (Table I).

TABLE I.—Summary of Clinical Details

Case No.	Histological Diagnosis	Previous Treatment*	Total Dose HN2 (mg./kg.)	Estimated Effective Tumour Dose (mg./kg.)	Therapeutic Response
1	Anaplastic carcinoma post-nasal space	1	2.0	3.7	+++
2	" "	2	1.86	3.4	+
3	" "	1	1.5	2.75	++
4	" "	2+3	1.6	2.9	++
5	Undifferentiated carcinoma oesophagus	4	1.6	2.9	Died
6	Anaplastic carcinoma post-nasal space	4	1.8	3.3	+
7	" "	4	2.5	4.5	+
8	" "	4	2.5	4.5	+
9	Carcinoma oesophagus	4	3.0	5.5	+++
10	Anaplastic carcinoma post-nasal space	4	1.5	2.75	+

* 1=Continuous interarterial infusion of methotrexate and intermittent intramuscular injection of "leucovorin." 2=Methotrexate, chlorambucil, and actinomycin D combined, single daily doses. 3=HN2 1 mg./kg., two courses. 4=No previous treatment.

+ = Moderate decrease in tumour size. ++ = Marked partial regression of tumour. +++ = Complete tumour regression and negative biopsy from previous site of tumour.

Case 1

An African man aged about 30 was admitted to hospital on November 1, 1960, complaining of a swelling in the left neck, pain in the left ear, and sore throat with dysphagia of two months' duration. On examination there was a mobile swelling 3 by 2 in. (7.5 by 5 cm.) overlying the left sternomastoid muscle. A friable, readily bleeding tumour 1 by $\frac{1}{4}$ in. (2.5 by 0.6 cm.) was visible in the nasopharynx on the left side. Biopsy of this showed an anaplastic carcinoma.

Treatment.—Metabolite/antimetabolite chemotherapy (leucovorin and methotrexate) failed to produce tumour regression, and by January 2, 1961, the soft palate was displaced forward by the tumour. On January 10 and 12, HN2 2 mg./kg. was given with occlusion.

Post-operative Course.—Severe vomiting and diarrhoea persisted until January 18, necessitating intravenous fluids. Marked improvement in the intraoral picture was noted on January 18, and by February 21 there was no visible tumour in the post-nasal space (P.N.S.). The large left neck tumour had disappeared, leaving some small hard discrete neck glands. On March 15 a biopsy from a P.N.S. curettage showed "the only evidence of neoplasia to be a minute collection of cells with bizarre nuclei and mitoses in a corner of the specimen."

A repeat biopsy on March 30 showed no evidence of malignancy in the specimen. April 2: Marked shedding of the scalp hair; no palpable neck glands. May 1: No intra-oral growth or neck glands apparent. On May 5 the patient was discharged symptomless and apparently free from disease.

Case 2

An African boy about 16 years of age was admitted to hospital on September 22, 1960, complaining of deafness, persistent headache, nasal obstruction, pain on the right side of the face, and blindness in the right eye. On examination the boy was ill and wasted, with massive bilateral cervical adenitis and a neck circumference of 20 in. (51 cm.). A persistent purulent nasal discharge with complete obstruction to both nares was noted. There was no apparent growth in the P.N.S., although the mucosa appeared hypertrophic. Marked proptosis of the right eye, a sixth-nerve paresis, and blindness of the same eye were present. X-ray examination showed considerable destruction of the right posterior ethmoidal cell system. Biopsy of a neck gland showed anaplastic carcinoma.

Treatment.—A course of oral methotrexate, chlorambucil, and actinomycin D combined in conventional dosage failed to have any therapeutic effect. On January 17 and 19, 1961, HN2 1.86 mg./kg. was given with occlusion.

Post-operative Course.—After three days of severe vomiting and mild diarrhoea the patient noted a decrease in his facial pain, and the neck masses felt less tense. January 26: Neck circumference was 18 in. (46 cm.) and there was no facial pain. February 20: After being symptom-free for three weeks he had a recurrence of the pain. There had been no further decrease in the size of the glands. February 24: The general condition began to deteriorate, and it was not thought justifiable to attempt further occlusive therapy. February 28: After a steady worsening in the general condition and intractable pain the patient died. Post-mortem examination was not permitted.

