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APPLICATIONS OF RECENT ADVANCES IN NUCLEAR PHYSICS TO MEDICINE

With Special Reference to the Pile and the Cyclotron as sources of Radioactive Isotopes

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Introduction

It is becoming increasingly evident that the recent developments in nuclear physics will exert a far-reaching influence on medical research and practice. Quite apart from the new ideas involved, the physical and technical advances which led to the atomic bomb provide a new and extremely powerful method of preparation of large amounts of many radioactive isotopes. These should become widely used in medicine as:—

1. Radioactive tracers for the study of normal and pathological metabolic processes and in investigations in pharmacology and therapeutics.
2. Radioactive sources in radiotherapy.
3. Agents with therapeutic possibilities depending on the selective concentration of the radioactivity of suitable isotopes in particular cells and tissues.

This report summarises the present position with regard to the preparation of radioactive isotopes of interest in medicine by means of the new machine usually called the "pile" (Smyth, 1945), and in addition attempts to assess the relative values of the pile and the cyclotron from the point of view of the medical applications.

This account is based on two official reports by J. V. Dunworth and J. S. Mitchell, entitled, "Application of Nuclear Physics to Medicine and Biology" (March 26, 1945) and "Notes on the Preparation of Radioactive Isotopes for Use in Medicine and Biology" (October 17, 1945).

Summary of Requirements and Availability of Radioactive Isotopes

1. *Tracers*

Probably the most important scientific value of the pile will be to provide effectively unlimited amounts of many useful radioactive isotopes which should have far-reaching application as tracers, and lead to unprecedented developments in the chemical aspects of all branches of medical and biological research. Although only small quantities of most of the isotopes are required for individual experiments, and only very low concentrations are usually desirable, *e.g.*, of the order of 10^{-9} to 10^{-10} for P^{32}/P^{31}, total amounts of the order of curies* are likely to be required for use in tracer experiments in the country as a whole. It is obviously advantageous for these isotopes to have reasonably long half-lives, and a selection of those isotopes made in the pile which appear to be of interest in medical investigations as radioactive tracers is given in Table I. The pile can produce the majority of the radio-

* A curie of any radioactive isotope is defined in this connection as a source which decays so that $3{\cdot}7 \times 10^{10}$ atoms change per second.

