MEDICAL USES OF CYCLOTRONS: TREATMENT AND DIAGNOSIS

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Abstract.- The application of cyclotrons in medicine was foreseen very early in their development. The two main uses were expected to be production of artificial radionuclides and treatment of cancer with neutrons; today these are still the main uses together with activation analysis, radiobiology and treatment with charged-particle beams.

The first cyclotron designed exclusively for medical use is the one at Hammersmith Hospital: there are now at least ten in different countries and many more which are applied to medical problems for part of the time.

Neutron therapy was initiated from the desire to use a form of radiation whose effects were less dependent on the concentration of oxygen in tumours. Assessment of the value of neutron therapy has been plagued by technical difficulties with existing machines: poor penetration, beams fixed in the horizontal position, poor collimation, lack of adjustable field and hazards from radioactivity. New machines at present in production are designed to overcome these problems. Direct use of charged-particle beams is an attractive idea but high energies are needed for useful penetration into the body and ions heavier than He are needed to give reduced dependence on oxygen.

Neutron beams have also been used for measurement of total-body Ca and N by activation analysis in vivo. The dose received by the patient has to be severely limited but sufficient precision can be obtained to aid medical research.

Production of radionuclides remains the principal medical use of cyclotrons. ^{15}O and ^{11}C are particularly important and their use demands that the cyclotron should be in the hospital. Positron-emission tomography is now beginning to allow us to measure functional parameters in the brain, lungs and heart. This is the area in which the most exciting new developments seem likely.

INTRODUCTION

The application of cyclotrons to medical problems began with the earliest machines, largely promoted by E.O. Lawrence's brother, John. It was quickly realised that artificial radionuclides could be used as tracers in biological and medical research; in those days the nuclear reactor had not yet been invented so particle accelerators were the only source of artificial radionuclides. At the same time it was found that beams of fast neutrons could be produced with sufficient intensity for treatment of cancer. These two activities are still the mainstay of medical cyclotrons, to which have been added radiobiology, nuclear methods of analysis, and treatment with charged-particle beams.

A trial of neutron therapy was begun at Berkeley in 1938 and continued until 1943 when the cyclotron was needed for development of the atomic bomb. The rationale was an empirical one: treatment with X rays was often not successful and experiments had shown that the relative biological efficiency (RBE) of neutrons varied depending on the tissue and end-point chosen, so that there was a possibility that the RBE for human tumours might sometimes be greater than for relevant normal tissues.

After the war the results of the trial were analysed with an unfavourable conclusion [1]. However, in the United Kingdom many considered that this conclusion was premature and that the question should be reconsidered after a programme of radiobiological research.

The Medical Research Council therefore decided to install a medical cyclotron at the Hammersmith Hospital with the aims of producing those radionuclides which were not available from nuclear reactors and of re-assessing the therapeutic possibilities of fast neutrons. For both aims a high beam current and good reliability are the main requirements. The cyclotron, which was designed by our own staff, was first switched on in 1955 and can accelerate deuterons to 16 MeV and He ions to 32 MeV, giving an external beam of well over 100 μA.

The present machine runs continuously from the small hours of Monday morning until 10:00 p.m. on Thursday and again during the day on Friday. Fig.1. shows the division of time. About half is devoted to production of radionuclides, 10% each to radiotherapy and radiobiology and the remainder to miscellaneous purposes. Table I shows the timing of the various operations. The distribution of time and the types of radionuclide made are constantly changing; the advent of the positron emission tomographic scanner (PECAT) has resulted in a substantially greater use of short-lived gases than is suggested by the figure of 14% indicated in Fig.1. At present 4 external beam lines are in use. In this paper I shall discuss applications of cyclotrons in radiotherapy, activation analysis and imaging, the latter mainly with the PECAT.
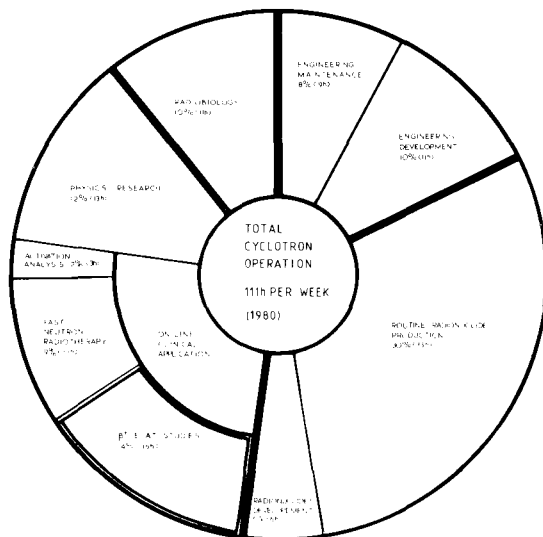
Fig.1. Allocation of time on MRC cyclotron.

Table I.