Case 3

An African girl aged 15 was admitted to hospital complaining of severe bleeding from the left nostril, toothache, and earache on the left side and a swelling in the left neck. On examination a hard fixed swelling involving the entire left half of the soft and hard palates was present. A friable bleeding growth filled the left nostril. There was a hard fixed gland, 2 by 1 in. (5 by 2.5 cm.), at the angle of the left mandible and small shotty glands were palpable in the right neck. X-ray examination showed destruction of the

posterior wall and floor of the left maxillary antrum. Biopsy from the nose revealed a markedly undifferentiated squamous-cell carcinoma.

Treatment.—Metabolite/antimetabolite chemotherapy via the left external carotid artery failed to produce satisfactory tumour regression, and the severe epistaxis was causing concern. On January 17 and 19, 1961, HN2 1.5 mg./kg. was given with an occlusion.

Post-operative Course.—A mild post-operative vomiting passed off in 48 hours. The drug otherwise was well tolerated. Diminution in the size of intraoral growth and the neck glands was noted at the end of the first week. March 3: Progressive improvement in the general condition occurred, and there was no further epistaxis. The left nostril was clear of growth and patent. A swelling in the palate, although smaller than before occlusion, was still present. March 18: Biopsy from the post-nasal space showed persistence of malignant cells. March 27 and 29: HN2 2.75 mg./kg. was given with occlusion, and there were no untoward effects. Progress was maintained until April 24, when the patient became jaundiced. Liver-function tests suggested a hepatocellular cause presumed due to the high dosage of HN2. This complication resolved on treatment with prednisone, vitamin K, and dietary restriction. Progress was then uneventful, except that moderate alopecia appeared on May 8. At this date no intraoral growth could be demonstrated. On May 30 a left Caldwell-Luc operation was performed for persistent opacity of the left maxillary antrum. At operation the posterior bony wall of the antrum was absent, and the cavity contained pus. There was no macroscopic evidence of malignancy in the P.N.S. Specimens from the P.N.S. and antral lining showed no microscopical evidence of malignancy.

Convalescence was uneventful and the patient was discharged on June 19, symptom-free.

Case 4

An African child aged 10 years was admitted to hospital on August 22, 1960, complaining of a swelling in the left side of the neck of three months' duration. On examination there was a large tumour overlying the left sternomastoid muscle, oval in shape and firmly fixed to underlying structures. The neck circumference was 16 in. (40.5 cm.). There was no evidence of disease in the nose or throat, and no other lymph nodes were palpable. Biopsy from the neck showed an anaplastic carcinoma but post-nasal curettage revealed normal adenoid tissue only.

Treatment.—HN2 was given without occlusion, using 1 mg./kg. as a total dose given over five days. One week after completion of the course the neck measurement was 14 in. (35.5 cm.). Two weeks later the measurement was 13 in. (33 cm.). Tumour was still present, but as the white-cell count was normal the course of HN2 was repeated. Two weeks after this second course the neck measured 15 in. (38 cm.) and 10 days later it was 17 in. (43 cm.). With the obvious advancement of the disease it was decided to give methotrexate, chlorambucil, and actinomycin D in conventional dosage. This therapy produced a 1-in. (2.5-cm.) decrease, which was sustained for one week only. At this juncture the patient caught chicken-pox. On January 25 and 27, 1961, HN2 1.6 mg./kg. was given, with occlusion. This was followed by mild vomiting and bloody diarrhoea. Culture of the stool revealed *Shigella flexneri*, which resolved on chloramphenicol. After this recovery was uneventful. The circumference was 18 in. (45.5 cm.) on January 27, 16 in. (40.5 cm.) on February 14, 14 in. (35.5 cm.) on February 25, and 16 in. (40.5 cm.) on March 10.

Although the general condition was still good on March 16, the disease was obviously progressing. It was decided that nothing further could usefully be done, and the patient was repatriated and was lost to follow-up.*

*This unfortunately occasionally happens, owing to the remoteness of some parts of the country and absence of communications.

Case 5

An elderly African man was admitted to hospital complaining of complete dysphagia. On examination a feeble, grossly cachectic, bedridden old man was seen. Oesophagoscopy revealed a large ulcerous mass obstructing his cervical oesophagus. Biopsy showed an undifferentiated carcinoma.

