PAPERS AND ORIGINALS

Treatment of Advanced Tumours of Head and Neck with Fast Neutrons

MARY CATTERALL, D. D. VONBERG

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Summary

Fast neutrons interact with matter in a different way from x and gamma rays. They have been used at Hammersmith Hospital for the past four years in the treatment of advanced tumours in several sites of the body, and the results of this treatment in the first 100 cases of tumours of the head and neck are described here. Altogether 62 patients who had been referred for fast neutron therapy because it was thought that no other treatment would be effective experienced complete regression of the tumours, and only two recurred. Tumours of the buccal cavity and salivary glands responded particularly well and the relief of pain and ulceration was striking. Side effects were not serious and did not differ from those seen with supervoltage radiation, apart from the reaction of the skin. Follow-up was short, however, owing to deaths from metastases, and out of 76 patients treated more than one year previously only 30 survived. Cases which have not metastasized must therefore be treated so that the effects on tumours and adjacent normal tissues can be observed for several years after treatment. The results obtained so far indicate that it is now justifiable to use neutrons in such cases.

Introduction

Fast neutrons can be produced by cyclotrons with sufficient intensity for use in radiotherapy. The first cyclotron to be used for the treatment of cancer was made by E. O. Lawrence in Berkeley, California, nearly 40 years ago. Between 1938 and 1943 more than 200 patients with advanced cancer had been treated on that machine (Stone and Larkin, 1942), and though some surprising cures were obtained the damage to the adjacent normal tissue was so great that Stone (1948) predicted that fast neutrons would never become useful clinically. This view effectively put an end to fast neutron therapy in the U.S.A..

In the United Kingdom, however, the mechanism of the biological action of fast neutrons was being studied experimentally (Gray *et al.*, 1940; Gray and Read, 1942) and differences in the responses of biological systems to fast neutrons compared with *x* and gamma rays were discovered (Gray and Read, 1944). Mitchell (1946) pointed out that the results of the American clinical investigation could not be regarded as conclusive for several reasons, including unsatisfactory data on the measurement of the doses used and the selection of patients with extremely advanced disease which prevented adequate assessment of the effects of fast neutrons. It was suggested that the possible usefulness of fast neutrons in malignant disease should be fully investigated, and the Medical Research Council decided to install a cyclotron in Hammersmith Hospital for the exclusive purpose of medical research and the reinvestigation of fast neutrons in the treatment of cancer. The building of this machine was started in 1950.

Fast neutrons interact with matter in an entirely different way from *x* and gamma rays. The latter interact with atomic electrons; the electron recoils have relatively large ranges and lose energy by producing ionization sparsely along their tracks. Neutrons, on the other hand, interact with atomic nuclei, producing nuclear recoils in the form of protons, alpha particles, and nuclei of carbon and oxygen. These have much shorter ranges and ionize densely along their tracks (see fig. 1). The density of ionization along the tracks is described as linear energy transfer (L.E.T.); *x* and gamma rays are referred to as low-L.E.T. radiations, and neutrons as high-L.E.T. radiation.

Gray *et al.* (1953) found that *x*-rays had much more effect in retarding and inhibiting the growth of cells when they were in an oxygenated rather than a hypoxic environment but that this protection by hypoxia was significantly less when high-L.E.T. radiation was used. Therefore, as many animal tumours, and probably also some human tumours, contain hypoxic cells, there was reason to expect greater effects against tumours when neutrons were used.

Ten years of physical and radiobiological research on cells,

Medical Research Council's Cyclotron Unit, Hammersmith Hospital, London W12 OHS
MARY CATTERALL, F.F.R. D.M.R.T., Consultant Radiotherapist
D. D. VONBERG, B.SC., M.I.E.E., Director

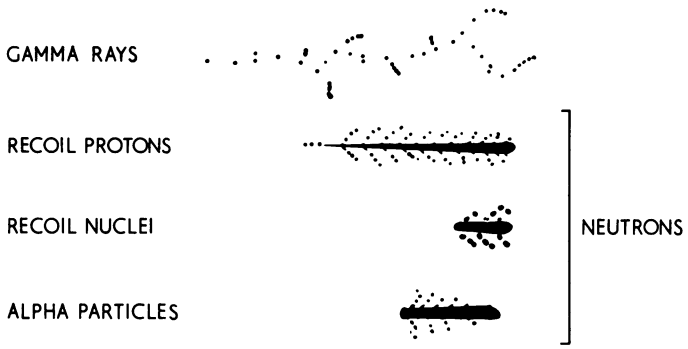

FIG. 1—Ionization tracks of gamma rays (low L.E.T.) and fast neutrons (high L.E.T.) a Fast neutron radiation also contains some gamma-ray ionization.

mice, rats, and pigs with the Hammersmith cyclotron preceded any treatment of patients. During that time differences in the relative biological effects of neutrons and low-L.E.T. photons were found (Field *et al.*, 1968; Thomlinson, 1968; Field, 1969), and this and other work (Sheline *et al.*, 1971) gave an explanation for the severe effects on normal tissues which Stone had experienced.