Typical day on cyclotron

04-08	Radionuclides for other hospitals	$^{81}Rb (^{81}Kr^m)$
08-13	Radionuclides for immediate use. (Tues.Thur.) Neutron therapy (Mon.Wed.Fri.)	^{18}F ^{15}O ^{11}C ^{13}N
13-18	Radionuclides for immediate use Radiobiology Clinical neutron physics	^{15}O ^{11}C ^{13}N
18-04	Radionuclides for use the following day Experimental work Engineering	^{77}Br ^{111}In ^{43}K ^{52}Fe ^{203}Pb ^{87}Y

NEUTRON THERAPY

The rationale for neutron therapy was established in 1953 by Gray and his co-workers [2]. They showed that many animal tumours contained a fraction of hypoxic cells, that cells deprived of oxygen were less sensitive to damage by X rays, and that this radioprotection was much reduced when fast neutrons were used. Since then many other important factors have been elucidated, for example the variation in RBE of neutrons with dose level, the almost additive effect when a series of small doses of neutrons is given (not the case with X rays), and the differential absorption of energy in tissues, neutrons giving more energy to fat and less to the bone [3].

The outstanding features of radiotherapy during the last 60 years have been the introduction of ever more penetrating beams of X rays together with methods of accurately delivering the dose to the required volume. Nevertheless many primary tumours still cannot be sterilized by radiation. Many people therefore felt that what was needed was some means of increasing the effect of irradiation on the tumour without an increase in the reaction of normal tissues.

The first attempt to do this was by using high-pressure oxygen to increase the radiosensitivity of the hypoxic cells. Many series of patients were treated while breathing O_2 at 3 atmospheres. Only recently has a definite advantage been demonstrated.

This technique is so slow and cumbersome that the use of neutrons seemed the obvious next step. This was particularly so as pure O_2 is a vasoconstrictor, opposing the very effect one was trying to produce.

The first neutron treatment at Hammersmith was given in 1966. In 1971 we began a randomised trial to compare neutrons with photons (X or γ rays) in the treatment of advanced cancers in the mouth and throat. The results of this trial were highly favourable to neutrons in that tumours were controlled much more frequently than with photons [3]. There were, however, serious problems in interpretation; the photon patients mostly received their treatments at other hospitals and often received a lower dose, follow-up and further investigations were not equal on the two sides, and the disease was mostly so advanced that many patients quickly succumbed to secondary deposits.

Trials made at other centres have on the whole not supported our conclusions at Hammersmith but many trials are still under way and it is too early to reach a definite verdict. There is some suggestion that the relationship between local control and morbidity may be different for neutrons and that it may be necessary to accept more morbidity to take advantage of the curative potential of fast neutron therapy.

Technical factors.- One reason why neutrons have not fulfilled their promise lies in the serious technical shortcomings of all existing installations. Radiotherapy today is mostly given with highly-penetrating radiation, beams with very narrow penumbra, a mounting which enables the beam to be directed at any angle, and continuously adjustable diaphrams. No existing neutron installation has all these advantages and many have none of them. Our own neutron beam is equivalent to 250 kV X rays and gives a fixed horizontal beam. Until recently we used inserts to provide a few field sizes, although now we have a set of continuously adjustable diaphrams. In addition many cyclotrons, particularly in the USA, are far away from a hospital.

A proper assessment of the place of fast neutrons in radiotherapy must entail use of equipment technically equivalent to a modern megavoltage X-ray generator. With 6 MV X rays the 50% depth dose comes at about 15 cm deep; to achieve this with neutrons, one needs 60 MeV protons on Be and a 5 cm polyethylene filter [4] (Fig.2).

Actually a thin target is a better way of improving beam quality than filtration. A moving beam can be achieved by the method in use now at Edinburgh. Adequate shielding can be provided with pure iron (to minimise induction of radioactivity) and borated polyethylene. Measurements with different detectors have shown that the order in which slabs of iron and polyethylene are placed affects only the neutron component of the transmitted radiation. We see no reason why adjustable collimators should not be effective at these energies.