Treatment.—HN2 1.6 mg./kg. was given with occlusion. The patient succumbed on the fourth post-occlusal day. Post-mortem examination was not permitted.

Case 6

An African man aged about 50 was admitted to hospital on January 9, 1961, complaining of right-sided pain and headache of four months' duration with loss of vision in the right eye. On examination diffuse enlargement of the right face was present, with complete right ophthalmoplegia, and paralysis of the fifth, seventh, eighth, and twelfth cranial nerves on the same side. There were enlarged fixed glands on both sides of the neck. Rhinoscopy and biopsy confirmed the diagnosis of an infiltrating anaplastic carcinoma of the nasopharynx.

Treatment.—On January 29 and 31 HN2 1.8 mg./kg. was given with occlusion.

Post-operative Course.—The treatment was well tolerated apart from transient vomiting on February 6. Blistering was apparent, overlying the course of the superficial veins (in all cases they turned black and thrombosed). By February 12 the facial pain had decreased, and by February 23 the neck glands were smaller, discrete, and mobile. The pain had disappeared. Despite no change in the neurological status, he was still free from pain on March 20, and with the suggestion of further biopsy he discharged himself and did not return.

Case 7

An African woman aged about 45 was admitted to hospital on January 19, 1961, complaining of dysphagia, purulent nasal discharge, and trismus. On examination there were multiple shotty nodes on both sides of the neck and paresis of the third, fourth, sixth, and seventh cranial nerves on the right side. The right ear was partially deaf. Intraoral examination was impossible owing to trismus. Biopsy of the nasopharynx revealed an anaplastic carcinoma.

Treatment.—On February 5 and 7 HN2 2.5 mg./kg. was given with occlusion.

Post-operative Course.—Deterioration in her general condition from vomiting and mental confusion caused some concern, but these symptoms passed off after seven days. February 15: No nasal discharge, but superficial ulcers were apparent on the lips and nasal mucosa. February 21: No neck glands palpable; general condition good. She continued to gain weight, but there was no change in the neurology. The ulcers had healed with local toilet. April 14: Nasopharyngeal biopsy showed no evidence of malignancy. April 26: Repeat biopsy again negative. April 29: Audiogram showed a hearing loss of 50–70 decibels to all frequencies on the right and of 50 decibels to all frequencies above 1,000 c.p.s. on the left. May 5: Discharged asymptomatic, but with neurological status unchanged. May 10: Seen as an out-patient. General condition very good. Mentally bright. Still partially deaf but has adequate social hearing. No macroscopic evidence of disease.

Case 8

An African man aged about 50 was admitted to hospital on January 20, 1961, complaining of headache and left-sided neck swelling. Examination on January 30 showed a thin wasted man with a fixed round swelling in the left neck. Rhinoscopy revealed a hard nodular swelling in the nasopharynx, and biopsy of this and the neck swelling showed an anaplastic carcinoma.

Treatment.—On February 14 and 17 HN2 2.5 mg./kg. was given with occlusion. This was not well tolerated, and the

post-occlusal week was marked by severe vomiting and mild diarrhoea. On February 18 he had a generalized fit lasting about three minutes. Mental confusion was marked for about two weeks after this. On February 28 the neck glands were reduced in size, but biopsy of the glands was still positive on March 30, when they were about half the size at admission. A course of 2.5 mg. of HN2 per kg. was given on May 5 and 7. This course was not well tolerated. Severe mental confusion was noted, and vomiting and diarrhoea were severe. There was marked regression of the neck glands, which were impalpable by the end of the second week.

The patient's general condition, however, continued to deteriorate, and by May 27 he had become completely apathetic, incontinent of urine and faeces, and unwilling to take food. His condition remained the same until June 18, when he started getting generalized convulsions. On June 26 a lumbar puncture revealed a C.S.F. pressure of 300 mm. fluid and normal chemistry. Progression of the growth into the brain was suggested or cerebral metastasis. His general condition deteriorated until July 14, when he caught chicken-pox. He became progressively weaker and died on July 25.

Post-mortem Examination.—Almost complete destruction of the basisphenoid was seen. The sphenoidal sinus and pituitary fossa were filled with a mass of necrotic material which involved the infundibulum and hypothalamus. No healthy residual tumour tissue was noted.