The Hammersmith cyclotron produces fast neutrons of modal or mean energy of 7 MeV in a fixed horizontal beam. In comparison with supervoltage *x*-ray and gamma-ray machines, therefore, it has the disadvantage of not being able to rotate round the patient. It is necessary for the patient's position to be carefully adjusted in front of the neutron beam so that it enters at the required point and delivers the dose at the predetermined angle of entry. With good methods of adjusting the patient this becomes an inconvenience rather than a serious disadvantage. The penetration of the neutron beam, however, is less than that of supervoltage machines, and at 8 cm in tissue the neutron dose is reduced to 50% compared with 70% for *x*-rays from a 6 MeV linear accelerator.

From 1966 to 1969, 43 patients were treated by Morgan and Morrison (1969). The present investigation to assess the clinical value of fast neutrons was started in 1969, and the first eight months were spent in finding a dose of radiation which caused the disappearance of small subcutaneous tumours and produced a skin reaction from which healing was complete (Catterall *et al.*, 1971). Since then 350 patients with a variety of tumours have been treated.

In the past 18 months three cyclotrons in the U.S.A. have been made available for the treatment of patients. Though they have the advantage of more energetic and therefore more penetrating beams of neutrons none of them is situated within a hospital and patients have to travel up to 200 miles (320 km) for each treatment. Nevertheless, clinical investigations have started with these machines. In the United Kingdom the Medical Research Council and Cancer Research Council are installing a cyclotron at the Western General Hospital, Edinburgh. Two other neutron sources, one at Manchester and one at Glasgow, were installed four and two years ago for the Department of Health and Social Security, but to date technical difficulties have prevented the production of an adequate output of neutrons. Other clinical trials are being conducted or planned in Japan, East and West Germany, Holland, and Belgium.

In this paper we describe the results of treatment in the first 100 patients with advanced tumours of the head and neck treated at Hammersmith Hospital on the M.R.C.'s cyclotron.

Patients and Sites of Tumours

All the patients were referred by radiotherapists or surgeons either because it was thought that other forms of therapy would not be successful or because the tumours had recurred after surgery, chemotherapy, or supervoltage radiation. They were, therefore, a selected group with large or radioresistant tumours in whom the prognosis was poor; two of them died of cachexia during the course of treatment. The tumours were in the following sites.

Buccal Cavity and Oropharynx.—These two sites are considered together because most of the tumours were so large that it was impossible to say where they had originated. There were 23 patients, seven of whom had stage T3 tumours, with fixed nodes in two. Sixteen patients had T4 tumours, and 13 of these had fixed nodes. All the tumours were squamous cell carcinomas and 17 were well differentiated.

Salivary Gland.—Thirteen patients with advanced, inoperable salivary gland tumours were treated. In 10 cases tumour was infiltrating the skin and fixed deeply, and three other intraoral tumours were ulcerated and fixed deeply to adjacent structures. Histological appearances were adenoid cystic in six cases, mucoepidermoid in three, adenocarcinomatous in two, and poorly differentiated in two.

Antrum and Nasopharynx.—Seven patients had advanced antral tumours, all of which were destroying at least two walls of the antrum. Three others appeared to arise in the nasal cavity and involved adjacent structures such as the ethmoids and soft palate. Four were infiltrating the skin. Histologically five of the 10 tumours were of squamous cell type, two were adenocarcinomas, and there was one each of melanoma, chondrosarcoma, and osteosarcoma.

Cervical Lymph Nodes.—Altogether 23 patients had fixed metastatic nodes in the neck. The primary tumours, which were apparently cured, had been in the buccal cavity (7 cases), oropharynx (3), antrum (4), larynx (3), skin (2), and breast (1); in three cases the site of the primary tumour was unknown. Eight of the lymphnode masses had recurred after surgery and two after chemotherapy. Histologically all but two of the tumours were squamous cell carcinomas; the others were adenocarcinomas from the breast in one case, and in the other the site of the primary tumour was unknown. Nineteen tumours were well differentiated and four poorly differentiated.