Fig.3. shows a distribution for 66 MeV p/Be neutrons measured at Fermilab [5]. The beam is nearly equivalent to 6 MV X rays and has quite a sharp penumbra (at the 10% contour at the side the radiation is largely γ rays with a lower RBE).
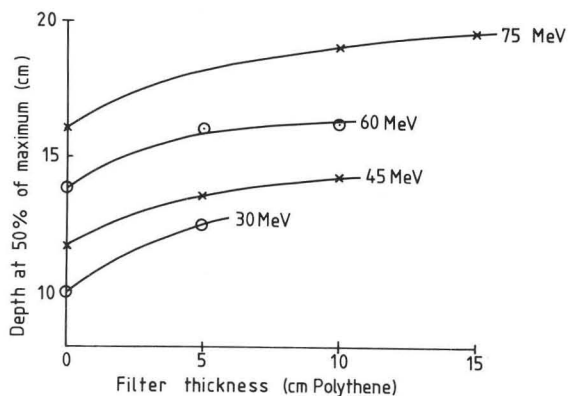
Fig.2. Depth of 50% isodose contour for a 12 x 12 cm field at 125 cm target-skin distance, as a function of proton energy and thickness of filter [4] (by permission of Phys.Med.Biol.)
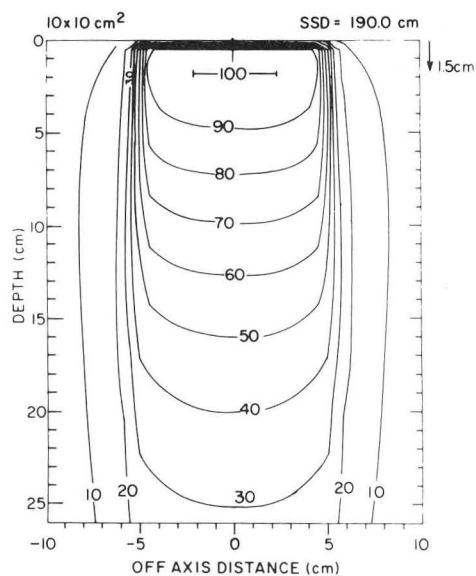

Fig.3. Isodose distribution for 10 x 10 cm field at 190 cm target-skin distance, 66 MeV p on B. By permission of Rosenberg and Awschalom [5].

As a final point in this section, Fig.4. shows a neutrogram taken during treatment. Bones are not visible in neutron radiographs because the principal way by which energy is transferred to tissue is via elastic scattering by hyrogen; the concentration of hydrogen in bone is lower than in soft tissues.

Radiotherapy with protons. –

The straight tracks and finite range of protons make them ideal for irradiation of sharply delineated volumes. An energy of 150 MeV gives a range of 15 cm of water, enough for most sites in the body. The Bragg peak is only a few mm wide so velocity modulation is necessary to irradiate tumours. So far the main use of photon beams has been for treatment of small tumours of the pituitary or behind the eye [6]. Protons have the same radiobiological properties as X rays; their advantage lies in the precision with which a specified volume can be irradiated while sparing surrounding tissues.

Fig.5. sums up the therapeutic properties of various types of radiation [7].
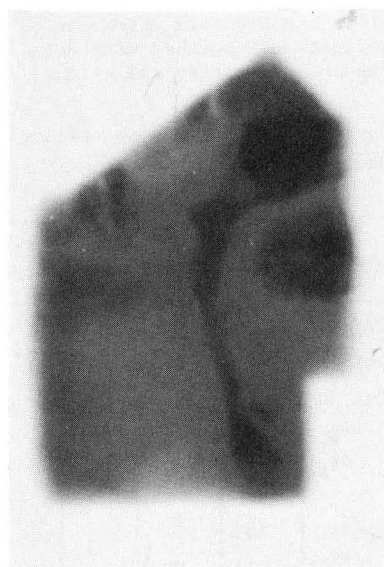

Fig.4. Neutrogram of patient taken during treatment of mouth and throat. Inserts used to obtain non-rectangular field. NE 102A scintillator with Kodak industrial film.
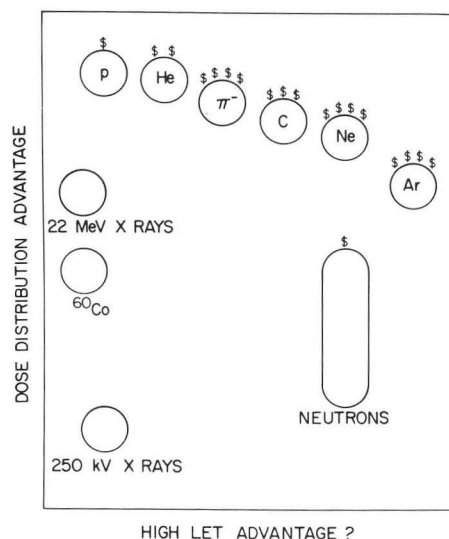

HIGH LET ADVANTAGE ?

Fig.5. Schematic comparison of different types of radiation for radiotherapy. Dollar signs indicate the relative cost. By permission of Raju [7].

CHEMICAL ANALYSIS IN VIVO

Neutron activation analysis is such a sensitive technique that it can be used in vivo without exceeding a safe limit of irradiation. The first experiment was done by Anderson et al [8] who used a d-T generator giving 14 MeV neutrons and measured the induced radioactivity in the body, thereby deriving the total-body content of sodium, chlorine and calcium. Today the elements most frequently studied are Ca and N. In addition certain trace elements which concentrate in particular organs, such as iodine and cadmium, can be estimated in vivo. Some elements are best measured using prompt γ radiation rather than radioactivity. A cyclotron is not the only way of generating the required beam of neutrons; the best source depends on the application.