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TABLE I

ISOTOPES FOR USE AS RADIOACTIVE TRACERS PRODUCED BY MEANS OF THE PILE

Isotopes	Reaction	Type of radiation	Half life	Energy of radiation in MeV	
				β particles	γ rays
H^3	H^2+n‖	$\beta-$	~30 years	0·013	—
H^3	Li^6+n	$\beta-$	~30 years	0·013	—
C^{14}	$N^{14}+n \rightarrow C^{14}+p$	$\beta-$	~20,000 years	0·145	—
Na^{24}	$Na^{23}+n$	$\beta-$, γ	14·8 hours	1·4	2·8†
P^{32}	$P^{31}+n$	$\beta-$	14·3 days	1·71	—
S^{35}	$S^{34}+n$	$\beta-$	87 days	0·107	—
Cl^{36}	$Cl^{35}+n$	$\beta+$, $\beta-$, K	~10^6 years‡	—	—
Ca^{45}	$Ca^{44}+n$	$\beta-$, γ	180 days	0·9 0·2	0·7
Sc^{46}	$Sc^{45}+n$	$\beta-$, γ, K	85 days	0·26 1·50	1·25
Cr^{51}	$Cr^{50}+n$	K, e^-, γ	26·5 days	—	0·51
Ti^{51}	$Ti^{50}+n$	$\beta-$, γ	72 days	0·36	1·0
Fe^{59}	$Fe^{58}+n$	$\beta-$, γ	47 days	0·26 0·46	1·30 1·10
Co^{60}	$Co^{59}+n$	$\beta-$, γ	5·3 years	0·31	1·30 1·10
Cu^{64}	$Cu^{63}+n$	$\beta-$, $\beta+$, K	12·8 hours	$\beta-$0·58 $\beta+$0·66	—
Zn^{65}	$Zn^{64}+n$	K, $\beta+$, γ, e^-	250 days	$\beta+$0·4	0·45 0·65 1·00
As^{76}	$As^{75}+n$	$\beta-$, $\beta+$, K, γ	26·8 hours	>1	>1
Br^{82}	$Br^{81}+n$	$\beta-$, γ	34 hours	0·465	0·547 0·787 1·350
Rb^{86}	$Rb^{85}+n$	$\beta-$	19·5 days	1·60	—
Sr^{89}	$Sr^{88}+n$ $U^{235}+n$	$\beta-$	55 days	1·5	—
Zr^{95}§ Cb^{*95}	$U^{235}+n$ $Zr^{95} \rightarrow Cb^{*95}+\beta-$	$\beta-$, γ	65 days	0·4	0·75
Mo^{99}	$Mo^{98}+n$	$\beta-$, γ	67 hours	1·5	0·4
$Ag^{108,\ 110}$	$Ag^{107,\ 109}+n$	K, e^-, γ	225 days	—	0·650 0·925 1·51
Sb^{124}	$Sb^{123}+n$	$\beta-$, γ	60 days	2·45 0·74	1·82
I^{131}	$U^{235}+n$	$\beta-$, γ	8·0 days	0·6	0·4
Cs^{134}	$Cs^{133}+n$	$\beta-$, γ	1·7 years	0·9	—
Cs^{137}	$U^{235}+n$	$\beta-$	~33 years	?	?
Ba^{140}	$U^{235}+n$	$\beta-$	12·7 days	1·2	—
La^{140}	$Ba^{140} \rightarrow La^{140}+\beta-$	$\beta-$	40 hours	1·41	2·04
Ta^{182}	$Ta^{181}+n$	$\beta-$, γ	97 days	1·0	<1·6
W^{185}	$W^{184}+n$	$\beta-$, γ	77 days	? 0·65	—
Au^{198}	$Au^{197}+n$	$\beta-$, γ	2·7 days	0·8	2·5 0·44 0·28
$Hg^{203,\ 205}$	$Hg^{202,\ 204}+n$	$\beta-$, γ	51·5 days	0·46	0·30
Tl^{206}	$Tl^{205}+n$	$\beta-$	3·5 years	0·87	—
Bi^{210} (RaE)	$Bi^{209}+n$	$\beta-$	5·0 days	1·17	—

‖ The growth of H^3 in a heavy water pile is a natural by-product.

† A proportion of this γ radiation consists of two softer γ rays in cascade.

‡ The data for Cl^{36} are very vague except for a definite neutron absorption cross-section believed to be due to the reaction stated.

§ Cb^{*95} is a metastable state of half-life 33 days of the stable isotope Cb^{95}. It comes into transient equilibrium with Zr^{95}.

NOTE: Fast Neutron Irradiation within Reacting Core of Pile.

The following isotopes are amongst those that can be produced in all probability in small amounts:—
C^{11}, Fe^{55}, Fe^{59}, As^{74}, Y^{88}.

$\beta-$ = negative beta-particles
$\beta+$ = positive beta-particles (positrons)
γ = gamma rays
α = alpha-particles
K = K-electron capture
e^- = internal conversion electrons

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active isotopes of interest in tracer investigations in medicine, in most instances in far larger amounts than required.

In many applications, too high concentrations must not be used, and already in the case of P^{32}, significant disturbances of the cellular metabolism by the radiation from the tracer introduced have proved very interesting in the study of the mechanism of the biological action of radiations.