Hypopharynx.—Fifteen patients had extensive carcinomas of the hypopharynx, and except for two in whom the growth was in the cervical oesophagus it was impossible to be more specific about the site of origin of the tumours. In 10 patients the tumours were well differentiated histologically, in two moderately so, and in the remaining three they were poorly differentiated. Eight patients had fixed nodes in the neck, and in four of these there was skin involvement as well. Four others had growth invading cartilage. All except two patients had hoarseness of the voice, and in six dysphagia was the presenting symptom. Four patients had stridor. The growths were all ulcerated but only six patients complained of pain. Two patients had hvpercalcaemia. Two others developed bronchopneumonia during treatment, and this had to be suspended, prolonging the overall treatment time to 52 and 59 days. In one there were technical difficulties with the fixed horizontal beam and the patient's anatomy and the treatment plan had to be changed with resulting underdosage.

Recurrent or Residual Tumours after Radiotherapy, Surgery, or Chemotherapy.—Treatment with fast neutrons was given to 16 patients with recurrent or residual tumours in areas which had previously been irradiated with *x* and gamma rays. Thirteen of these patients had also received surgery and chemotherapy to the area. The tumours were therefore situated in tissues which had been severely damaged by unsuccessful treatments and the risk of necrosis from further treatment was high. The patients were all apparently free of disseminated disease, however, and all had severe local symptoms. There were four with salivary gland

tumours, four with metastatic nodes, three with antral tumours, and five with tumours of the tongue and floor of the mouth. All except the salivary gland tumours were well-differentiated squamous cell carcinomas. The general condition of these patients was poor because of the debilitating effects of the previous treatments and the severe pain and malnutrition caused by fungation and trismus.

Fast Neutron Treatment Regimen

Patients were treated three times a week for four weeks and the total neutron dose to the tumour was 1,440 rads. Each treatment lasted about four minutes. In many instances the tumours were so large that fields of radiation measuring about 200 cm^2 were used, and this led to uneven dose distribution, so that the tumour dose was not always uniform. Single fields were rarely used; mostly a combination of two beams were arranged to converge on the tumour. Wedge filters and shields were also used when necessary.

The beam is fixed and horizontal, so that most patients were treated in the sitting position and were immobilized by Bexoid shells made for each subject. These shells also served for the attachment of a plastic material which was applied to improve the distribution of the dose throughout the treatment volume.

Results

The results of treatment of the tumours in various sites at intervals after the first treatment of six months, one year, and more than two years, together with the numbers of patients surviving in each group, are shown in tables I to III.

Six months after the first treatment 51 patients were alive with no sign of tumour in the treated area, in six others the tumour was, by serial measurements, still regressing, and in two it had not disappeared but was not regrowing (table I). Two patients had been treated only three and five months previously. A total of 39 patients had died (two of them during treatment) but in 11 of these there was no sign of tumour and in 16 others the tumour was regressing at death.

Out of 76 patients who had completed their treatment more than one year previously, 30 were alive with no sign of tumour, 17 had died with no tumour in the treated area, and 3 had died with residual tumour (table II). The remaining 26 had died within six months of treatment and are included in table I.

TABLE I—*Status of Patients and Tumour Area Six Months after Treatment*

Tumour Site	No. of Patients	Alive				Dead			
		No Sign	Regressing	Residual	Recurrent	No. Sign	Regressing at Death	Residual	Recurrent
Buccal cavity and oropharynx	23*	12	1			5	4		
Salivary glands	13	9	4						
Antrum	7	5				1		1	
Nasopharynx	3	3							
Cervical lymph nodes	23	9	1	1		2		10	
Hypopharynx	15†	10		1		1	1	1	
Retreated after low-L.E.T. recurrence	16	3				2	11		
Total	100	51	6	2		11	16	12	

*Includes one patient treated three months previously.
†Includes one patient treated five months previously.

TABLE II—*Status of Patients and Tumour Area One Year after Treatment*

Tumour Site	No. Treated More than 1 Year Previously	Alive				Dead			
		No Sign	Regressing	Residual	Recurrent	No Sign	Regressing at Death	Residual	Recurrent
Buccal cavity and oropharynx	20	9				3			
Salivary glands	9	7				2			
Antrum	6	3				1			
Nasopharynx	2	2				2			
Cervical lymph nodes	20	5				3		1	
Hypopharynx	9	4				4		1	
Retreated after low-L.E.T. recurrence	10					2		1	
Total	76	30				17		3	

TABLE III—*Status of Patients and Tumour Area More than Two Years after First Treatment*

Tumour Site	No. Treated More than 2 Years Previously	Alive				Dead 1-20 Years after Treatment		
		No. Sign	Regressing	Residual	Recurrence	No Sign	Residual	Recurrence
Buccal cavity	7				1	2		
Salivary glands	7	4				3		
Antrum	4					1		1
Nasopharynx	1					1		
Cervical lymph nodes	14	1				3		
Hypopharynx	4	1						
Retreated after low-L.E.T. recurrence	4							
Total	41	6			1	10		1

Altogether 41 patients had received their treatment more than two years previously, and of these six were alive with no tumour and one had tumour which had recurred 28 months after treatment. Eleven patients died one to two and a half years after treatment, of whom 10 had no tumour in the the treated area and one had recurrent tumour (table III). The remaining 23 patients died within six months of the treatment and are included in table I.