Table 2 lists the elements which can be estimated by neutron activation, together with details of the nuclear reactions and emitted radiations.

Table 2.
Body elements which can be measured by neutron-induced radioactivity.

Element	Reaction	Abun-dance	Thres-hold MeV	$T_{\frac{1}{2}}$ min	Principal γ rays MeV
C	$^{12}C(n,2n)^{11}C$	99	21	20	0.51
N	$^{14}N(n,2n)^{13}N$	100	11	10	0.51
O	$^{16}O(n,2n)^{15}O$	100	17	2	0.51
O	$^{16}O(n,p)^{16}N$	100	10	0.12	6
Na	$^{23}Na(n,\gamma)^{24}Na$	100	0	900	1.4) 2.7)
P	$^{31}P(n,\alpha)^{28}Al$	100	5	2.2	1.8
Cl	$^{37}Cl(n,\gamma)^{38}Cl$	24	0	37	1.6) 2.2)
(K	^{40}K activity	0.01	–	10^9y	1.46)
Ca	$^{48}Ca(n,\gamma)^{49}Ca$	0.2	0	8.8	3.1
Ca	$^{40}Ca(n,\alpha)^{37}Ar$	97	3	35d	2.6 keV el.
I	$^{127}I(n,\gamma)^{128}I$	100	0	25	0.44) 0.53)

Calcium.-   Calcium is a good indication of the strength of the skeleton.   With advancing age the skeleton gradually becomes demineralised, particularly in women, often leading to fractures and compression of the spinal column.   Various metabolic disorders lead to the same result.   Existing methods of measuring the calcium content of bones are either not accurate enough or measure Ca at only one point which is convenient for the measurement but may not be medically very significant.   CAT scanning measures Ca in a body section and distinguishes between trabecular and cortical bone.   Neutron activation can be used to measure regional or total-body Ca.

The usual method of measurement is by the reaction $^{48}Ca(n,\gamma)^{49}Ca$.   The product has an 8.8 min half-life and emits γ rays of 3.1 MeV which are well separated from most other activity.   The low abundance of ^{48}Ca reduces the sensitivity of the method.   Use of ^{37}Ar is a much more sensitive method but the Ar is released from the body very slowly and at a rate which depends on the fat content of the body as Ar is soluble in fat.   About 40% appears not to be released at all but to be "permanently" retained in the bone lattice [9].

At Hammersmith we measure ^{49}Ca produced by activation with our cyclotron-generated beam.   The patient is irradiated bilaterally.   As activation depends mainly on thermal neutrons, a premoderator of 5.5 cm polyethylene is used to obtain the best degree of uniformity of activation.   The patient stands at 4 m from the target.   Irradiation takes about 30 seconds and the patient is then transferred quickly to the whole-body counter where counting begins 3 minutes after the end of irradiation.

Gamma-ray spectra are obtained before irradiation, immediately after and at $1\frac{1}{2}$ hours   (Fig.6). The contribution of ^{24}Na under the ^{49}Ca peak is estimated from the count at $1\frac{1}{2}$ hours.
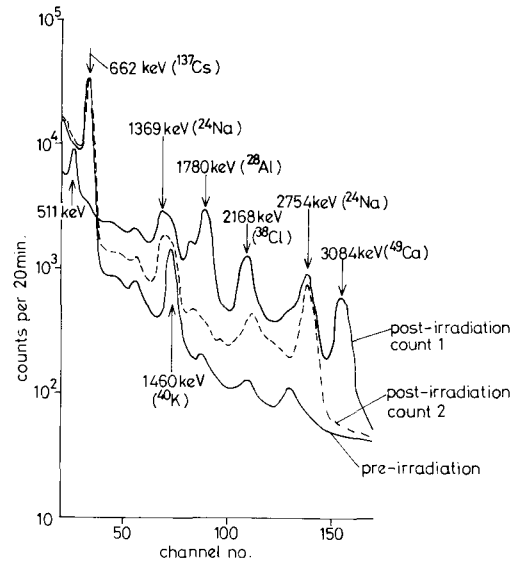

Fig.6. Pulse-height spectra from a patient before irradiation and 3 minutes and $1\frac{1}{2}$ hours after. The peak at 662 keV is from a calibration source.

