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PRACTICAL ASPECTS OF RADIOACTIVE ISOTOPES IN RELATION TO MEDICAL TREATMENT*

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At the present time the use of artificial radioactive isotopes seems to be of considerable value in a few very limited fields of practical medical treatment. These applications are recent and still very incompletely understood, so that a conservative approach is essential.

Radio-phosphorus was first used clinically in 1936 by J. H. Lawrence and his colleagues at Berkeley, California. Its use was recommended in the treatment of chronic myeloid and chronic lymphatic leukaemia and polycythaemia vera by Lawrence, Scott, and Tuttle (1939) and Lawrence (1940). With accumulating experience, mainly during the last five years, it appears that the only disease in which radio-phosphorus therapy has given consistently better results than x-ray therapy is polycythaemia vera, and it is widely considered to be the treatment of choice in this not very common disease.

The use of radio-iodine in the treatment of thyrotoxicosis was described in 1942 by Hertz and Roberts, and by Hamilton and Lawrence. In the same year the first successful attempt to demonstrate selective concentration of radio-iodine in cancer of the thyroid was reported by Keston, Ball, Frantz, and Palmer (1942).

Many clinical trials of the use of radio-iodine in the treatment of thyrotoxicosis have been carried out, mainly in the U.S.A., and it is evident that selected cases respond very satisfactorily. In this country it has been thought wise to proceed rather cautiously, mainly because of concern over the possibility of the development of malignant changes, perhaps many years after the administration of the radio-iodine. While it is recognized that this risk is small and subsequently may be shown to be negligible, it is considered that at present more evidence is required, and that there is no justification for abandoning lines of treatment of proved value in favour of radio-iodine therapy. It is recommended as a general principle that in the treatment of thyrotoxicosis radio-iodine should not be given to patients of either sex under the age of 45 unless other methods of treatment have failed or are contraindicated. It is likely that with accumulating experience the use of radio-iodine will increase in the treatment of selected cases of thyrotoxicosis in which the thyroid gland shows a moderate degree of diffuse enlargement without clinically detectable nodularity or tracheal compression.

Radio-iodine is of value in only a small proportion of cases of carcinoma of the thyroid, probably in the region

of 10%. Nevertheless, it is wise at the present time to test most cases of carcinoma of the thyroid for radio-iodine uptake, while emphasizing that surgery is the most important line of treatment and that x-ray therapy is still very useful.

A practical development which is becoming important is the use of artificial gamma-ray-emitting isotopes as substitutes for radium. Radio-cobalt appears to be satisfactory for interstitial and intracavity application and for use on external applicators and "moulds"; its value has yet to be proved as a practical source in large teletherapy units. Meanwhile, radio-iridium seems to be of value in routine use as a gamma-ray source in a teletherapy unit.

Surface applicators utilizing the beta-rays of radio-phosphorus are entering the field of practical radiotherapy and appear to be useful in the treatment of selected cases of cavernous naevus in infants and children.

General Principles

The use of radioactive isotopes in treatment is essentially a form of radiotherapy, and in general requires the experience of a radiotherapist and the collaboration of a hospital physicist who is trained in radiotherapeutic dosimetry and also has gained experience of the techniques of handling and measuring radioactive isotopes. The clinical problems are among the most difficult in medicine, and include those met with in the uses of external radiation; further, it is essential to try to estimate from the amount of the radioactive isotope administered the dose of radiation, specified in roentgen units or rep (roentgen equivalent physical), received by both the abnormal cells and the normal ones, especially the radio-sensitive cells of the bone marrow and reproductive organs and the less radio-sensitive cells of the kidney, which may be exposed during excretion. At the present stage, dosimetry is largely empirical, and correlation with the roentgen unit is an incompletely solved problem, though nevertheless the only available logical guide.

The risks of internal administration of any radioactive substance must be considered carefully for each isotope and especially for each patient, and may be far from negligible. Probably the most important unsolved question in radio-isotope therapy is whether there is any real risk of late carcinogenesis. One can be reasonably certain that with the present uses of radioactive isotopes

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the risk is small. Nevertheless, until it can be shown that the risk of carcinogenesis is negligible—for example, is in the region of 0.1% after 25 years—it is not in general justifiable to use radioactive isotopes in patients under 45 with non-malignant conditions, or in patients with cancer or allied diseases in whom the expectation of life exceeds five years. It is essential to assess quantitatively the risk of late carcinogenesis for comparison with the risks associated with other forms of treatment, including surgery.

The protection of staff and other patients is an important routine problem which can be solved by careful planning and organization, with constant supervision and forethought and frequent quantitative measurement and monitoring of the various radiation hazards.

The radioactive isotopes of interest in treatment are surveyed in Table I, in which an attempt is made to

TABLE I.—*Therapeutic Applications of Radioactive Isotopes*

1. Administered internally:	
Selectively concentrated:	
Soluble inorganic	Practical treatment . . . P^{32}, I^{131}
	Clinical trials . . . I^{130}
Colloidal inorganic	Preliminary studies . . . $Ca^{45}, Sr^{89}, Ga^{67}, As^{76},$ At^{211}, ThC
	Clinical trials . . . Au^{198}
Organic	Preliminary studies . . . $CrP^{59}O_4, Mn^{55}O_4, Zn^{65},$ $Cu^{64}, Y^{90}, Zr^{95}, Ag^{111}$
	Uniformly distributed
Experimentally distributed	Experimental . . . Na^{24}
	Clinical trials . . . Co^{60}, Ir^{192}
2. Gamma-ray sources	Practical treatment . . . Ta^{182}
	Clinical trials . . . Na^{24} (intracavitary application)
3. Beta-ray sources	Preliminary studies . . . Br^{82}, I^{131}
	Practical treatment . . . P^{32}
Clinical trials	Clinical trials . . . Sr^{90}, Y^{90}
	Preliminary studies . . . $Ru^{106}, Rh^{106}, Ce^{144},$ Pr^{144}

classify the value of the individual isotopes at the levels of practical treatment, clinical trials with definite promise of practical value, and preliminary studies. These isotopes fall into three main groups: those administered internally, those used as gamma-ray sources, and those used as external beta-ray sources. Each of these groups is considered, and the use of the more important individual isotopes is discussed in detail.

There are many tables of the properties of isotopes; one of the most useful is that published by Seaborg and Perlman (1948). Of especial medical interest is the catalogue (No. 2, published in 1950) of Radioactive Materials and Stable Isotopes of the Atomic Energy Research Establishment. The properties of selected isotopes of special interest in medicine have often been discussed (Lawrence and Hamilton, 1948; Clarke *et al.*, 1948; Mitchell, 1947a, 1947b, 1951); special mention must be made of a monograph by Mayneord (1950) and books by Low-Beer (1950) and Hahn (1951). From the point of view of protection and safe handling of radioactive isotopes, the "Introductory Manual on the Control of Health Hazards from Radioactive Materials," prepared for the Medical Research Council by the Ministry of Supply, Atomic Energy Research Establishment in 1949, is extremely useful.