Two tumours recurred in this group of 100 patients, one of which was in the antrum and one was in the buccal cavity.

The clinical assessment of complete regression was confirmed at necropsy in eight patients. Two other patients who came to necropsy had no macroscopic tumour but microscopical examination showed recognizable tumour cells; whether these were viable could not be definitely decided. The causes of death were metastases, cardiovascular accidents, and broncho-pneumonia.

The effects of treatment on symptoms and the complications observed are summarized in table IV. In all sites pain and ulceration were nearly always completely relieved except where patients had already received an ineffective course of low-L.E.T. radiation, and in these cases palliation was achieved in only about half.

Buccal Cavity and Oropharynx.—Symptoms were of marked severity when tumours were in the buccal cavity and oropharynx, and the consistent relief of pain, healing of ulceration, and resumption of eating were striking in these 23 cases. Twelve patients were alive with no sign of tumour six months after treatment and nine had died, five without tumour in the treated area. Nine out of 20 patients were alive one year after treatment and three others had died without tumour. These patients were nearly all old and in poor condition and metastases accounted for 40% of the deaths. Tumours of the floor of the mouth responded particularly well to treatment (table V).

Salivary Glands.—All 13 patients with salivary gland tumours had pain, ulceration, or trismus, and in each case these symptoms were relieved and none recurred. These patients had the longest survival time, and three out of seven patients who had been treated two and a half to three and a half years previously were alive, and one other, who had been treated four years previously, died of coronary thrombosis 44 months after treatment (see fig. 2). When the seventh nerve had been paralysed for more than six months it did not recover, but in two patients with paralysis of shorter duration than this recovery was complete when the tumour regressed. No tumour recurred (table VI).

Cervical Nodes.—Of the 23 patients with cervical nodes invaded by carcinoma 12 suffered severe pain. This was relieved in all cases but recurred in one. The nodes were fungating through the skin in three patients, and this healed completely in two and was improving in the third at the time of her death. Twelve patients died of generalized metastases within six months of treatment; the tumour regressed completely in only 12 of the 23. The remaining 11 tumours, which were residual at the time of death, were from primary tumours in the buccal cavity (5), oropharynx (3), and antrum (1); in two cases the source was unknown. Ten of the patients had either had previous surgery or suffered from anatomical deformities such as kyphosis which made it impossible, with the physical limitations of the beam, to deliver the full dose of fast neutrons, and they all, therefore, had an inadequate amount of radiation. The one exception to this died one month after treatment with a regressing mass of adenocarcinoma from a primary tumour in the breast. One other patient with a large fixed mass of nodes of well-differentiated adenocarcinoma obtained relief of ulnar nerve

TABLE V—*Response of Tumours of Floor of Mouth and Tongue (14 Patients)*

	No. of Patients
Died within 3 months	4
Clinically no sign of tumour	8
Alive with residual ulceration or induration; biopsy negative	2
Tumour-free period:	
More than 18 months	2
More than 11 months	3
More than 6 months	3
Recurrence	0
Morbidity:	
Dry mouth	7
Fibrosed salivary glands	2

TABLE IV—*Effects of Treatment on Symptoms and Complications Observed*

Tumour Site	No. of Patients	Symptoms Relieved				Complications
		Pain	Ulceration	Muscle Spasm	Other	
Buccal cavity	23	17/18	21/22 (Recurred in 1)	5/5		Dryness of mouth 7, slight deafness 2, recurrent parotitis 2, fibrosed salivary duct 2
Salivary glands	13	12/12	6/6	5/5	7th Nerve palsy recovered 2/4	None
Antrum	7	5/5	4/5			*Conjunctivitis 6, distortion of eyelid contours 6,
Nasopharynx	3	2/2			6th Nerve palsy recovered 1/1, nose bleeding stopped 1/1	loss of corneal sensation 3, cataract 1
Cervical nodes	23	12/12 (Recurred in 1)	3/3 (Partially in 1)	3/7	Horner's syndrome relieved 1/2, ulnar nerve paraesthesia relieved 1/1	None
Hypopharynx	15	6/6 (Recurred in 1)	12/15		Stridor relieved 4/4, recurred 1; dysphagia relieved 6/6; hoarseness of voice improved 7/13	Oedema of larynx 2, aspiration pneumonia 4, necrosis of cartilage at necropsy 1
Retreated after low-L.E.T. recurrence	16	8/16 (Recurred in 1)	5/16	2/4		Rapid deterioration of general condition 13
		6 Patients obtained no relief at all				

*Details of changes in irradiated eyes will be subject of separate paper.