With a total-body dose of 1 mGy (10 mSv or 1 rem) the precision of the measurement is about 3% and the absolute accuracy 8% ($\pm\sigma$). This dose is considered acceptable for patients above child-bearing age and can be compared with the maximum permissible dose for occupationally-exposed workers of 50 mSv (5 rem) per year and with the dose given in diagnostic radiology, for example about 10 mGy equivalent whole-body dose received in certain abdominal examinations. Fig.7 shows the total-body calcium content of patients with various disorders, estimated by my colleague, T.J. Spinks, who has been able to take into account variations in body shape and composition [10,11].
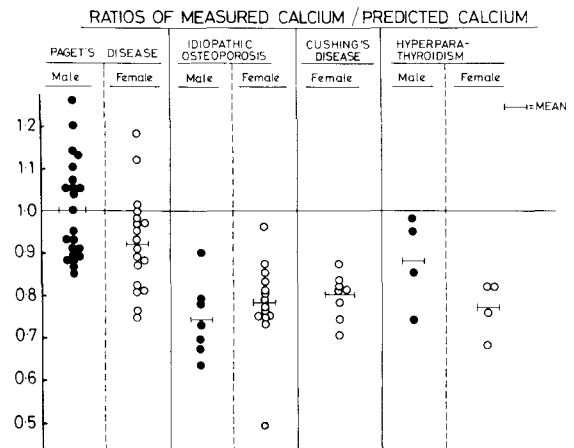

Fig.7. Ratio of measured total-body calcium to predicted value for normals based on height, weight, age and sex [10].

The best neutron spectrum to use is a compromise between getting the most activation per unit absorbed dose, which demands a low-energy beam, and achieving the highest degree of uniformity of activation for which a high energy is needed. A mean energy in the range 1 - 5 MeV is a reasonable compromise so ^{252}Cf and Pu-Be sources are possible alternatives.

Fast neutron reactions - nitrogen.- Nitrogen occurs mostly in protein and indicates the nutritional status of the body. Measurement of total-body N is becoming more popular in the study of severely ill patients, particularly those undergoing major surgery [12]. It is usually measured by the fast neutron reaction $^{14}N(n,2n)^{13}N$.

The radioactive products of C, N and 0 all emit positrons and have half-lives not very different from one another. N can therefore be analysed best by using neutrons in the range 14 - 17 MeV which do not induce ^{15}O or ^{11}C. (Fig.8).
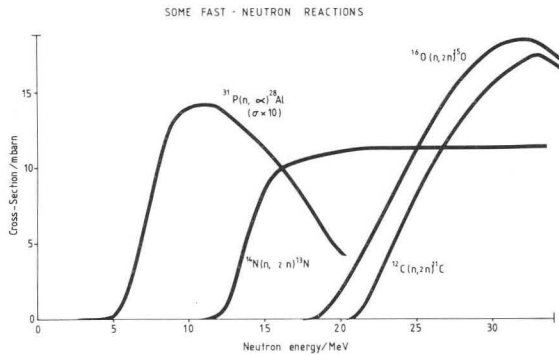

SOME FAST - NEUTRON REACTIONS

Fig.8. Neutron cross sections for activation of C, N, 0 and P.

Thus a d-T neutron generator is indicated for this application. Even then some additional ^{13}N is produced by the reaction $^{16}O(p,\alpha)^{13}N$, the protons being produced by elastic scattering on H. This interference typically amounts to about 20%. Our own cyclotron-produced neutron beam extends to about 18 MeV and produces a significant amount of ^{15}O, while most of the neutrons are below the threshold for the $^{14}N(n,2n)$ ^{13}N reaction and merely irradiate the patient to no purpose.

Prompt γ-ray analysis.- The difficulty of separating positron-emitting radionuclides lead Harvey et al to suggest a new method of analysing N based on prompt γ-ray emission following the reaction $^{14}N(n,\gamma)^{15}N$ [13]. This reaction is induced mainly by thermal neutrons. The process of thermalisation and capture takes a few hundred μs. To take advantage of this, the cyclotron beam was pulsed with 150 μs intervals between 10 μs pulses, the counting being restricted to the inter-pulse periods to reduce background. Fig. 9 shows the arrangement with two large NaI crystals to detect the 10.4 MeV γ rays. An advantage of this system is the low dose needed, 1 mSv (100 mrem).

Prompt γ-ray analysis can be used for many other elements, for example Cd which is a very toxic element concentrated in liver and kidneys. Cd has an exceptionally large cross section for absorpoion of thermal neutrons and emits numerous γ rays, particularly one at 559 keV. A dose of less than 10 mSv to a limited volume of the body is sufficient to measure toxic concentrations of Cd in the liver. A cyclotron is not strictly necessary for this application; ^{252}Cf can be used in a portable apparatus but the ability to pulse the neutron beam from a cyclotron reduces the background and so improves accuracy [14]. Prompt γ rays can in principle be used also to measure other elements such as H, O and Ca. Oxygen can also be measured by the reaction $^{16}O(n,p)^{16}N$ (Table 2) using a pulsed neutron source to take advantage of the 7.1 s half-life of ^{16}N.
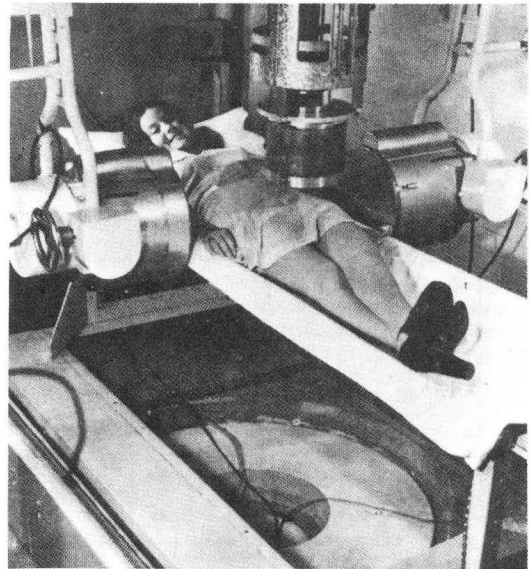