Therapeutic Possibilities of Artificial Radioactive Isotopes Administered Internally

These are either more or less uniformly distributed throughout the body—as in the case of radio-sodium, Na^{24} , which has already received limited practical application to produce effects comparable to total body

gamma radiation in the treatment of chronic myeloid and lymphatic leukaemia and polycythaemia vera (Hamilton and Stone, 1937; Thygesen, Videbaek, and Villaume, 1944; Lindgren, 1944; cf. Evans and Quimby, 1946; Evans, Lenz, Donlan, and LeMay, 1948)—or are capable of selective concentration in particular cells and tissues. Radio-phosphorus and the radio-iodines are practical examples of radioactive isotopes, used in soluble inorganic form, whose therapeutic action depends on selective concentration of the radioactivity in particular cells. The usual therapeutic applications of P^{32} in the form Na_2HPO_4 appear to be due to its synthesis into important cell constituents, including the ribo- and thymo-nucleic acids of multiplying cells, with greater rate of uptake into the dividing abnormal cells of malignant type than into the normal ones, which are probably also the less radio-sensitive. It is easy to understand the concentration of the radio-iodines by the thyroid in hyperthyroidism and not unreasonable to find that relatively few cases of carcinoma of the thyroid retain, even potentially, the function of iodine concentration. The radioactive iodine isotope I^{131} , of half-life 8 days, is the only radio-iodine now in practical use for treatment or tracer investigations; the pioneer clinical trials were made with mixtures of the 12.6-hour isotope I^{130} and smaller amounts of I^{131} , made by means of the cyclotron.

Therapeutic trials, mainly at the experimental level, have been carried out in the case of a number of other soluble inorganic isotopes which are to some extent selectively concentrated in particular cells or tissues. No promising results have been obtained by the attempted use in the treatment of osteogenic sarcoma of the weakly radioactive calcium isotope Ca^{45} , of half-life 152 days, and the radio-strontium Sr^{89} , of half-life 53 days (Pecher, 1941, 1942; Lawrence, 1942; Treadwell *et al.*, 1942), which is now recognized as at least potentially dangerous from the point of view of the risk of induction of malignant tumours of bone (Brues, Lisco, and Finkel, 1946; Lisco, Finkel and Brues, 1947). Recently, radio-gallium (Ga^{72}) has been shown to concentrate in areas of osteogenic activity (Dudley, Imirie, and Istock, 1950). The effect of the radio-arsenic, As^{76} , of half-life 26.8 hours, on the clinical course of patients with leukaemias, polycythaemia vera, multiple myeloma, mycosis fungoides, and metastatic carcinoma has been studied by Block, Jacobson, and Neal (1949), with the conclusion that under the conditions of this work As^{76} offers no advantages over types of therapy already in use. Of especial interest is the artificial alpha-ray-emitting element, astatine (At^{211}), of half-life 7.5 hours, which is selectively concentrated in the thyroid to almost the same degree as radio-iodine (Hamilton and Soley, 1940; Hamilton, 1942). Deucher and Leigh-Smith (1943) reported temporary retrogression of cutaneous metastases in a case of carcinoma of the bronchus by the use of thorium C, which is a bismuth isotope; I have used Th C in three extremely advanced cases and obtained indications of a high value of the order of 10 for the relative biological efficiency per ion pair with the alpha particles.

The possibility of selectively concentrated organic compounds containing radioactive isotopes, especially radio-iodine, is of great interest, but as yet this apparently promising but difficult line of approach has met with little success. It is relevant to mention the work of

Moore (1948) on the localization of cerebral tumours with radioactive di-iodo-fluorescein, and the studies by Seligman, Shear, Leiter, and Sweet (1948) with the polysaccharide from *Serratia marcescens* modified by the introduction of radio-iodine.

Numerous experimental studies of the therapeutic possibilities of insoluble radioactive colloids have been made. The main investigations have been of radioactive colloids which either are taken up more or less selectively by the reticulo-endothelial system after intravenous administration, or could be developed for local interstitial infiltration in and around regions of inoperable tumour, to effect what I suggest may be termed an "injection implant"; or could be introduced into the peritoneal or pleural cavity to inhibit the accumulation of effusions produced by secondary carcinomatous deposits. This method of approach appears likely to have considerable practical possibilities, especially in the use of radioactive colloidal gold for interstitial infiltration (Hahn *et al.*, 1947; Hahn and Carothers, 1950) and for intraperitoneal and intrapleural application (Müller, 1945, 1947a, 1947b, 1949). The other radioactive colloids used have included anhydrous chromic phosphate $\text{CrP}^{32}\text{O}_4$ (Jones *et al.*, 1944; Dobson *et al.*, 1948; Low-Beer, 1950); manganese dioxide, Mn^{52}O_2 (Hahn and Sheppard, 1946; Sheppard and Hahn, 1946a, 1946b); Zn^{63} , zinc sulphide in pectin solution (Müller, 1946; Müller and Rossier, 1947); colloidal radioactive copper, Cu^{64} —in the attempted treatment of malignant melanoma (Marcus and Rotblat, 1950); colloids derived from oxides and hydroxides of the fission products of yttrium, zirconium, and columbium (Dobson *et al.*, 1948; Gofman, 1949); and radio-silver, Ag^{111} (Hahn *et al.*, 1947). The localization of the various radioactive colloids after intravenous injection appears to depend mainly on the particle size.

Radio-phosphorus

Radio-phosphorus P^{32} has a half-life of 14.3 days and emits only beta-particles, of which the average energy is approximately 0.70 meV. Its relevant physical properties and approximate dosimetry are summarized in Table II. As with all isotopes, the term "dose" should, so far as

TABLE II.—Physical Properties and Dosimetry of Radio-phosphorus (P^{32})

Half-life	14.3 days	β -emitter.	No gamma radiation.
Maximum energy of β -particles	1.712 $\pm$ 0.008 meV.		
Mean	"	"	0.70 meV.
Maximum range	"	"	0.82 cm. water.

1 $\mu\text{c.}$ per g. of tissue delivers 38.5 rep per 24 hours (assuming constant concentration)

Without Excretion:

1 $\mu\text{c.}$ destroyed per g. gives a dose of 795 rep.
1 rep is delivered by 1.26 $\mu\text{c.}$ per kg.

