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The medical uses of fast neutrons (**)

The neutron was discovered by Sir James Chadwick when he was working in Cambridge in 1932. Twenty years later, the first medical cyclotron built by the British Medical Research Council exclusively for medical uses and research was installed in Hammersmith Hospital, London. After many years of scientific and biological research, patients were treated in 1970. Since then regular treatments with neutrons have been given three times weekly. A course of treatment lasts four weeks and consists of 12 attendances.

The neutrons are of 7.5 MeV and emerge from the cyclotron in a beam fixed in the horizontal position. These are disadvantages in that the neutrons are poorly penetrating and adequate doses can only be given to superficially placed tumours, for example those in the head, neck and limbs. Because the beam is fixed horizontally, most patients have to sit, stand or kneel for their treatment, instead of lying comfortably as for modern X-ray therapy.

Despite these difficulties and disadvantages, the Hammersmith neutrons cause complete disappearance of most of the tumours which are treated. These tumours are all advanced and of the types which do not usually respond to X-rays, for example in the salivary glands, paranasal sinuses, glands in the neck, oropharynx, soft tissue sarcoma and melanoma. Such advanced tumours regress in about 70% of cases after neutrons, compared with about 35% after X-rays. Five to 15% recur after neutron therapy. The cosmetic effects after neutrons to tumours of the paranasal sinuses and salivary glands are much better than after radical surgery which removes the upper half of the face or the facial nerve. Neutrons do not do this and patients can lead normal social lives.

Tumours of the salivary glands and paranasal sinuses were originally part

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(**) Relazione presentata al Convegno «I neutroni e loro applicazioni» nel cinquantenario della scoperta della radioattività indotta da neutroni. (Roma, 4-5 giugno 1984).

TABLE 1

Histology	Number	Complete Regression	Partial Regression	Recurrence
Adenoid cystic	26	26	0	3
Adenocarcinoma	12	10	2	2
Mucoepidermoid	10	9	1	1
Mixed malignant	6	5	1	1
Anaplastic	2	2	0	0
TOTAL	56	52 (93%)	4 (7%)	7 (12.5%)

of the MRC trial at Hammersmith Hospital but this had to be abandoned because radiotherapists and surgeons, on seeing the results, referred patients specifically for neutrons. Table 1 gives the results of advanced tumours of the salivary glands.

Following neutron therapy there is a high rate of local control (93% complete regression — 12.5% recurrence = 80%). This compares favourably with similar tumours treated with surgery, where 58% recurred. In certain histological types, (adenoid cystic, squamous and mucoepidermoid) 50% recurred after surgery.

The control rate of 80% after neutrons is about the same as that achieved on much smaller tumours treated with surgery and X-ray therapy. But this procedure is associated with a high incidence (54%) of damage to the facial nerve (causing paralysis of the face, dribbling, slurring of speech and watering of the eye). Furthermore, a combined regime of surgery and radiotherapy requires 8 or more weeks, a period of hospitalisation and an operation. Neutron

TABLE 2

	Number Treated	Complete Regression	Recurrence	Complication
Adenocarcinoma	7	6	1	0
Adenoid cystic	6	6	1	3
Malignant Melanoma	1	1	0	0
Squamous	12	11	1	3
Transitional Cell	5	5	1	4
TOTAL	31	29 (94%)	4 (13%)	10* (32%)

* Six Patients had received previous surgery and/or radiotherapy.

therapy is given on an outpatient basis and requires only 12 attendances (three times a week for 4 weeks). The facial nerve has been damaged in only one case and paralysis may in fact be relieved, thus the cosmetic and functional results with neutron therapy are good.

All the tumours responded to neutron therapy with regression of the measurable mass and improvement in symptoms. Complete regression of the tumour was achieved in 29 of 31 (94%). Four recurred, 75, 26, 17 and 6 months after treatment. Median survival time was 36 months. There were 10 complications, three of which were in patients who had previously received full courses of radiotherapy.

Cancer of the maxillary sinus is frequently lethal and cure rates at three years are of the order of 40% in the best series, whether by radiotherapy or combined surgery and radiotherapy. These cancers produce severe disfigurement through ulceration of the skin, and involvement of nerve and bone. Death from uncontrolled tumours can be appalling. In view of this, Harrison advised that the surgeon's responsibility is to clear the whole tumour-bearing area as widely as possible, despite the cosmetic and functional results, which shatter the morale of some patients. In selected cases, teams of three surgeons from the specialties of plastic, oral and ear, nose and throat surgery can undertake an extensive procedure, lasting 9-10 hours, of excision and reconstruction. Even with such radical approaches, the control rate is only 35%.

Despite the very advanced stage of the tumours treated, neutron therapy controlled 81% and the cosmetic and functional results were much more acceptable than after surgery. No removal of bone, nerves or skin was required. Survival was also longer after neutron therapy, but this may be considered to be of less importance than the cosmetic effects since, if these are bad, they can make survival of any length miserable. For those patients whose survival is short, either due to the advanced stage of disease or age, it is important not to be confined to hospital for long periods. The combined surgery and radiotherapy management is a prolonged one, extending over 12-14 weeks. Neutron therapy requires only 12 attendances over a period of four weeks followed by four attendances over two to four weeks while the skin reaction heals.

Using the Hammersmith dose of 1560 cGy in 12 treatments over four weeks, there is close correlation between the clinical effects and those seen in radiobiological experiments on laboratory animals. The late effects seen clinically correlate with the intensity and duration of the acute reaction and these depend on the exact dose received at the site. The Hammersmith late reactions are not unexpectedly severe and the skin changes include telangiectasis and shrinkage. Higher energy neutrons from the new machines can reasonably be expected to reduce these. If necrosis appears there has been a previous precipitating factor such as trauma, infection, or a large area of the tumour has received a higher dose.

Controlled clinical trials have been done in various centres throughout the world. Where neutrons have been used, either as part or the whole of the

treatment, for advanced tumours they have given better control and usually longer survival than X-rays. Where tumours are only moderately advanced neutron results are as good as X-rays, but not better. This is encouraging in view of the inferior technical qualities of the neutron machines used, in comparison with modern linear accelerator X-rays. These results indicate that although neutrons are superior to X-rays for advanced and « radioresistant » tumours, neutrons will not make X-ray therapy unnecessary. X-ray therapy is highly successful for many small or moderately advanced tumours and gives excellent results in some sites, for example the larynx, where cancers are controlled in 70% of cases and the voice remains normal.

Complications after neutrons may always be higher than after X-rays because of the large size of the tumours. This both causes damage to the normal tissues and requires large areas to be irradiated.

From the one neutron machine at Hammersmith in 1970 there are now 17 centres throughout the world giving neutron therapy. Five of the new high energy cyclotrons with steerable heads are being installed in the USA, UK, South Korea and South Africa. It is from such machines that treatments to the commonly occurring tumours of the bladder, uterus, bowel, stomach, pancreas and lung can be effectively given. If the results obtained so far are repeated in these sites, then neutron therapy will provide a significant advance in the treatment of cancer.