Fig.9. "patient" in position for measurement of N by prompt γ-ray analysis. Neutrons come from below and two large NaI detectors are on either side. By permission of Harvey et al [13].

High-energy protons would be particularly useful for partial-body activation because of their straight paths and sharply-defined range. Eilbert et al have proposed using 160 MeV protons to measure Ca by the reaction $^{40}Ca(p,n2p)^{38}K$ [15]. Use of velocity modulation can give an activation efficiency independent of depth over a certain range. ^{38}K decays with a half-life of 7.7 min giving 2.2 MeV γ rays. The main problem seems to be interference from 0 and Cl.

Metabolic studies. - Following the pioneering work of Comar et al [16] we have used neutron activation to investigate the metabolic activity of Na in the human hand [17]. The left hand is irradiated with fast neutrons whilst the right hand is shielded. Both hands are then counted between two pairs of scintillation counters, the shielded hand providing a continuous background for subtraction from the activity in the irradiated hand. Over a 24 hour period loss of Na follows a power law (Fig.10).
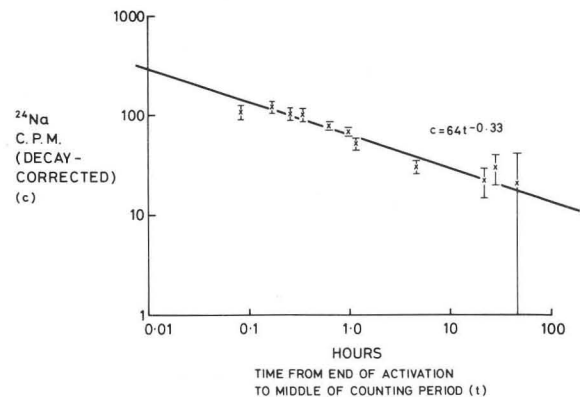

^{24}Na C.P.M. (DECAY-CORRECTED) (c)

$c = 64t^{-0.33}$

HOURS
TIME FROM END OF ACTIVATION
TO MIDDLE OF COUNTING PERIOD (t)

Fig.10. Loss of ^{24}Na from an irradiated hand.

Fig.11 shows statistically significant differences between the rate of turnover of Na in normals and in diseased groups. Over this period of time the observed activity must represent Na in bone.
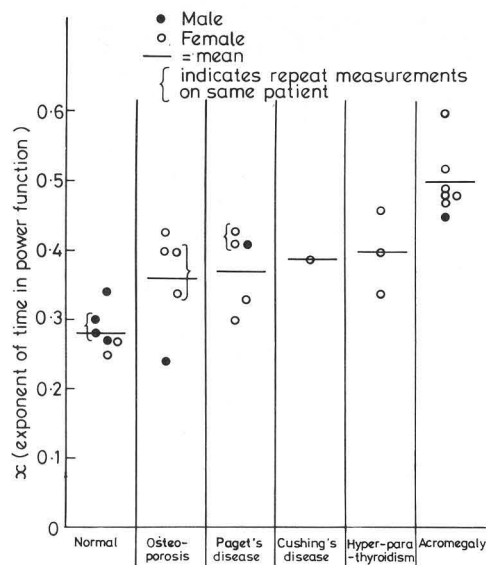
Fig.11. Exponent x in the function $A = BE^{-x}$ describing loss of Na from the hand.

The significance of this measurement is that the Na is labelled in situ regardless of site; because of the very slow turnover of elements in bone it is difficult to ensure uniform labelling with injected radio-nuclides.

IMAGING

Proton radiography.- Another possible medical use of high-energy cyclotrons is proton radiography. The most straightforward way of doing this is with photographic detectors placed at the end of the proton range, to take advantage of the very sharp change of dose and proton fluence with depth [18]. To keep the dose as low as possible intensifying screens must be used and the response is then roughly proportional to dose. Although theoretically there should be a big increase in contrast compared to conventional radiography, the method has not been used in practice. This may be due to two difficulties: multiple scattering of the protons which causes blurring of the order of a few mm, and ambiguity of interpretation when one is not sure if the film is lying on the front or back edge of the Bragg peak.