Of especial interest for isotopic tracer research is C^{14}. Satisfactory amounts should be prepared from compounds such as ammonium nitrate and urea by means of the n–p† reaction in N^{14}. It now appears (Yankwich, Rollefson, and Norris, 1946) that the C^{14} will be produced in the form of very simple compounds such as CO_2, CO, HCN, CH_3OH and H·COOH on account of the large energy release in the reaction (Q = 0·62 MeV). It will be necessary to develop special techniques of chemical and biological synthesis of compounds of biochemical interest starting from $C^{14}O_2$ and probably also nitriles, formic acid, and methyl alcohol. Moreover, special methods of measurement will have to be developed, *e.g.*, it may be necessary to convert to $C^{14}O_2$, which is introduced into a Geiger counter or may be fixed as barium carbonate, which is spread in a thin layer for measurement by a counter with an extremely thin window, *e.g.*, 3 mg. per sq. cm.

2. *Sources for Use in Radiotherapy*

One of the most important practical applications of the new developments will probably be to provide artificial γ-ray sources for use in radiotherapy as a substitute for radium and radon.

A list of isotopes made in the pile and suitable for use as radioactive sources in radiotherapy is given in Table II. The isotopes are listed in descending order of probable suitability as substitutes for radium.

TABLE II

RADIOACTIVE ISOTOPES FOR USE IN RADIOTHERAPY PRODUCED BY MEANS OF THE PILE

(The isotopes are listed in descending order of probable suitability as substitutes for radium)

Isotopes	Reaction	Type of Radiation	Half life	Energy of radiation in MeV.		No. of rays per disintegration
				β particles	γ rays	
1. Co^{60}	$Co^{59}+n$	$\beta-$, γ	5·3 years	0·31	1·30 1·10	2
2. (*a*) Ta^{182}	$Ta^{181}+n$	$\beta-$, γ	97 days	1·0	< 1·6	< 1
(*b*) Sc^{46}‡	$Sc^{45}+n$	$\beta-$, γ, K	85 days	0·26 1·50	1·25	< 1
(*c*) Sb^{124}	$Sb^{123}+n$	$\beta-$, γ	60 days	2·45 0·74	1·82	< 1
3. (*a*) Ba^{140}	$U^{235}+n\rightarrow$	$\beta-$	12·7 days	1·2	—	—
La^{140}	$Ba^{140}\rightarrow La^{140}+\beta-$	$\beta-$, γ	40 hours	1·41	2·04	~1
(*b*) Zr^{95} Cb^{*95}†	$U^{235}+n\rightarrow$ $Zr^{95}\rightarrow Cb^{*95}+\beta-$	$\beta-$, γ	65 days	0·4	0·75	~1

‡ It is doubtful whether adequate supplies of Scandium could be obtained.

† Cb^{*95} is a metastable state of half-life 33 days of the stable isotope Cb^{95}. It comes into transient equilibrium with Zr^{95}.

It will be seen that the most promising substitute for radium is now considered to be radio-cobalt, Co^{60}, of half-life 5·3 years. The second choice includes tantalum, Ta^{182} of half-life 97 days, together with scandium, Sc^{46}, and antimony, Sb^{124}. Scandium is, unfortunately, a rare and expensive element.

The fission product La^{140}, to be used in transient equilibrium with its parent body Ba^{140} of half-life 12·7 days, was suggested in the first memorandum of March 1945 as a possible substitute for radium and radon. Later, another fission product, zirconium, Zr^{95}, with a longer half-life of 65 days, together with its daughter product, metastable columbium,

† A nuclear reaction whereby by bombardment with neutrons one nucleus is transformed into another and the transformation is accompanied by the emission of a proton is conveniently summarised as an n–p reaction. The reaction referred to here, for instance, is:— $N^{14} + n \rightarrow C^{14} + p$.

A reaction in which the bombardment is done with deuterons and protons are released may similarly be summarised as a d–p reaction.