With Excretion:

Approximate calculations assume effective half-life 11 days. 1 $\mu\text{c.}$ destroyed per g. gives a dose $\sim$ 610 rep in mean time $\sim$ 16 days. 10 rep is delivered by 1.15 millicuries* destroyed in a patient weighing 70 kg. (11 st.), assuming uniform distribution.

Differential Absorption Ratio (D.A.R.)

Approximate value for normal red bone marrow 1.5
and normal lymph node 2.5

Surface applicator: thin active layer.

Surface dose from 1 $\mu\text{c.}$ per cm.² is 5.1 rep per hour.

N.B.—These calculations are based on the relation that 1 r of the usual filtered gamma radiation from radium, of mean energy 0.8 meV, corresponds to the absorption of 93.1 ergs per g. of water, and 1 rep corresponds to the absorption of 93.1 ergs per g. of tissue.

* The curie is a unit of radioactivity defined as the quantity of any radioactive nuclide in which the number of disintegrations per second is 3.700×10^{10} . One millicurie (mc.) is that quantity of any isotope which undergoes radioactive transformation at the rate of 3.7×10^7 disintegrations per second; one microcurie ($\mu\text{c.}$) corresponds to 3.7×10^4 disintegrations per second.

is possible, be restricted to the dose of radiation in r or rep, and its use avoided when referring to the amount of isotope administered orally or parenterally.

Radio-phosphorus is preferably administered intravenously in the form of an isotonic solution of Na_2HPO_4 , which usually contains the order of 5 mc. of radio-phosphorus per ml.

However, oral administration is often convenient, and appears to be satisfactory if the phosphate solution is administered in the morning after a twelve-hour period of fasting and three hours before the next meal, with avoidance during the period before and during treatment of milk and foods rich in phosphorus, and medicines, such as iron compounds and alumina, which precipitate phosphate. Under these conditions it is safe to assume that 75% of the dose administered orally will be absorbed.

The results on excretion in Table II are based on the value of 11 days for the effective biological half-life of P^{32} in the human body. It is obvious that this value is not likely to be in general exact, especially in conditions of disease, and the biological half-life will vary in different individual patients and in different organs and tissues. However, this value enables one to make a crude approximation probably correct to within $\pm 50\%$, to correlate the dose of radio-phosphorus with the tissue dose in rep. The mean life-time of the isotope, which takes into account both radioactive and biological decay, appears to be the best analogue of the overall time of classical radiotherapy. The next approximation, which is often essential, is to measure the differential absorption ratio (D.A.R.)—that is, the ratio of the concentration of the radioactive isotope in a particular tissue to the mean concentration in the body as a whole. The possibility of delivering useful doses of radiation in any particular case may be determined by measuring the differential absorption ratio by means of tracer studies on biopsy and operation specimens (cf. Kenney, Marinelli, and Woodard, 1941), which, if possible, include normal tissues (Low-Beer, 1951, private communication). In this way, for example, it was found impossible to deliver therapeutically useful doses of beta-radiation from P^{32} to the primary tumour or lymph-node metastases in cases of carcinoma of the breast, and in osteogenic sarcoma.

Treatment of Polycythaemia Vera with Radio-phosphorus

The usual method of administration of radio-phosphorus, except in the treatment of polycythaemia vera, is based on the fractional dosage outlined by Low-Beer, Lawrence, and Stone (1942). In polycythaemia vera different patients vary greatly in their response to the same dose. It is very important to think in terms of the whole clinical picture as well as the haematological findings, and wise not to use radio-phosphorus in atypical cases, and essential to be certain of the diagnosis. The first injection of radio-phosphorus is usually of 5 to 7 mc.; Low-Beer (1951, private communication) recommends two initial injections each of 3 mc. on consecutive days. However, if oral administration is used a higher initial dose of 8 to 10 mc. is often required. Relatively smaller doses should be given to elderly patients. It is important to note that it usually takes three to six weeks before a significant fall in the red-cell count is observed, and two to three months after a single

dose of P^{32} for the red-cell count to settle down at a lower level because of the long life-span of the human red-blood cell.

In cases in which the polycythaemia is uncontrolled, venesection may be necessary to reduce the risk of thrombosis and haemorrhages during the latent period between the administration of the isotope and the production of a significant depression of erythropoiesis. The patient should have further blood counts every fortnight if possible. It is important to watch not only the red-cell count and the haematocrit reading but also the total and differential white-cell count, especially the absolute lymphocyte count, as in conventional radiotherapy, bearing in mind that the lower limit of the normal absolute lymphocyte count is approximately 1,200 per c.mm. and that it is not wise during radiotherapy to allow the absolute lymphocyte count to fall below 300 per c.mm. Platelet counts may be very useful in some cases. It is suggested that radio-phosphorus therapy should be used with great caution in patients with low platelet counts.

The second dose of radio-phosphorus should never be given in less than two, and preferably three, months after the first, and if there is no response and a second dose is necessary it should usually be smaller than the first, probably 3 to 5 mc. Once a satisfactory remission has been obtained the patient is seen for follow-up with full blood counts every two to four months. Recurrences of the polycythaemia are treated as in the initial course, but, one suspects, may ultimately need larger doses. Satisfactory remissions of 12 to 18 months appear to be common.

The advantages of radio-phosphorus therapy in polycythaemia vera are the reliable production of remission, the reduced incidence of thromboses and haemorrhages, the absence of immediate obvious toxic reactions, and the ease of administration of the treatment. Radio-phosphorus therapy certainly can produce good immediate palliative results and reduce the incidence of complications in some cases, but polycythaemia still remains an incurable disease. Its course is very chronic. The average duration of life appears to be about seven years. It is said that death usually takes place in three to eight years from diagnosis, but some cases live for 10 to 15 years and occasionally longer. There is some evidence for increased expectation of life after radio-phosphorus therapy (Lawrence, 1948).

The disadvantages of radio-phosphorus therapy in polycythaemia vera must be considered very seriously. It is impossible to reverse the effects of the radio-phosphorus or any other radioactive isotope after its internal administration, and one cannot detect beforehand the unusually radio-sensitive patient. Should an effective over-exposure occur, with the added risks of haemorrhage and infection, one would suggest the use of blood transfusions, penicillin, and "aureomycin." These measures may turn the scale in borderline cases, but there is no really effective antidote known.

It is important to recognize that all proliferating cells, normal and malignant, concentrate radio-phosphorus. The reality of the possible dangers has been demonstrated histologically by Platt (1947) in the organs of patients treated with radio-phosphorus. In many of these cases the doses of radio-phosphorus used were less than those generally used in the treatment of polycythaemia vera. In general, the histological changes were similar to those caused by external radiation.