TABLE VI—*Response to Treatment of Salivary Gland Tumours (13 Patients)*

Tumour Type	No. of Patients	Tumour-free Period (Months)	No. of recurrences	No. who Died with no Tumour Present
Mucoepidermoid	3	45, 39, 11	0	1 (45 months)
Adenoid cystic	6	35, 24, 26, 12, 6, 4	0	3 (35, 12, 6 months)
Adenocarcinomatous	2	6, 4	0	2 (6, 4 months)
Poorly differentiated	2	12, 10	0	1 (12 months)

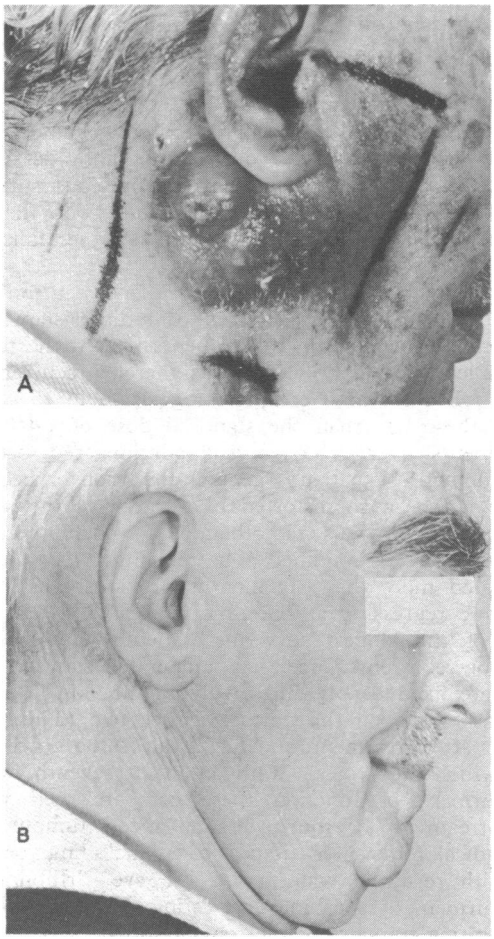

FIG. 2—(a) Advanced mucoepidermoid carcinoma of parotid, fixed deeply and fungating through skin. (b) Appearances after treatment, with no tumour and minimal skin changes and intact seventh nerve.

paraesthesia and a Horner's syndrome and remained well eight months after treatment.

Antrum and Nasopharynx.—The effects of treatment in the 10 patients with tumours of the antrum or nasopharynx were difficult to assess apart from relief of symptoms and regression of visible and palpable parts. There was no marked radiographical change of either recalcification or further destruction except in one case of transitional cell carcinoma which showed a definite reduction of a mass within the antrum. Two patients died of generalized metastases within six months of treatment, and two others, with chondrosarcoma and osteosarcoma, died two years after treatment, with recurrent tumour in the case of the chondrosarcoma. Pain was relieved in all five cases where this was present, and in four out of five patients in whom the tumour had infiltrated the skin and caused puckering or frank ulceration treatment resulted in complete healing. The patient with melanoma of the postnasal space, inferior turbinate, and maxillary antrum had complained of nose bleeding for many years, and this stopped after the neutron therapy until his death from a cerebral thrombosis 15 months after treatment. A patient who complained of diplopia lost this symptom; clinically, however, a sixth nerve palsy could still be shown six months after treatment though this had improved. The original complaint of seven patients was of facial swelling, and in all cases this regressed and a normal contour was achieved.

Recurrent Tumours after Surgery, Radiotherapy, or Chemotherapy.—The tumours which responded well to fast neutrons after previous unsuccessful treatment were those where the buccal mucosa and tongue could be avoided. They included adenocarcinoma of the parotid, adenoid cystic carcinoma of palate, lymph nodes invaded with squamous cell carcinoma, and a huge squamous cell carcinoma of the antrum which was fungating into the nose, orbit, skin, and lymph nodes. In six patients neutron treatment did not give worthwhile palliation. These included four with buccal cavity tumours which had been heavily irradiated and perfused with cytotoxic drugs and who had undergone extensive surgery; the tissues, particularly the tongue, were too devitalized to respond to any further radiation. Two others with fixed neck nodes had received all three types of treatment and had fistulae and were unable to complete the course of treatment.