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Cb^{*95}, of half-life 33 days, was thought to be more suitable. The possibility of using unseparated fission products should be considered. However, in view of the undesirability of the necessary chemical separation processes which would be involved in the preparation for use of separated fission products, we have considered in detail the production of artificial radioactive isotopes by irradiation in the pile. Fortunately, it now appears possible to prepare suitable sources with reasonably long lifetimes in adequate amounts by means of irradiation in the pile.

It is to be noted that the γ radiation from Co^{60} is eminently suitable for use in radiotherapy, being approximately monochromatic and of slightly higher mean energy (1·2 MeV) than the mean energy of the usual filtered γ radiation from radium, which has the approximate value of 0·8 MeV. There are two γ-ray photons of energy, 1·10 and 1·30 MeV per disintegration of Co^{60}; moreover, the accompanying β radiation from Co^{60} of energy 0·31 MeV is relatively soft and easily removed by filtration.†

There is no doubt as to the practicability of the manufacture of the necessary quantities of Co^{60} by means of the pile. The Canadian pile could easily produce several hundred curies of radiocobalt every six months and a specific activity of the order of one curie per gm. should be obtained.

It now appears to be an eminently practical possibility for Canada to supply all the requirements of radioactive sources for radiotherapy for the British Commonwealth.

Of considerable interest, although of less importance in radiotherapy than the production of artificial γ-ray sources, is the possibility of development of β-ray applicators by utilising β-emitting isotopes such as P^{32} and Sr^{89}, perhaps incorporated in plastics.

3. *Therapeutic application of selectively absorbed radioactive isotopes*

It appears probable that a few isotopes, of which the most important are listed in Table III, will find a limited application in medicine as therapeutic agents on the basis of selective concentration of the radioactivity in particular cells and tissues. The total quantities of such isotopes required are likely to be of the order of a few curies only at any one time. Much further investigation of these selectively absorbed isotopes is necessary before their therapeutic value can be properly assessed.

TABLE III

PRODUCTION BY MEANS OF THE PILE OF ISOTOPES WITH POSSIBILITIES OF THERAPEUTIC APPLICATION BY MEANS OF SELECTIVE ABSORPTION

Isotopes	Reaction	Type of Radiation	Half life	Energy of Radiation in MeV	
				β particles	γ rays
P^{32}	$P^{31}+n$	$\beta-$	14·3 days	1·71*	—
Ca^{45}	$Ca^{44}+n$	$\beta-$, γ	180 days	0·2 0·9	0·7
Sr^{89}	$Sr^{88}+n$ } $U^{235}+n$ }	$\beta-$	55 days	1·5	—
I^{131}	$U^{235}+n$	$\beta-$, γ	8·0 days	0·6	0·4 CE†

* Mean energy of β particles approximately 0·70 MeV.

† CE—Chemical extraction is possible leading to a high concentration.

Promising results have been reported by the use of P^{32} in the treatment of chronic myeloid and lymphatic leukæmias, lymphosarcoma and polycythæmia (*e.g.*, Low-Beer, Lawrence and Stone, 1942; Kenney, 1942; Lindgren, 1944; Reinhard *et al.*, 1946). It is essential to correlate the dose of radioactive isotope with the röntgen, *e.g.*, in the case of P^{32}, one microcurie per gm. of tissue delivers 43 r per day, and one gm. r corresponds to 1·13 microcuries destroyed per kilogram of tissue.

Probably the greatest therapeutic application of selectively absorbed radioactive isotopes will be in the case of P^{32} and I^{131}.

† "The five-year isomer (Co^{60}) decays by the emission of negatrons of maximum energy 0·308 ± 0·008 MeV, followed by two γ rays in cascade, of energies 1·10 ± 0·03 MeV and 1·30 ± 0·03 MeV respectively" (Deutsch, Elliott, and Roberts, 1945).

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With the exception of these two isotopes, the materials which will become available are new to medicine. It is evident that before there can be any question of clinical trials of new agents with therapeutic possibilities, there must be extensive physical, chemical, and biological investigations.