Striking changes were, of course, found in the bone marrow, lymph nodes, and spleen, although the latter organ was never reduced in size. Significant renal changes were observed and "can probably be attributed to the concentration that occurs in the nephron during the process of filtration and reabsorption." "Finally, serious consideration must be given to the changes in the testes and ovaries of patients who are in the reproductive period of life. Observation of these organs confirms the possibility that spermatogenesis and oogenesis may decrease or disappear, with development of sterility in young persons given radio-phosphorus."

One must attempt to assess the risk of genetic injury. Administration of 5.8 mc. of radio-phosphorus would deliver a dose of about 100 rep to the testis, assuming a value of 2, which is not likely to be too high, for the D.A.R. Genetic effects of repeated administration of radio-phosphorus are almost certainly additive. The most relevant experimental evidence is that in the mouse. New mutations occur in about 1% of sperm for each 100 r exposure at low-dosage rate; per 100 r there are 0.4% of chromosome translocations, 0.4% of recessive gene mutations, and about 0.3% of dominant gene mutations which would have immediate effects on the offspring (Charles, 1950). The problem of the genetic effects of radiation is very difficult (see Müller, 1950; Sewall Wright, 1950), and the quantitative application of these experimental results to man is very uncertain. However, from the point of view of the individual patient who is treated with radio-phosphorus in the reproductive period of life, it must be concluded that the risk of genetic injury is not negligible.

No final assessment can yet be given on the possibility or frequency of the induction of acute leukaemias, and perhaps also of osteogenic sarcoma, as a late complication of the radio-phosphorus therapy of polycythaemia vera. In a few cases an acute fulminating leukaemia has developed (Hall, 1948; Stroebel and Hall, 1951). It seems that this condition appeared very rarely in cases of polycythaemia vera treated before the use of radio-phosphorus (Tinney, Hall, and Giffin, 1943), despite the well-known natural history of polycythaemia vera and its tendency to the development of leukaemoid states with a terminal blood picture indistinguishable from that of chronic myeloid leukaemia in about 10% of cases. On the other hand, it is important to note that Lawrence (1948) after 12 years' experience of the radio-phosphorus therapy of polycythaemia vera had not observed any cases of acute fulminating leukaemia or any other evidence of carcinogenesis, so that the risk of this complication is almost certainly small.

From the evidence available it must be concluded that it is usually unwise to employ radio-phosphorus in the treatment of patients of either sex in the reproductive period of life, and caution is necessary in patients in whom the expectation of life exceeds five years.

It is important that radioactive isotopes should in no circumstances be used in the treatment of children suffering from non-malignant diseases. From a quantitative point of view, growth retardation may be expected after administration of about 0.8 mc. of radio-phosphorus in a child of 5 years weighing 40 lb. (18 kg.) if one can apply the results of experiments with growing rats (Kligerman, 1950). Further, there is no information about the really long-term effects of radio-phosphorus administered during the period of growth, and I personally would exclude the internal administration of this

isotope even in tracer doses to children under any conditions until more evidence is available.

It is useful to consider the effects and possible risks of larger amounts of radio-phosphorus than those usually given. Animal experiments show that in mice about 11% of delayed deaths were produced by 0.55 μ c. per g. of body weight, and that the LD50 was in the region of 4 μ c. per g. (Anthony and Snyder, 1947); for 42-day-old rats the LD50 was found to be about 3.6 μ c. per g. If these values can be transferred to man, about 10% of delayed deaths would be produced by 35 mc. and the LD50 would be about 270 mc. Probably the largest safe amount for routine use is 10 mc.

Radio-phosphorus in Other Diseases

The results of radio-phosphorus therapy in diseases other than polycythaemia vera are much less satisfactory.

In *chronic myeloid and chronic lymphatic leukaemia* the results and limitations appear to be similar to those of x-ray therapy. The course of treatment often takes a longer time, and supplementary x-ray therapy to the spleen or to enlarged lymph nodes may be needed. It is certain that great care is necessary to avoid serious damage to the bone marrow. Even in the treatment of chronic myeloid leukaemia there appears to be a tendency to rely on x-ray therapy and to discard the use of radio-phosphorus as less safe. The risk of damage to the reproductive organs and of possible genetic injury are such serious matters that it seems to be an inescapable conclusion that radio-phosphorus therapy should not in general be used in patients in the reproductive period of life.

In most cases of *lymphosarcoma* treatment with radio-phosphorus is much less beneficial than with x rays. However, it is suggested that further clinical trials of radio-phosphorus, perhaps with supplementary x-ray therapy, are desirable.

The response of *Hodgkin's disease* to radio-phosphorus appears to be very variable and on the whole unsatisfactory, and inferior to that produced by x-radiation.

The limited results available do not encourage the use of radio-phosphorus in the treatment of *monocytic leukaemia* or *multiple myelomatosis*.

It is important to emphasize that radio-phosphorus, as used at present in the form of inorganic phosphate, seems to be of no therapeutic value in cancers generally. Clinical trials have been made in some cases of advanced cerebral tumours, and in some cases of anaplastic carcinoma and neuroblastoma where other methods of palliative treatment are contraindicated. However, in most cases of advanced malignant tumours, including those with multiple metastases, it is unjustifiable to give radio-phosphorus and usually much wiser and safer to employ the more accepted methods for palliative treatment and for the relief of pain.

Radio-iodine

The assumption of a uniform distribution of the radio-iodine is a simple one and appears to be of some value at the present stage, but it must be emphasized that it is incorrect in almost all cases of thyroid disease and in normal thyroid tissue, as has been shown by radio-autography.

The dose contribution received by the thyroid tissue from the gamma rays of radio-iodine is not important

in treatment of hyperthyroidism, but is not negligible in the treatment of some cases of carcinoma of the thyroid. The accurate determination of the volume of thyroid tissue is an important unsolved question. Clinical examination, confirmed by studies of operation specimens and by making models, is difficult but is probably the best method at present. Radioactivity measurements on models in phantoms show that great errors are introduced by incomplete collimation of the counter, but are necessary to obtain information on back-scatter and extrathyroid radioactivity.

Oral administration of the radio-iodine is almost invariably used. However, it is much more satisfactory to use the intravenous route to administer the small tracer amounts—for example, 10 μ c.—used in the investigation of cases of hyperthyroidism and other non-malignant diseases of the thyroid.

Treatment of Thyrotoxicosis with Radio-iodine

Radio-iodine therapy appears to have a very useful place in the treatment of those patients in whom: (1) the symptoms have recurred or persisted after surgery, and/or (2) there is failure of response or the development of toxic symptoms and intolerance following the use of the antithyroid drugs; or (3) surgery is contraindicated as unduly hazardous because of some serious complication such as age, poor general condition, heart disease, or threatened mental breakdown; or (4) surgery is definitely refused.