Case 9

An African man of about 35 was admitted to hospital on February 2, 1961, with a six-months history of dysphagia, and ability to swallow only fluids. Barium-meal examination revealed a stenosis of the mid-oesophagus with rat tailing, and oesophagoscopy confirmed an ulcer at 23 cm., histologically due to an anaplastic carcinoma. No secondaries were found.

On February 13 and 15 3 mg. of HN2 per kg. was given with occlusion. There was no significant vomiting, but the patient complained of tinnitus. After one week he was swallowing semi-solids with little difficulty. A barium-meal examination on March 10 showed a near-normal oesophagus with a marked improvement of flow compared with the pretreatment pictures. On March 17 the dysphagia returned, he was unable to take semi-solids, and fluids regurgitated. Oesophagoscopy showed no ulceration, but there was a tight constriction at 23 cm., which was dilated. A biopsy taken at this time showed sheets of fibrous tissue containing nests of malignant cells.

On April 5 and 7 further treatment with HN2 3 mg./kg. was less well tolerated than the first course. Vomiting and diarrhoea were severe and dizziness, headache, and marked tinnitus were complained of. There was severe mental confusion for two weeks. On April 11 dysphagia became complete again and a Ryle tube was passed. Oesophagoscopy on April 19 revealed a tight stricture at 23 cm. and an intact mucosa. Biopsy showed no evidence of malignancy on serial section. A Jaques tube was inserted, being left in place until May 2. A barium swallow on May 2 showed a stricture 1 in. (2.5 cm.) above the aortic arch. The patient still complained of tinnitus and loss of balance. Audiograms showed a severe loss beyond 1,000 c.p.s. Swallowing was still difficult, necessitating tube-feeding. Oesophagoscopy on May 31 showed a non-ulcerating stricture. This was dilated and a biopsy taken. There was no evidence of malignancy in serial sections. Swallowing improved after this until June 24, when dilatation was again performed. Biopsy was again negative. On June 28 the patient complained of hoarseness and pain in the throat, and an oedematous paralysed left cord was seen, thought to be due to involvement of the left recurrent laryngeal nerve by fibrosis. Oesophagoscopy and dilatation were carried out on July 11. Biopsy was negative. The left cord was still oedematous and paralysed. At this juncture it was decided

to bypass the stricture by bringing up a loop of colon. This was performed on July 31. Despite an apparently favourable operative course, the patient died the same night.

Post-mortem Examination.—No obvious cause of death was apparent at necropsy. The oesophageal primary appeared as a tight ball of fibrous tissue. Ulceration was not present. The laryngeal symptoms were due to an abscess containing a small bone, which had penetrated the oesophagus and localized itself just below the vocal cords. Microscopy of the specimen revealed a dense stroma of fibrous tissue in which were embedded nests of malignant cells. The change from frank anaplasia to this fibrotic appearance is interesting.

Case 10

An elderly African man was admitted to hospital on January 16, 1961, complaining of pain and swelling of the left side of the face for six months. On examination he was wasted, dehydrated, and very weak. The left side of the face was diffusely swollen, with a marked seventh nerve palsy. The third, fourth, sixth, and twelfth cranial nerves were paralysed on the left. There was a large hard fixed swelling 3 by 2 in. (7.5 by 5 cm.) overlying the right sternomastoid muscle. Marked trismus precluded adequate intraoral examination. Rhinoscopy and biopsy under anaesthesia confirmed the diagnosis of an infiltrating anaplastic carcinoma of the nasopharynx.

Treatment.—On February 27 and March 1 HN2 1.5 mg./kg. was given with occlusion.

Post-operative Course.—Apart from mild transient vomiting and mental confusion, the drug was well tolerated. On March 5 the tumour was noticeably smaller and on March 10 it measured ½ by ¼ in. (1.3 by 0.6 cm.) and was mobile. On March 30 a small tumour was still palpable in the neck. Despite all measures the patient remained thin and weak. It was thought not justifiable to subject him to further treatment and he was repatriated. The neurological status remained the same.

The haematological response in each of the cases is outlined in Table II.