TABLE IV

PRODUCTION OF SELECTED ISOTOPES BY MEANS OF THE CYCLOTRON

Radio-element	Type of radiation	Half life	Energy of radiation in MeV		Approximate yield* in microcuries per micro-ampere hour	Produced by §
			β particles	γ rays		
H^3	β−	~30 years	0·013	—	0·1	Be−d−H^3
C^{11}†	β+	20·5 min.	0·95	—	500	B−d−n
C^{14}	β−	~20,000 years‡	0·145	—	0·00005	N−n−p
N^{13}†	β+, γ	9·93 min.	1·20, 0·92	0·28	1000	C−d−n
Na^{22}	β+, γ	3·0 years	0·58	1·3	1	Mg−d−α
Na^{24}	β−, γ	14·8 hours	1·4	2·8‡	10	Na−d−p
P^{32}	β−	14·3 days	1·71	No γ	200	P−d−p
S^{35}	β−	87 days	0·107	—	0·1	S−d−p
Ca^{45}	β−, γ	180 days	0·2, 0·9	0·7	0·01	Ca−d−p
Mn^{54}	K, γ	310 days	—	0·85	1	Fe−d−α
Fe^{55}	K, e−	~4 years	—	0·08	—	Fe−d−p
Fe^{59}	β−, γ	47 days	0·26, 0·46	1·10, 1·30	0·03	Fe−d−p
Cu^{64}	β−, β+, K	12·8 hours	β− 0·58 β+ 0·66	No γ	3000	Cu−d−p
Zn^{65}	β+, K, γ, e−	250 days	β+ 0·4	0·45, 0·65, 1·0	0·5	Cu−d−2n
As^{74}	β−, β+, γ	16 days	β− 1·3 β+ 0·9	0·582	2	Ge−d−n
As^{76}	β−, β+, K, γ	26·8 hours	> 1	> 1	10	As−n−γ (Be−d−n)
Br^{82}	β−, γ	34 hours	0·465	0·547 0·787 1·350	10	Br−n−γ (Be−d−n)
Rb^{86}	β−, γ	19·5 days	1·60	—	10	Rb−d−p
Sr^{89}	β−	55 days	1·5	No γ	7	Sr−d−p
I^{131}	β−, γ	8·0 days	0·6	0·4	20	Te−d−n
85^{211}	K, α	7·5 hours	5·94 (α)	—	1	Bi− α−2n (32 MeV α's)

* The yields with the cyclotron are taken from the table given by J. G. Hamilton (*Radiology*, 1942, xxxix, 570), and are included to enable comparison with production by means of the pile.

† Data for production in the pile are not available.

‡ See Table I.

§ This column specifies in order, the nucleus bombarded, the particle used for bombardment and the particle emitted.

PRODUCTION OF RADIOACTIVE ISOTOPES BY MEANS OF THE CYCLOTRON

Small quantities of radioactive isotopes can readily be prepared by deuteron, proton or α-particle bombardment of suitable materials. In many cases, fast neutrons are liberated in the bombardment and may be used for the preparation of further radioactive isotopes by allowing them to fall on the appropriate material.

A selection of isotopes made with the cyclotron is given in Table IV (*cf.* J. G. Hamilton, *Radiology*, 1942, xxxix, 570), which demonstrates that, in general, the yields with the cyclotron are very much less than those with the pile.

In most cases it is possible, using a cyclotron, to arrange that the product element is different from the bombarded element. Hence chemical separation is possible, thereby resulting in preparation of the radioactive element in a state of high concentration. Even in the case of d–p reactions, where no change of element is involved, the resulting activity may be in a fairly high state of concentration due to the intense bombardment that is possible.

The cyclotron is, therefore, very suitable for the preparation of small quantities of radioactive isotopes in a state of high concentration.