Most of the patients are over 45. It is evident that in most of them the disease has already proved resistant to other forms of treatment. In passing, it is suggested that x-ray therapy still has a limited field of application in the treatment of a few mild cases of primary thyrotoxicosis in which there is failure of response or intolerance to antithyroid drugs. Patients with recurrent thyrotoxicosis in whom the thyroid remnant has not appreciably enlarged appear to be especially suitable for radio-iodine therapy because further surgery is usually unsatisfactory and only small amounts of thyroid tissue can be removed; also these patients seem to be particularly liable to recurrence of the hyperthyroidism after treatment with antithyroid drugs.

The best results are obtained in those cases of thyrotoxicosis in which the thyroid gland shows a moderate degree of diffuse enlargement without nodularity or tracheal compression. Any clinically detectable nodularity of the thyroid before radio-iodine therapy is an indication for surgery. Poor results are sometimes obtained with radio-iodine therapy in cases with auricular fibrillation.

Other contraindications to radio-iodine therapy include (1) primary thyrotoxicosis in children and adolescents; (2) pregnancy, at least after the 12th week, when the foetal thyroid tissue starts to differentiate and concentrate iodine; (3) non-toxic goitre; and (4) uncertain diagnosis of hyperthyroidism.

Until the risk of late carcinogenesis can be assessed quantitatively it is not possible to compare the probably very small hazard to life of radio-iodine therapy with the known very small hazards of surgery and antithyroid drugs.

Before radio-iodine therapy all cases must be investigated carefully as in-patients. The importance of the general medical examination and assessment of the clinical condition cannot be over-emphasized. Records

of weight are very useful. The most essential laboratory investigations required are determination of the B.M.R. and plasma cholesterol, and serum protein-bound iodine if possible. The preliminary tracer investigation of radio-iodine uptake is usually essential for assessment of the amount of radio-iodine required for treatment, and often appears to be at least as useful an index of the severity of the disease as the B.M.R. determination, which estimates the response of the body tissues to the circulating hormone. The literature on the investigation of thyroid function and disease with radio-iodine is very extensive; of particular interest is the recent survey by Pochin (1950). It is necessary to estimate the percentage radio-iodine uptake into the thyroid tissue. The tests usually employ direct counts over the thyroid and, less frequently, measurement of the amount of radio-iodine excreted in the urine in the first 48 hours, about 90% appearing in the first 24 hours.

The estimation of the weight of the thyroid gland is subject to very considerable error, of the order of $\pm 50\%$ even with practice. The normal gland weighs 20 ± 5 g.; the minimum detectable diffuse enlargement corresponds to a gland weight of about 35 g.; it is rare for a diffusely enlarged thyroid to exceed 100 g. in weight.

For the initial administration of radio-iodine, the amount to be given is calculated in terms of microcuries per gramme of thyroid tissue. Different workers have used a wide range of values, mainly lying between 50 and 250 μ c. per g. There is as yet insufficient evidence for a decision on the best values. It is tentatively suggested that the initial amount should correspond to 60–100 μ c. of radio-iodine collected per g. of thyroid tissue, so that the mean dose of beta radiation delivered is approximately 6,000–10,000 rep in a mean time of about nine days. The exact dose must be evaluated for each individual patient, taking into account the volume of thyroid tissue and the biological decay.

The uptake of radio-iodine into the thyroid should be re-determined for the therapeutic amount. The values of the fractional uptake and the biological decay are usually substantially the same for the tracer and the therapeutic amounts.

Clinical improvement is observed sometimes after 10 days, and usually after four weeks, from the time of administration of the radio-iodine. A similar interval is generally required before there is a definite decrease in size of the thyroid gland. The maximum clinical improvement and retrogression of the enlarged thyroid are usually reached at about three months after the initial treatment.

Between 70 and 90% of the patients treated appear to be controlled by the initial single dose. In those cases showing little response a second treatment, with a smaller amount, is often effective; occasionally a third treatment may be necessary. A few cases show a relapse after apparently responding to the first treatment, and then a second treatment is indicated. Some cases show a temporary hypothyroidism. However, a small but not negligible proportion of the cases treated develop myxoedema. The frequency of this complication varies between 0 and 17% in different reported series of cases. With initial amounts of radio-iodine corresponding to the collection of about 80 μ c. per g. of thyroid the incidence of myxoedema seems to be in the region of 5%. Occasional cases have been reported in which an acute exacerbation of thyrotoxic symptoms followed radio-iodine therapy.

Radiation sickness is minimal after radio-iodine therapy, although a few patients receiving the higher doses have had transient nausea and malaise, and occasionally there has been a slight increase in the size of the gland and a slight fever for a few days. Blood count changes are probably never observed; the possibility of renal damage during excretion of the radio-iodine appears to be negligible in hyperthyroidism treated with radio-iodine I^{131} . The possibility of ovarian damage is considered to be negligible, and will be discussed in connexion with the use of much larger doses in the treatment of carcinoma of the thyroid.

The ocular manifestations respond as a rule much more slowly to radio-iodine therapy than the general condition and the thyroid size; progressive exophthalmos may develop after radio-iodine therapy as after surgery.

Pre-iodination and the use of antithyroid drugs interfere of course with the uptake of radio-iodine, and their administration must be discontinued at least four weeks before starting treatment with radio-iodine. Tracer studies of radioactive iodine uptake are essential to ascertain that the case is ready for radio-iodine therapy.

It is evident from this discussion that the use of radio-iodine therapy in hyperthyroidism requires much further investigation.

Mention must be made of the related subject of the treatment of selected euthyroid patients with intractable angina pectoris and congestive heart failure by destruction of the thyroid gland by means of radio-iodine (Freedberg *et al.*, 1950).

Treatment of Thyroid Carcinoma by Radio-iodine

1. General Indications

Radio-iodine therapy of carcinoma of the thyroid is still in an early stage of development and probably should be limited to a relatively small proportion of carefully selected cases. X-ray therapy is still very useful. Surgery is the most important first line of treatment, and its place must be considered in every case. Even if radical surgery cannot be carried out, it is usually desirable to remove surgically as much normal and malignant thyroid tissue as possible, including any technically operable metastases.