Hypopharynx.—Ten of the 15 patients with hypopharyngeal growths survived with no sign of tumour for six months, and stridor, dysphagia, and pain were relieved in all cases in which these symptoms were present. Ulceration healed in 12 out of 15 cases. Only four out of nine patients, however, who received their treatment more than a year previously were alive with no tumour, four others had died with no sign of tumour, and one had died with residual tumour. More than two years after treatment only one of the four patients was alive with no tumour. Hoarseness improved in seven out of 13 patients. Laryngectomy was performed three and four months after treatment in two patients, both of whom had received less than the standard dose. In one the

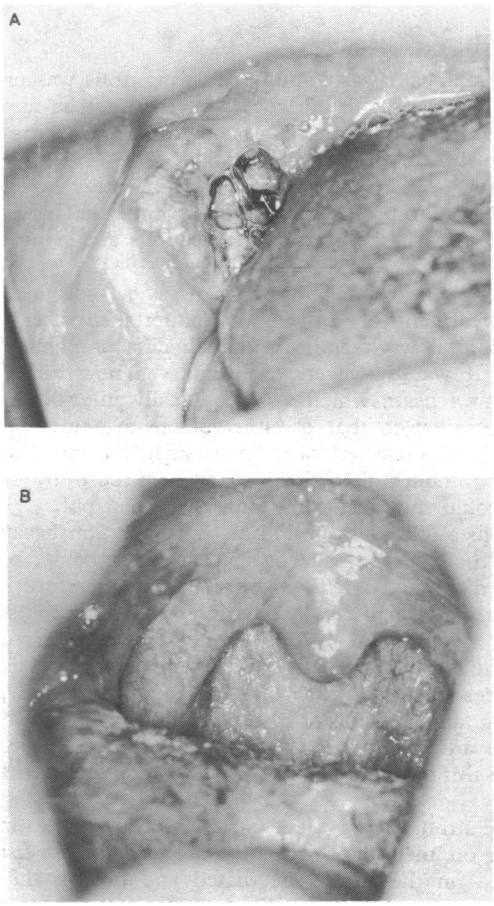

FIG. 3—(a) Well-differentiated squamous cell carcinoma involving tonsil, fauces, tongue, floor of mouth, buccal mucosa, and alveolus and causing pain and trismus. (b) Appearances one year after treatment, with regression of tumour, relief of trismus, and drying of mucosa restricted sharply to right of buccal cavity and uvula.

operation was said to be difficult due to oedema, and in this patient macroscopic tumour was present.

COMPLICATIONS

Patients were observed closely and often to assess the effects of fast neutrons on normal tissues which were unavoidably irradiated. A list of 36 such adverse effects is given in table IV. Apart from the reaction produced on the skin, which consisted of bright pink erythema and moist desquamation which healed two to four weeks after treatment, none was different in character from those seen with low-L.E.T. radiation. Drying of the buccal mucosa was restricted to the irradiated side, as shown in fig. 3. The only probable quantitative difference was in the oedema of the larynx in three patients, all of whom had T4 tumours and in whom the oedema was severe, a tracheostomy being required in one patient.

Aspiration pneumonia was seen in four cases, but all these patients were aspirating liquids before treatment and in all of them the tumour involved the epiglottis.

The eyes of all relevant patients were fully examined before, during, and after treatment by Mr. Nicholas Brown, of the Institute of Ophthalmology and Moorfields Hospital, and his findings and the correlation with the exact dose received are the subject of a separate paper. Essentially there were no effects produced by neutrons which are not also produced by low-L.E.T. radiation.

Discussion

The first clinical investigation of fast neutrons was undertaken only six years after the discovery of the neutron and without the necessary data from radiobiological experiments. Though the clinical results were such that Stone (1948) decided to discontinue the investigation it is interesting to note that, "The general impression of one watching the patients being treated is that marked tumour regressions are being produced when they were not expected" (Stone, 1944).

The present investigation into the effects of fast neutrons in the treatment of cancer was undertaken after extensive radiobiological work and with much data on their effects on animals. It was, however, regarded as a new form of treatment with a beam which was technically inferior in mobility and penetration to that of supervoltage machines. Therefore, patients were selected who had such advanced or radioresistant tumours that their chances of cure by any other means could not be compromised. This policy inevitably resulted in a follow-up period of short duration because many patients died of generalized metastases, cachexia, or cardiovascular disease. No firm conclusions can therefore be drawn about the late effects of fast neutrons on normal tissues—for example, necrosis or fibrosis—nor the long-term recurrence rate of tumours which clinically completely regressed. These recurrences of tumours in the head and neck are generally agreed to appear within two years of treatment, but apart from the advanced state of the disease causing early deaths only one-third of these patients were treated for that length of time.