It is considered that the cyclotron is an essential supplement to the pile in order to produce:—

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(*a*) Alternative isotopes of a given element and some important isotopes which cannot be made in the pile because no slow or moderately fast neutron reaction is possible or practicable. For example, the valuable isotopes Na^{22} (half-life 3·0 years) and Fe^{55} (half-life approximately 4 years) are conveniently made by the cyclotron and impossible or difficult to produce in the pile, while Na^{24} (half-life 14·8 hours) and Fe^{59} (half-life 47 days) are easily prepared in the pile and also, in smaller amounts by the cyclotron. Further, Mn^{54} (half-life 310 days) and 85^{211} can only be produced by the cyclotron.

(*b*) Higher concentrations of activity in certain instances, *e.g.*, Zn^{65} (half-life 250 days), As^{74} (half-life 16 days), where preparation in the cyclotron involves a change in element from that bombarded and hence chemical separation is possible.

(*c*) Short-lived isotopes of interest, which are difficult or impossible to prepare in the pile, *e.g.*, C^{11} (half-life 20·5 mins.), N^{13} (half-life 9·93 mins.), F^{18} (half-life 112 mins.).

Further, the cyclotron can be used to prepare small amounts of *any isotope* which may be required and for which it may not be convenient or practicable to use the facilities of the pile.

PRODUCTION OF RADIOACTIVE ISOTOPES IN THE PILE

The pile is without a rival for producing isotopes in the very large number of cases when a simple slow neutron capture process is available.

$$e.g., \ P^{31} + n \rightarrow P^{32}$$

Since no change in chemical element occurs, concentration of the resulting radioactive material with respect to the parent material is not possible by chemical means, but in some cases it may be possible by the Szilard-Chalmers technique.

The question of the concentration of the induced radioactivity is important. In a pile, there is a considerable escape of slow neutrons from the surface and the placing of absorbing material outside the reacting core in order to catch these neutrons has little effect on the pile. Consequently, large amounts of material can be irradiated so as to produce a moderate concentration of activity. In the centre of a pile, the neutron fluxes are much higher and greater concentrations of active material result if elements are placed there for irradiation. Such materials will, unfortunately, have a marked effect on the pile, and, therefore, only small amounts can be irradiated in this way. There is, therefore, the choice of production of either:—

(1) Large amounts of active material of moderate concentration;

or (2) small amounts of active material of high concentration.

Examples of specific activities obtainable are P^{32} one-third curie per gm. for the n-γ reaction and S^{35} 10 millicuries per gm. for the n-γ reaction.*

In addition to the slow neutron capture process, there is one slow neutron (n, p) reaction of especial importance:— $N^{14} + n \rightarrow C^{14} + p$. It is of interest that this process is probably responsible for 50–80 per cent. of the biological effects of thermal neutrons.

In the centre of the pile there are many higher energy neutrons and it is possible to prepare sources by (n, 2n), (n, p) or (n, α) reactions. The yields are invariably small by comparison with most slow neutron reactions, *e.g.*:—

$$S^{32} + n \rightarrow P^{32} + p$$
$$Co^{59} + n \rightarrow Fe^{59} + p$$
$$As^{75} + n \rightarrow As^{74} + 2n$$

In addition to the preparation of materials by direct irradiation, a certain number of radioactive isotopes are found as fission products in the uranium rods in a pile. Their production is a natural consequence of pile operation and their use, if suitable, is solely one of the convenience, and safety, of chemical extraction. The most interesting fission products are probably, barium and lanthanum (Ba^{140} + La^{140}) and Zirconium and Columbium (Zr^{95} + Cb^{95}) which may possibly find application as γ-ray sources in radiotherapy, and iodine (I^{131}) which appears to have possibilities of therapeutic application by means of selective absorption.

INADEQUACY OF THE PILE AS A SOURCE OF FAST NEUTRONS FOR RADIOTHERAPY

The pile cannot compete with the cyclotron as a source of fast neutrons for practical radiotherapy. It is doubtful whether it could even be used for clinical trials of fast neutron therapy in selected patients. However, it should prove valuable as a

* I am indebted to Dr. J. D. Cockroft for these values of specific activity.