Both effects can be largely overcome using fine slits and digital techniques with scintillation detectors [19]. But proton radiography should perhaps be compared with the best modern techniques such as CAT scanning. In principle protons could also be used for three-dimensional reconstructions which would give the distribution of tissue density rather than atomic number [20, 21].

Axial tomography with positron emitters.- One of the most exciting applications of cyclotrons lies in the use of radioactive isotopes of the 3 major constituent elements of the human body C, N and O. Except for ^{14}C, the useful radioactive isotopes of these elements have short half-lives and emit positrons. A positive-ion accelerator in the hospital is needed to make use of them. Fortunately the thresholds of the nuclear reactions are low and an accelerator giving protons or deuterons up to 10 MeV is usually adequate.

Positrons are specifically useful for imaging as the annihilation γ rays are emitted in opposite directions. Coincidence counting provides an electronic form of collimation. The ECAT machine at Hammersmith Hospital has 6 rows of detectors arranged in a hexagon operating in coincidence between individual detectors of opposite rows. By taking account of attenuation in the tissues one can measure quantitatively the distribution of radioactivity in a section of the body. The principle is the same as that of the X-ray CAT scanner, but whereas the CAT scanner gives the distribution of density and atomic number, the ECAT shows the distribution of a particular radioactive tracer.

The performance of the machine has been tested with a cylindrical phantom divided into sections each containing a different concentration of positron-emitter. The reconstructed image demonstrates excellent linearity of response.

The medical application of the instrument has been pioneered by my colleague, Mr. T.Jones. He introduced the idea of continuous inhalation of gas containing tracer to give a steady-state image of physiological function. When $^{15}O_2$ is breathed, the radioactive label is attached to oxy-haemoglobin which is transported by the blood stream and is used by the tissues for metabolism.

The ECAT then measures the distribution of oxygen consumption by tissue. Carbon dioxide $C^{15}O_2$ in the lungs immediately dissolves in the blood and the oxygen exchanges with OH ions in water. The concentration of label in the tissues is then proportional to blood flow. By dividing oxygen consumption by oxygen supply (blood flow) one obtains the distribution of oxygen extraction efficiency.

Carbon monoxide labelled with ^{15}O or ^{11}C attaches to red blood cells and shows the distribution of blood volume. $^{13}N_2$ is inert and shows lung volume. All these labelled gases decay by positron emission and are measured with equal efficiency by the ECAT.

Fig.12 shows distributions of oxygen metabolism and blood flow in two sections of the brain of a normal subject.
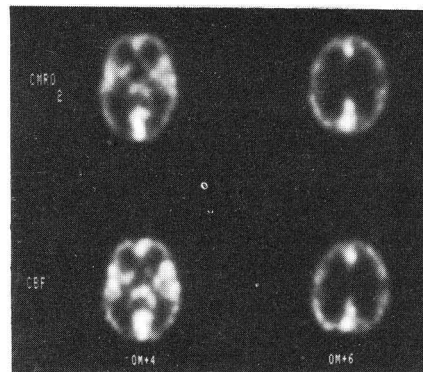

Fig.12. Distribution of oxygen metabolism and blood flow in two sections of the normal brain.

The distinction between grey and white matter is obvious. The information can be quantitated as in Fig.13 which shows the utilisation of oxygen by grey and white matter separately as a function of age. In a similar way we have measured the effect of dementia on oxygen consumption in different regions of the brain. These examples show that at present the best use of the ECAT is in elucidating the physiology and pathology of the human body rather than in diagnosis of individual patients. [25])
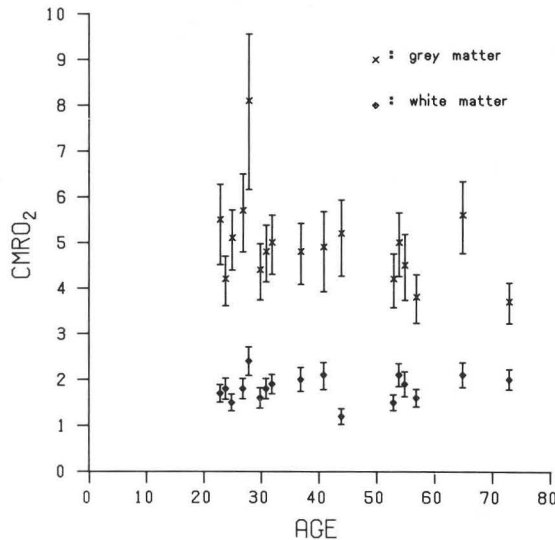

Fig.13. Metabolic rate of oxygen in normals as a function of age.

We have also shown that tumours are usually well perfused with blood but have a low efficiency of oxygen extraction. Oxygen consumption by the tumour is mostly lower than by white matter of brain but not markedly so except in necrotic areas. The hypoxia observed in radiobiological experiments occurs on a microscopic scale and co-exists with a substantial blood supply.