As a minimum, a satisfactory biopsy specimen should always be obtained. The importance of biopsy cannot be overemphasized, because without a biopsy it is very difficult to select the correct type of treatment. If the general condition is poor, intensive palliative x-ray therapy should be started at once, and is often of great value, especially in producing relief of pressure symptoms and relief of pain in metastases in bone. Advanced cases should not be regarded as hopeless. When the condition of the patient justifies it, as much of the tumour should be removed as possible and then x-ray treatment started. By this means real palliation is often possible, and useful life is sometimes surprisingly prolonged.

2. Examination of Cases for Radio-iodine Therapy

In addition to the histology it is essential to measure the uptake of radio-iodine, if any, in the primary growth and/or metastases with tracer amounts. The first step is external counting with a collimated Geiger or scintillation counter and mapping regions of uptake. However,

the best criterion for uptake is counting on a biopsy or surgical specimen after a tracer dose of 250 μ c. of radio-iodine given three to four days before operation. Radio-autography of the specimens is a valuable supplementary research tool and requires tracer doses of the order of 1 mc. or therapeutic doses.

In addition to the general medical examination, the importance of which cannot be overemphasized, the most essential routine laboratory investigations required before and during treatment are the determination of the B.M.R. and plasma cholesterol and serum protein-bound iodine, and the full blood count, including total and differential leucocyte count and platelet count if possible.

3. Selection and Preparation of Cases for Radio-iodine Therapy

The not very common cases of anaplastic carcinoma of the thyroid, without demonstrable uptake of radio-iodine, will not benefit from radio-iodine therapy, but should be treated either by radical surgery with radical post-operative x-ray therapy or by radical x-ray or tele-radiation therapy only.

Probably all cases of the histologically differentiated types of thyroid carcinoma, including the papillary adenocarcinoma, which is relatively the most frequent type, should be considered for radio-iodine therapy if previous surgery is likely to have been incompletely curative, as is generally the case. The most favourable type is the so-called benign metastasizing struma. Normal thyroid tissue is usually the only strong competitor for radio-iodine. It now appears to be accepted that for these patients with proved residual or metastatic carcinoma of the thyroid the first step must be elimination of all the functioning normal thyroid tissue, either surgically or, in my opinion preferably, by means of radio-iodine.

Surgical removal of all normal thyroid tissue with as much tumour as possible has been widely recommended, despite its severity, largely because it is expeditious and because the remaining primary tumour and metastases can be tested for radio-iodine uptake, and the radio-iodine treatment started if indicated, without the delay of four to six weeks required in the case of radio-elimination of the normal thyroid tissue. However, after thyroidectomy a considerable proportion of the differentiated tumours which previously showed no uptake never develop a therapeutically useful uptake of radio-iodine in the residual tumour tissue or metastases. These cases should receive radical or palliative x-ray therapy without unnecessary delay. Accordingly, it is suggested that in most technically inoperable cases of histologically differentiated carcinoma of the thyroid, showing no evidence of radio-iodine uptake, it is wiser not to attempt surgical removal of the normal thyroid tissue but to rely on radiological thyroidectomy by means of radio-iodine. The minimum amount of radio-iodine required in most cases to destroy all the normal thyroid tissue is probably about 35 mc., administered orally on a single occasion. However, to secure a quicker and more certain effect, a larger amount such as 50 to 75 mc. of radio-iodine is often given, preferably in 25-mc. fractions on alternate days.

4. Technique of Radio-iodine Therapy and its Limitations

The principles of radio-iodine therapy in the selected cases of carcinoma of the thyroid are as yet incompletely understood. The most widely used technique is the

method of multiple large "doses," which consists in the administration of a "therapeutic drink"—a term introduced by Paterson (1950)—of 100 mc. of radio-iodine (I^{131}) and its repetition at intervals of 8–12 weeks, until the uptake as estimated with tracer amounts falls to a very low level. If the patient is thyrotoxic the initial amount should be lower—for example, 25 mc. Apart from this limitation there is a recent tendency to use still larger initial amounts, such as 200 mc., which have apparently been safely repeated three or four times at intervals of four to six weeks. The largest single "dose" given appears to have been 315 mc. On the other hand, an alternative method, which I prefer, is the repeated administration of 25-mc. amounts at weekly intervals until the uptake of radio-iodine is abolished or greatly reduced. As yet there is insufficient experience to decide with certainty which is the best plan of treatment in any individual case. In those cases in which only one region of the primary tumour or one, or part of one, metastasis assumes the function of iodine uptake at any one time the repetition of treatment at intervals of three to six months would seem to be logical. A practical point which may be controversial is the suggestion that the patient can be sent home 48 hours after receiving 25 mc. of radio-iodine.

At the present stage it seems that the only possible plan is to state the estimated mean beta-ray dose in reps, assuming uniform distribution in a particular region of the tumour, and also if possible the approximate gamma-ray dose in reps and the corresponding mean lifetime of the radio-iodine in the region, taking into account both radioactive and biological decay. It is tentatively suggested that a mean beta-ray dose of at least 20,000 rep must be delivered with radio-iodine (I^{131}) in a mean time of the order of 10 days to each region of the more radio-responsive types of histologically differentiated thyroid carcinoma in order to produce prolonged retrogression. Some cases of carcinoma of the thyroid appear to be completely radio-resistant and radio-incurable, despite apparently adequate concentration of radio-iodine.

Radiation sickness is rarely a problem. The limiting factor in the safety of the large amounts of radio-iodine used is the dose of beta- and gamma-radiation received by the bone marrow and lymphoid tissue. This dose is probably between 1 and 2 rep per mc. As would be expected from this value, taking into account the mean lifetime of about 10 days, no changes in the peripheral blood count are usually found after 25-mc. amounts, but after the administration of 100 mc. most cases show temporary moderate leucopenia and lymphopenia. From the haematological point of view it would seem to be wise to avoid the repeated use of single amounts larger than 100 mc.

The radiation dose received by the ovaries is somewhat higher on account of the proximity of the bladder, probably about 3 rep per mc., of which about 2.3 rep is from gamma-radiation and 0.7 rep from beta-radiation. (There is no evidence of concentration of radio-iodine in the human ovary, but this factor must be considered, together with indirect effects via the pituitary.) It is therefore not unexpected that amenorrhoea with menopausal symptoms has been observed in some female patients after radio-iodine therapy of carcinoma of the thyroid (Trunnell *et al.*, 1949).

One of the major problems is that after removal or destruction of all the normal thyroid tissue at least

one-half and probably a considerably larger proportion of the cases do not develop any useful uptake of radio-iodine into the residual tumour or metastases. In some cases uptake has been observed to develop as late as six months after elimination of the normal thyroid tissue. It is evident that attempts must be made to increase the uptake by the tumour cells. These cases must be treated by radical or intensive palliative x-ray therapy without delay; it is conceivable that increased differentiation may follow the x-ray therapy and that this change may be associated with increased uptake of radio-iodine, but as yet there is no evidence of this effect. Of great interest are the attempts to induce uptake by injections of thyrotrophic hormone (Seidlin, Oshry, and Yalow, 1948) and by the use of thiouracil and its derivatives (Rawson *et al.*, 1949). Much further work is required in this field, especially with preparations of thyrotrophic hormone of known activity.