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source of both fast and thermal neutrons* for the experimental work in radiobiology involving the irradiation of laboratory animals, tissue cultures, dilute aqueous solutions of biochemical reagents, etc., which must precede any clinical trials.

The essential difficulty is that the neutron energies are not sufficiently high for the treatment of deeply situated malignancies. The mean energy of the fast neutrons from the pile is approximately 1–2 MeV depending on the conditions of use, and only an insignificant proportion have energies exceeding 4 MeV. It is estimated that the depth dose at 10 cm. (in tissue) for the fast neutrons from the pile is only approximately 20 per cent.

For comparison, it may be mentioned that in their clinical trials of the use of fast neutrons in the treatment of advanced cancer, Stone and Larkin (1942) used D–Be† neutrons of maximum energy 21 MeV, produced by a 60-inch cyclotron. The intensity of their beam was approximately 30 r equivalents per minute at the surface of the patient with focal-skin distance 100 cm., but the 10 cm. depth dose for a field 10 × 10 cm. was approximately 42 per cent. of the surface exposure.

The energy of the pile neutrons cannot be easily controlled and there is inadequate intensity of fast neutrons to use satisfactory filtering devices. Other difficulties of the pile from the point of view of routine radiotherapy which are probably not insuperable include:—

1. Difficulty of collimation of the beam and of production of beams of fast neutrons with really sharply defined edges (comparable with the case of 200 kV X radiation).
2. Difficulty of reduction of the background intensity of γ radiation and fast neutrons, which give undesirable total body irradiation, to less than $\frac{1}{4}$ per cent. of the intensity of the direct beam.
3. The fact that the beam and applicator are fixed, which introduces an important practical difficulty in the accurate positioning of a patient for radiotherapy.
4. The practical difficulties associated with the treatment of elderly, often ill, patients at the isolated location of the pile.

It must be pointed out that a number of beams of fast neutrons, probably up to ten, could be used simultaneously.

SUMMARY

1. The pile will produce the majority of the radioactive isotopes of interest for tracer investigations in medicine and biology, in most instances in far larger amounts than required (*see* Table I).

2. The pile is essential for the production of large quantities of γ-ray sources of reasonably long life, as substitutes for radium for use in radiotherapy (*see* Table II).

3. The best substitute for radium made in the pile appears to be radio-cobalt, Co^{60}, of half-life 5·3 years. The second choice is radio-tantalum, Ta^{182}, of half-life 97 days.

4. In general, for the preparation of isotopes, the yields with the cyclotron are very much smaller than those with the pile (*see* Table IV). However, the cyclotron is an essential supplement to the pile in order to produce:—

(*a*) Alternative isotopes of a given element and the few important isotopes which cannot be made in the pile because no slow or moderately fast neutron reaction is possible or practicable.

(*b*) Higher concentrations of activity in certain instances where preparation in the cyclotron involves a change of element from the bombarded material.

(*c*) Short-lived isotopes.

5. The pile is not a satisfactory source of fast neutrons for practical radiotherapy.

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* It is useful to remember that a dose approximately equivalent in biological effects to 0·1 r of the usual filtered γ radiation from radium, of mean energy 0·8 MeV, is delivered in 8 hours by the following fluxes:—

100 neutrons per cm.^{2} per sec. for neutrons of energies 1–20 MeV.

12,500 neutrons per cm.^{2} per sec. for thermal neutrons.

4200 photons per cm.^{2} per sec. for γ radiation of energy 2 MeV.

80 β particles per cm.^{2} per sec. for β particles of energy 2 MeV.

It must be emphasised that these values are only approximate: the uncertainty is greatest in the case of thermal neutrons.

† *i.e.*, Neutrons obtained by bombarding Beryllium with deuterons.

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