Discussion

Ten patients with inoperable neoplastic disease were treated with HN2 administered intravenously in doses far higher than are normally regarded as safe. It has been demonstrated in nine cases that the technique described provides adequate protection of the pelvic bone-marrow against up to 3 mg of HN2 per kg.

Only two patients (Cases 3 and 9) have admitted to having symptoms referable to the eighth nerve after doses of 1.5 and 3 mg./kg. Audiometric studies in four cases revealed a marked loss of auditory function in the range above 1,000 cycles per second, suggesting eighth-nerve damage. The nature of these effects is being investigated further.

McFarland *et al.* (1959) noted at necropsy severe maceration of the gastro-intestinal mucosa after 1.4 mg. of HN2 per kg. Despite doses ranging from 1.5 to 3 mg./kg. fulminating gastro-intestinal toxicity has not been noted. Anorexia, nausea, and vomiting, common side-effects even after conventional doses of HN2, were observed in all patients during the first days after drug administration.

Alopecia was noted only when doses of 1.8 mg./kg. or more were administered. Three patients appeared mentally confused. So far as can be judged at the present time, alopecia and confusion would appear to be reversible. These factors are being further investigated.

One patient (Case 5) was admitted in poor general condition due to long-standing malignant stricture of the upper oesophagus. He died on the fourth day after I.A.O. Permission for necropsy was not obtained. There was no clinical or laboratory evidence that his death was related to treatment with HN2. Cases 1, 3, 4, and 9 showed remarkable tumour regression. This and the fact that no positive biopsy could be obtained in two cases after treatment can be fully evaluated only after a longer follow-up period. The fact that Case 4 had not responded previously to two courses each of 1.6 mg./kg. with aortic occlusion, would appear to deserve attention.

The effect of further fractionation of the total dose of HN2 on frequency and severity of toxic symptoms, particularly those related to the central nervous system, is under investigation at the present time.

TABLE II.—Results of Haematological Studies

Case No.	Before I.A.O.		After I.A.O.					
	Bone-marrow		10 Days		6 Weeks	Days to Lowest W.B.C.	Lowest W.B.C.	Days to Normal W.B.C.
	Sternal	Iliac	Sternal	Iliac	Sternal Bone-marrow			
1	3	3	1	4	2	22	4,050	24
2	3	3	0	4	N.T.	11	2,100	15
3	3	3	0	4	3	11	1,000	22
4	3	3	1	4	N.T.		No data	
5			No data					
6	3	3	0	4	3	10	1,600	17
7	3	3	1	4	3	10	2,600	15
8	3	3	1	4	2	7	350	14
9	3	3	0	4	3	11	850	14
10	N.T.	N.T.	N.T.	N.T.	N.T.		No depression	

0=Aplastic. 1=Very hypoplastic. 2=Hypoplastic. 3=Normoplastic. 4=Hyperplastic. N.T.=Not taken.

TABLE III.—Toxic Effects Observed in 10 Patients

Case No.	Immediate				Delayed		
	Vomiting	Diarrhoea	Mental Confusion	8th-nerve Impairment	Life-threatening Complications Due to Leucopenia	Gastro-intestinal Disturbance	Alopecia
1	3	3	0	1	0	0	1
2	3	1	0	0	0	0	0
3	2	0	0	1	0	0	0
4	1	Shigella	0	0	0	0	0
5			No data				
6	1	0	0	0	0	0	2
7	2	0	2	1	0	0	1
8	3	1	2	0	0	0	3
9	0	0	1	1	0	0	4
10	1	0	1	0	0	0	0

Estimated effective tumour dose as in Table I. 0=Absent. 1=Mild. 2=Moderate. 3=Severe. 4=Very severe.

Summary

A simple technique of intermittent occlusion of the abdominal aorta and of collateral arteries is described.

The occlusion is effective enough to allow the administration of up to 3 mg. of HN2 per kg. divided into four doses without fatal bone-marrow injury, as shown in 10 cases of inoperable cancer localized above the diaphragm.

Toxic effects have been vomiting, diarrhoea, alopecia, mental confusion, and decrease of auditory function.

Preliminary evidence of tumour regression justifies further studies with this method of treatment.