Radio-sodium Na^{24}

The results of the limited clinical trials suggest that radio-sodium is effective in the palliative treatment of some cases of chronic myeloid and chronic lymphatic leukaemia and polycythaemia vera, and in a few cases of other generalized radio-sensitive neoplastic diseases, but that, as yet, it has not shown sufficient advantage to justify its general use as a therapeutic agent in these conditions.

Radio-gold

For almost all the medical applications the isotope Au^{198} appears to be satisfactory, but in some instances higher specific activities may be desirable, and Hahn and Carothers (1950) have suggested the use of the carrier-free isotope Au^{199} .

It is suggested that there may be a restricted scope for the application of the "injection implant" in radiotherapy, especially in the treatment of inoperable recurrences of carcinoma of small volume which are inaccessible either to further surgery or to further irradiation by the usual methods. The limiting factor appears to be the capacity of the infiltrated tumour and adjacent normal tissue to retain the injected colloidal gold *in situ*. Secondary carcinoma in lymph nodes seems to be almost ideal in this respect, while carcinoma of the uterine cervix seems usually to be unsatisfactory. One must envisage the possibility of using injection implants of radioactive colloidal gold in conjunction with surgery in the treatment of some inoperable tumours. The development of the injection implant raises anew the questions of optimal dosage and tissue tolerance, especially in relation to the treatment of tumours which are regarded in the usual way as radio-resistant.

It seems likely that the intraperitoneal and intrapleural injection of radioactive colloidal gold may be accepted as a palliative method of treatment of some cases of peritoneal and pleural carcinomatosis to inhibit temporarily the accumulation of fluid.

Artificial Gamma-ray Sources in Radiotherapy

The possibility of production of artificial gamma-ray sources for use in radiotherapy became evident during the first few years of the working of the atomic pile. Probably similar ideas about this development arose simultaneously in several places. In a number of confidential reports and published papers (Dunworth and Mitchell, 1945; Mitchell, 1946a, 1946b, 1947a, 1947b)

it was suggested that the most promising substitute for radium was radio-cobalt, Co^{60} , of half-life 5.3 years; the second choice was considered to be radio-tantalum, Ta^{182} , of half-life 117 days. Experimental studies of radio-cobalt were made by Mayneord (1946) and Mayneord and Cipriani (1947). W. G. Myers (1948) was the first to use radio-cobalt as a practical source for interstitial irradiation; he employed an alloy, "cobanic," consisting of 45% cobalt and 55% nickel, in the form of wire 1 mm. in diameter, cut to required lengths and activated in the pile. The soft beta-particles can be filtered off easily by thin-walled metal jackets—for example, 0.125 mm. of stainless steel. From a number of clinical trials it is becoming evident that radio-cobalt is a practical substitute for radium for employment in needles, tubes, and beads for interstitial implantation, for external use on "moulds" and other surface applicators, and for intracavitary application—for example, in the treatment of carcinoma of the uterine cervix and carcinoma of the bladder and antrum (Low-Beer, 1950). The possibility of production of large amounts of radio-cobalt of high specific activity in the pile raises the question of the practical development of large teletherapy units, which may compete with 2 meV x-ray therapy apparatus. The problems of protection and handling present substantial difficulties, but plans are being made for very large teletherapy units containing, for example, 1,000 curies of radio-cobalt (Grimmett, Fletcher, and Brucer, 1950).

Radio-iridium Teletherapy

Recently, the possibility of using other isotopes as gamma-ray sources in teletherapy units has been reconsidered. Radio-iridium Ir^{192} , of half-life 70 days, appears to be the most suitable of the shorter-lived isotopes for practical development. A radio-iridium teletherapy unit has been described by Freundlich, Haybittle, and Quick (1950). A unit containing about 20 curies of radio-iridium has been in routine use at the Radiotherapeutic Centre, Addenbrooke's Hospital, Cambridge, since May, 1950 (Figs. 1-4).

Details of the physical measurements made with the teletherapy unit are given by Freundlich, Haybittle, and Quick (1950).

The gamma-radiation of radio-iridium has a mean energy of approximately 400 keV; its half-value layer was found to be 8.1 mm. in copper and 2.4 mm. in lead. Hence the quality of the radio-iridium gamma-radiation is similar to that of filtered 800 kV x-radiation. From the point of view of application in radiotherapy this quality of radiation combines the advantages of the higher-energy gamma-radiation with considerably greater ease of protection.

The general appearance and constructional details of the radio-iridium teletherapy unit are shown in Figs. 1-4. The radioactive source itself is made up of four short concentric cylinders of 0.1 mm. thickness iridium metal mounted for mechanical strength on aluminium bases. The source (Fig. 4) is set into the side of the lead cylinder (2) of diameter 7.5 cm., which rotates inside the larger lead block of cylindrical section 12.5 cm. diameter and 17 cm. long with hemispherical ends. In the "off" position, the source is shielded by the thickness of the lead rotating cylinder (2). The head weighs about 60 lb. (27 kg.) and is mounted on a diagnostic x-ray stand. The source is rotated into the "on" and "off" positions by remote control. The half-life of Ir^{192} is 70 ± 3 days, so that it is necessary to have two sources, one for use in the unit and the other undergoing reactivation in

the pile. It has proved convenient to change the sources once a month. No serious practical difficulty is introduced by the decreasing dose rate; it is convenient to prescribe for each individual case a fixed time for each of the daily treatments in any one week, so as to give a constant weekly dose throughout the course of treatment.

The radio-iridium teletherapy unit in use gives a surface dose-rate of 12–13 r a minute at the usual focal-skin distance of 8 cm. The two standard applicators give

FIG. 1.—Radio-iridium teletherapy. General view of the Cambridge teletherapy unit in use in the treatment of a patient with intrinsic carcinoma of the larynx.

FIG. 2.—Radio-iridium teletherapy. Treatment of a patient with intrinsic carcinoma of the larynx, showing positioning with the aid of a perspex former.

FIG. 3.—Radio-iridium teletherapy. Treatment of a patient with carcinoma of the posterior third of the tongue, showing positioning with the aid of a beam director.

circular fields of 3 and 5 cm. diameter. Smaller fields of other shapes can be obtained with the aid of apertures in lead diaphragms of 1 cm. thickness or occasionally

FIG. 4.—Radio-iridium teletherapy. Diagram showing the construction of the unit. (1) Source. (2) Lead cylinder. (3) External applicator. (4) Safety knob. (5) Knob for locking rotation round horizontal axis.