Fast neutron therapy is a strictly localized treatment and no effect on metastases can be expected. Its effects have to be judged on the tissues irradiated and not on the survival of the patients, though if the tumour has not metastasized and if it is sterilized the patient's life, from the cancer standpoint, will be prolonged. For an adequate period of follow-up it is therefore necessary to treat earlier cases in the future where tumours are less likely to have metastasized.

Most tumours of the head and neck can be easily and thoroughly examined and recurrences cannot go unnoticed; the tumours are not deep-seated and therefore the full dose of radiation can usually be given to all parts of the tumour from this neutron beam. The close proximity of vital normal structures, however—for example, the spinal cord and base of the brain—which must not be damaged sometimes make the arrangement of beams of radiation extremely difficult, especially when such large tumours as those described are treated. Distortion of the anatomy by previous surgery and devitalization of local tissues and debility of the general condition by chemotherapy also increased the difficulties of treating some of these patients.

The results leave little doubt that fast neutrons caused regression of these very advanced or radioresistant tumours in most cases. In 62 of the 100 patients treated the regression was complete and in only two was there a recurrence. Fast neutrons failed to cause complete regression in 15 cases, but in 13 of these less than the standard dose of 1,440 rads in 12 treatments over 26 days was administered because of deterioration in the patient's general condition or because the anatomy had been so distorted by surgery or the tissues so devitalized by previous radiotherapy or chemotherapy that treatment had to be modified. The remaining 19 patients who were treated more than six months previously had tumours which were regressing at the time of death.

Some of the longest surviving patients with no sign of residual or recurrent cancer had inoperable salivary tumours which were fixed deeply and involving the skin. There were no serious effects on the normal tissues two to three and a half years after treatment, and fig. 2 shows the good cosmetic results, which are typical. With an intact seventh nerve and no impairment of function these compare well with the surgical treatment of much less advanced tumours, which entails radical removal of tissues, often including the seventh nerve, with resulting watering of the eye, dribbling saliva, and impairment of speaking and eating. Similarly, ulcerating and infiltrating tumours of the tongue and floor of the mouth have been successfully and completely ablated without the morbidity which results from radical surgery in less advanced cases. Where involved neck nodes received fast neutrons as the first treatment there was no operative risk and little or no morbidity, compared with those resulting from radical surgical dissection.

It may be argued that the 36 complications are greater than would be expected with supervoltage radiation and that the successful treatment of the tumours was due to a higher dose being given at the expense of inflicting damage to normal tissues. It must be remembered, however, that because of the damage to normal tissues described by Stone (1948) these patients were subjected to more frequent and more critical examinations than are normally given to patients receiving supervoltage radiation by well established methods, and so complications were noted which otherwise might not have been. Also these early complications were acceptable to the patients, and if the later ones are also, any improvement in the clearance of tumours by fast neutrons must be due to differences in the quality rather than the quantity of radiation. But to observe late complications it is necessary for the patients to survive more than two years, and so it is essential to treat patients with smaller tumours which have not metastasized.

While there is no justification for using a new method of treatment where existing ones give good results—for example, *x* and gamma radiation for early cancer of the larynx and lip—there exists a spectrum of tumours which are larger than these and for which treatment is often with a combination of radiotherapy and radical surgery. Cure in these cases is uncertain, however, and morbidity is often severe. These are among the locally extensive but smaller tumours which might be better treated with neutrons.

Since the efficacy of different treatments can be properly assessed only by randomized controlled trials there is an urgent need for such trials to assess the value of and in-

dications for the various regimens available for the treatment of tumours of the head and neck. Until this evidence is available inappropriate management will continue to be given in some cases. A patient's first treatment is vital and dictates the whole prognosis of his disease, but at present this is selected by the clinician who first examines him and who, lacking data from controlled trials, usually chooses the treatment with which he is most familiar.

Fast neutrons are at present the subject of such a controlled clinical trial, and consultant radiotherapists and aural surgeons in London, Birmingham, and south-east England are collaborating. The early results of this trial will be the subject of a separate paper.