My final example is included to demonstrate the versatility of the technique, Fig.14. The chest is imaged with $^{13}N_2$ (lung volume), $^{15}O_2$ (oxygen metabolism, plus blood and lung volume), $C^{15}O_2$ (blood flow and volume) and $C^{15}O$ (blood volume). By subtraction one obtains images of oxygen metabolism and blood flow in the heart muscle.
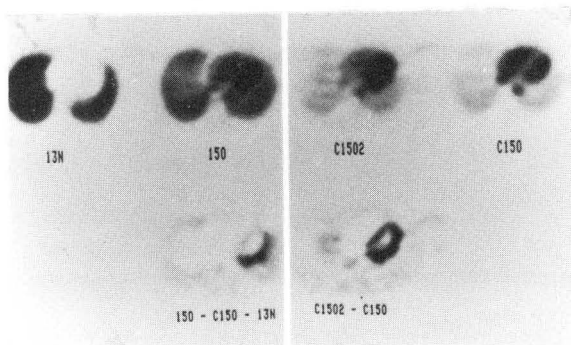

Fig.14. The human chest imaged with ^{13}N, $^{15}O_2$, $C^{15}O_2$ and $C^{15}O$.

The radiation dose received by the patient during these investigations is of the same order as the dose in whole-body activation analysis. The biggest dose is received by the lungs. Four scans of the brain, involving 27 minutes breathing ^{15}O, results in a dose of 2 - 5 rad to the lungs. The long breathing time arises because our machine has only a single plane of detectors. With a modern multi-ring machine several tomographic sections can be recorded simultaneously with a corresponding reduction in radiation dose [22].

In the future one can foresee many developments. Use of more than one ring of detectors has been mentioned already. The methods of imaging can be improved. New detector materials such as bismuth germanate can be used to increase the detection efficiency. Gamma-cameras based on wire counters which give better spatial resolution can be used instead of the arrays of detectors employed in the ECAT [23]. Biochemical molecules present in the body can be labelled with ^{11}C in spite of its short half-life of 20 minutes [24]. At present we have barely scratched the surface of what can be done with cyclotron-produced radionuclides of C, N and O.

I would like to record my debt to the many colleagues who have participated in this work, and particularly to the engineering team, Dr. Mary Catterall, Dr. T.J. Spinks and Mr.T. Jones.

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" DISCUSSION "

M.A. CHAUDHRI : There are various institutions who
are using or suggesting the use of mixed gamma and
neutron beams for therapy. Could you please comment
on such modalities ? What is the state of art regar-
ding the application of hyperthermid in neutron thera-
py ?

D.K. BEWLEY : Mixed schedules (neutrons for some frac-
tions and gamma or X rays for the remainder) are used
extensively in the U.S.A.. This technique was intro-
duced because the cyclotrons used for neutron therapy
in U.S.A. have mostly been far away from the hospital
radiotherapy departments and were usually not avai-
lable for treatments 5 days a week. In addition, there
have been a few radiobiological experiments indicating
that mixed schedules might be more effective than
neutrons alone. However, most radiobiologists are
doubtful about the conclusions to be drawn from these
experiments. The benefit to be derived from neutrons
is not likely to be great enough that it would still
be significant if neutrons were added for only part of
the treatment. Personally, I would recommend against
mixed schedules provided the cyclotron is close to the
hospital and provided it gives a technically satisfac-
tory beam.

Hyperthermia is a method of treating cancer which is
at present coming into vogue and is the subject of con-
siderable research. It could be used either in combi-
nation with radiotherapy or as a supplementary treat-
ment. Whether the radiotherapy is given with X rays,
γ rays or neutrons, does not affect the use of hyper-
thermia.

G. SCHATZ : Could you comment on the use of drugs which
counteract the oxygen enhancement ratio ?

D.K. BEWLEY : At present, there are many trials in
progress of the use of misonidazde , a hypoxic-cell
sensitizer. Unfortunately, the neurotoxicity of this
drug limits the concentration which can be used, so
that the OER is reduced only by a factor of 1.1.
Fast neutrons cause a reduction by a factor 1.6.
However, many new hypoxic-cell sensitizers are being
investigated. If the problem of toxicity can be over-
come, the best treatment of many tumours would be a
combination of proton therapy with a hypoxic-cell
sensitizer.

P. MANDRILLON : Could you comment on the optimal cha-
racteristics of a neutrontherapy dedicated cyclotron :
energy of protons, extracted beam intensity, target
choice ?

D.K. BEWLEY : X rays generated at 6-8 MeV are close to
the optimum for conventional radiotherapy. To match
this with neutrons, one needs protons of about 60 MeV.
A thin target of Be backed by C gives the highest
mean neutron energy at an acceptable dose rate. One
should aim at 40 rad/min at 150 cm from the target.
With a thin target and a wedge filter, a beam current
up to 30 μA may be needed.