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CAROTID PAIN: REPORT OF SIX CASES

BY

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As a presenting symptom, severe spontaneous pain felt over the bifurcation of the common carotid artery has been reported by few medical writers. Fay (1927, 1932) described that physical sign which he termed "carotidynia," tenderness along the course of the common carotid which may be elicited during an attack of atypical facial neuralgia. He used this in support of his hypothesis that in such cases headache was brought about by abnormal behaviour of the carotid tree.

The first description of spontaneous carotid pain as a symptom appears to have been made by Truffert (1948). He recorded, in a man of 38, episodes of severe pain at the level of the carotid bifurcation, sometimes radiating upwards into the face. He described a feature which is very characteristic of the syndrome, the extreme sensitiveness of the artery to the slightest pressure, so that the wearing of a light scarf would cause an intolerable aggravation of the pain. He also noticed, during attacks, the appearance of a pulsating tumour at the level of the hyoid. In the same paper two other cases were also described. In 1949 Hilger published an account of five cases similar to those of Truffert, and Riser, Dardenne, and Gleises (1949) described the case of a 78-year-old man whose carotid pain evidently fell into a clinical category distinct from the previous cases and indeed from all subsequently published cases. In this case, although bilateral carotid pain was a presenting symptom, a diagnosis of temporal arteritis was made, and was supported by biopsy.

A case of recurrent carotid pain associated with angioneurotic oedema was reported by Martorell (1955). The most recent and the largest series is that of Lovshin (1960), who analysed the case histories of 100 patients seen in two years at one clinic. Though only three detailed histories are used in illustration, he drew a vivid composite picture of the syndrome which he regarded as "a vascular headache in the neck," and he made a plea for its wider recognition. I have been unable to find any British references to this striking and singular clinical phenomenon.

The six cases described below were first seen during the period April, 1959, to June, 1961.

Case Reports

Case 1.—A married woman of 47 was sent by her G.P. to an ear, nose, and throat surgeon, complaining of a very

painful swollen "gland" in the left side of her neck. This had troubled her intermittently for seven months in about 10 episodes of between one and seven days' duration. The pain would sometimes spread up the left side of the face to the temporal and parietal region. For 12 years she had been subject to migraine, paroxysms of fronto-parietal headache lasting 48 hours, which she regarded as entirely distinct from her pains in the neck. She was a tense, anxious woman obviously in great pain. A pulsatile tumour was seen and felt on the left side at the level of the carotid bifurcation. The lightest palpation of it caused great distress. Elsewhere the vascular system appeared normal and the patient was normotensive. A slow intravenous injection of ergotamine tartrate, 0.5 mg., failed to relieve her pain or to lessen the tumour. She has been reviewed at intervals over the two-year period and has had a number of similar attacks. During this time there have been many other complaints for which no organic basis could be found. They included soreness of the eyes, low back pain, and pain on micturition. She suffered also from neurodermatitis. She gave, and continued to give, the impression of a sad, rather lonely woman in need of sympathy.

Case 2.—A married woman of 58 complained of soreness in an "inflamed gland" in the neck on the left. She had a long history of ill-health, including three nervous breakdowns of many months' duration. These appeared to have been exacerbations of a long-standing and almost continuous phobic anxiety state. She had within the previous year complained of abdominal pains which had defied diagnosis, and she had been treated by manipulation, and, unsuccessfully, for low back pain. She was a sad-looking woman with a fear of cancer. The left common carotid was readily palpable and was very tender at the level of bifurcation. There was no glandular enlargement in the neck. Her blood-pressure was 160/90.

Case 3.—A machine-tool fitter aged 51 complained of pain below the right angle of the jaw in episodes of two hours at exactly the same time every afternoon for the previous five days. He had had "a nervous breakdown" at the age of 16 and a tendency to occasional headache of short duration all his life. A well-built man of healthy appearance, he gave his story simply and without embroidery. The right common carotid was very tender at its bifurcation and pulsated more amply on this side. The fauces were healthy and there was no lymph-node enlargement. The blood-pressure was 195/100. The pain was unrelieved by intravenous ergotamine tartrate. The E.S.R. was 26 mm. in one hour. A week later there was still a complaint of occasional dull pain but tenderness was no longer apparent. Within a further week all pain had gone and the E.S.R. had fallen to 6 mm. in the hour. During the next two years he experienced occasional attacks of neck pain but was never again observed in one of these.