References

Catterall, *et al.* (1971). *British Journal of Radiology*, **44**, 603.
Field, S. B., (1969). *Radiology*, **92**, 381.
Field, S. B., Jones, T., and Thomlinson, R. H. (1968). *British Journal of Radiology*, **41**, 597.
Gray, L. H., *et al.* (1940). *British Journal of Radiology*, **13**, 371.
Gray, L. H., *et al.* (1953). *British Journal of Radiology*, **26**, 638.
Gray, L. H., and Read, J. (1942). *British Journal of Radiology*, **15**, 72.
Gray, L. H., and Read, J. (1943). *Nature*, **152**, 53.
Gray, L. H., and Read, J. (1944). *British Journal of Radiology*, **17**, 271.
Mitchell, J. S., (1946). Personal communication.
Morgan, R. L., and Morrison, R. M. (1969). Personal communication.
Sheline, G. E., *et al.* (1971). *American Journal of Radiology*, **111**, 31.
Stone, R. S. (1944). *Medical Physics*, ed. O. Glasser, p. 816.
Stone, R. S. (1948). *American Journal of Roentgenology*, **59**, 771.
Stone, R. S., and Larkin, J. C. (1942). *Radiology*, **39**, 608.
Thomlinson, R. H. (1968). *Frontiers of Radiation Therapy and Oncology*, **3**, 109.

Effect of Prolonged Thiazide Treatment on Renal Lithium Clearance

V. PETERSEN, S. HVIDT, K. THOMSEN, M. SCHOU

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Summary

Renal lithium clearances were determined after the administration of a small test dose of lithium carbonate in 22 patients when they were on long-term treatment with thiazides and when they were not on such treatment. Thiazide administration led to a 24% reduction in the lithium clearance. Diuretic drugs should be used with caution in patients given lithium treatment, and lithium should be used with caution in patients receiving diuretic treatment.

Introduction

Lithium salts are used for the treatment and prophylaxis of recurrent manic-depressive disorders (Schou, 1968). During lithium administration the serum levels of lithium must be maintained within a relatively narrow range: low levels lack effect and high levels are associated with a risk of side effects or intoxication. Lithium is excreted almost exclusively through the kidneys and the serum lithium level is therefore determined by the maintenance dosage and the renal elimination of lithium. Drugs and procedures which alter the renal lithium clearance are potentially dangerous to patients on lithium treatment. Among such drugs may be the diuretics.

In Denmark 11% of the population over 50 years of age take diuretics regularly (Skovbo *et al.*, 1972). Diuretic drugs may be prescribed to manic-depressive patients on lithium treatment if they develop hypertension or oedema; lithium treatment itself occasionally leads to oedema formation (Demers and Heninger, 1970). Diuretics may also be prescribed for the treatment of lithium-induced obesity (*British Medical Journal*, 1974).

The effect of diuretic drugs on the renal lithium clearance has been examined in healthy human subjects and rats. Single doses of frusemide, bendrofluazide, and ethacrynic acid given to the human subjects failed to affect the lithium clearance significantly (Thomsen and Schou, 1968). Daily administration of hydrochlorothiazide to rats over two to four weeks led to a reduction of the lithium clearance by 30-35% (Thomsen and Schou, 1973).

We have examined whether the renal lithium clearance is influenced by long-term administration of thiazides given in ordinary therapeutic doses to patients.

Patients and Methods

Altogether 22 patients (8 men and 14 women) were studied. They were admitted to the department of internal medicine at Thisted Centralsygehus during February to September 1973. All had oedema from various causes for which prolonged thiazide treatment was indicated.

Determinations of lithium clearance (after the administration of a small test dose of lithium carbonate), creatinine clearance, and urinary sodium excretion were carried out twice at intervals of about two months during and before or after treatment with thiazides. The thiazides used were hydroflumethiazide (Rontyl) and bendrofluazide (Centyl). Hydroflumethiazide was given in a dosage of 25 mg daily together with 3·4 g of potassium chloride; the bendrofluazide dosage was 2·5 mg daily. Clearance determinations during thiazide treatment were carried out after treatment periods of two months or longer, determinations after the discontinuance of thiazides being carried out when the patients had been without treatment for two months.

The patients had ordinary hospital food except on the days of examination, when they avoided caffeine-containing food, drinks, and drugs.

The examination procedure was as follows. At 9 p.m. the patients emptied their bladder, the urine sample being discarded. They then took 600 mg of lithium carbonate by mouth; this corresponds to 16·2 mmol of lithium. During the next 11 hours urine was collected for determination of the night creatinine clearance. At 8 a.m. a blood sample was drawn for determination of the serum lithium and creatinine concentrations.

Department of Internal Medicine, Thisted Centralsygehus, Thisted, Denmark
V. PETERSEN, M.D., Senior Registrar
S. HVIDT, M.D., Medical Superintendent

Psychopharmacology Research Unit, Aarhus University Psychiatric Institute, Risskov, Denmark
K. THOMSEN, PH.D., Research Associate
M. SCHOU, M.D., Professor of Biological Psychiatry and Research Director