FIG. 5.—Radio-iridium teletherapy. Calculated dose distribution in the transverse plane through the lesion in a man of 54 with intrinsic carcinoma of the larynx (posterior two-thirds, right vocal cord. No glands). Histology: moderately differentiating keratinizing squamous carcinoma. Three fields: anterior, 3-cm. diameter circle; right and left lateral, 5-cm. diameter circles. The dotted line includes the region to be treated, which was determined with the aid of soft-tissue radiographs and tomographs. The correctness of the position of the former was checked radiographically.

more. Fields of diameter up to 7.5 cm. can be obtained by the use of longer F.S.D., but at present it is not practicable to exceed this field size on account of the inconveniently low dose-rate. Isodose distributions have been published. Routine use of the radio-iridium unit confirms that the dose distributions obtained with it differ very little from those obtained with telerradium units. A practical example of the calculated dose distribution in the treatment of a case of intrinsic carcinoma of the larynx is given in Fig. 5. Photographs of this patient undergoing treatment are shown in Figs. 1 and 2. As a routine technique the fields are positioned with the aid of individually prepared "perspex" formers or with the beam-directing calliper (Fig. 3) and checked radiographically. Provisionally it is assumed that the biologically equivalent dose of radio-iridium gamma-radiation is 1.2 times the dose of filtered 220 kV x-radiation under comparable conditions. It may be concluded that, from the point of view of practical radiotherapy, the radio-iridium teletherapy unit appears to be equivalent to a standard radium-beam unit.

Intracavitary Irradiation with Artificial Gamma-ray Sources in Solution

A number of studies have been made of the intracavitary use of gamma-ray-emitting isotopes in solution in closed elastic applicators. Most of this work has been on the treatment of lesions of the bladder. Müller (1949) employed solutions of cobalt chloride containing radio-cobalt, Co^{60} (together with sodium iodide for radiographic localization), and Wallace, Walton, and Sinclair (1949) used radio-sodium, Na^{24} . Low-Beer (1950) has been using a radioactive cobalt bead in an elastic bag as a convenient central source. Recently Walton (1950) has used bromide solutions containing Br^{82} of half-life 34 hours, which has the advantage over radio-sodium of beta-particles of much lower energy.

This type of treatment must be considered in those cases in which there are non-infiltrating carcinomatous or pre-malignant papillomatous lesions of the vesical mucosa arising over a wide area or from multiple foci. These cases have always presented a difficult problem, and it is considered that total cystectomy is not the treatment of choice for the greater number of these patients; partial cystectomy, diathermy, and deep x-ray therapy usually give poor results. It is obviously much too early to make any claims for intracavitary gamma irradiation of the bladder mucosa, but the results are of sufficient interest to justify further clinical trials.

Artificial Beta-ray Sources in Radiotherapy

It has long been known that the beta rays of radium are of value in the treatment of very superficial skin lesions, and that their biological effects are similar to those of other ionizing radiations in comparable doses. The view widely held at one time that beta rays were caustic in their effects was due to gross overdosage. During the past 20 years the therapeutic use of beta rays has suffered because of the absence of accurate dosimetry and planned dosage distribution in the case of the classical beta-ray plaque. However, recently, appreciable progress has been made towards solving these problems, and at the same time there has been a renewed interest in the therapeutic uses of beta rays from artificial radioactive isotopes.

Radio-phosphorus P^{32} has already been investigated as a practical external therapeutic agent in the treat-

ment of skin lesions, including very superficial basal-cell carcinoma, hyperkeratosis, verruca of the hands, plantar and subungual warts, and cavernous haemangioma (Low-Beer, 1946, 1947, 1950). In these pioneer clinical trials the applicators were cut out of a single layer of ordinary office-type blotting-paper, soaked in Na_2HPO_4 solution containing measured activities of P^{32} , and dried. It is safer and more convenient to enclose the dried radioactive blotting-paper applicator between two layers of "cellophane" film, which are sealed together around the edges.

The real need for accurate dosimetry with beta-ray applicators in r units or rep cannot be overemphasized. In the case of radio-phosphorus (see Table II) it is suggested that it is safer to rely on the dose rate measured with thin-walled ionization chambers than on the calculated values. The most valuable use of P^{32} beta-ray applicators so far appears to be in the treatment of selected cases of cavernous angioma in infants and young children. Measured surface doses of 500 r of beta-radiation, given in times of the order of one hour for the individual applications, seem to be satisfactory. The applicators are held in position with adhesive strapping and bandages. For larger naevi the area of the lesion can be subdivided into small rectangles and irregular areas with sides not exceeding 5 cm. and outlined with thin lead sheet; one area is treated each day, and the irradiation to each area is repeated if necessary at intervals of two to four months.

An applicator utilizing the beta-ray-emitting isotope Sr^{90} of half-life 25 years with its daughter product Y^{90} has been described by Friedell, Thomas, and Krohmer (1950), and has been employed in the treatment of superficial lesions of the eye.

Preliminary studies have been made with other beta-active isotopes (Freundlich, 1949). A group of isotopes has been studied in which there is a long-lived parent which emits low-energy beta particles, but has a short-lived daughter product which emits the required high-energy beta particles, together with weak gamma-radiation. The most promising isotopes of this group are the fission products, radio-ruthenium, Ru^{106} , and radio-cerium, Ce^{144} .

A further possible therapeutic application of beta-ray-emitting isotopes is their use as linear and point sources—"needles" and "seeds"—for *beta-ray implants*. Possible advantages of the beta-ray implant over the conventional gamma-ray implant are better dosage distribution, localization of the radiation field, and ease of protection.

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THEORETICAL ASPECTS OF ISOTOPES IN RELATION TO MEDICINE*

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The use of radioactive and stable isotopes, the so-called "tagged" atoms or isotopic tracers, in the study of biochemistry and medicine is a development of recent times, and indeed this story is largely one covering the past 15 years. Now there is a veritable avalanche of papers describing the use of these tracers or labels in biochemical, physiological, and pharmacological research. Other papers describe their use in clinical medicine, where they serve as diagnostic aids (for example, the use of radio-sodium in the study of peripheral vascular diseases) and therapeutic agents (for example, radio-phosphorus in some of the leukaemias and radio-iodine in diseases of the thyroid).

It would be difficult to think of any major branch of biochemistry in which these tracers are not being used, usually with considerable success, and it may safely be prophesied that this technique will be applied to many branches of medicine and surgery. In my own department we are using both stable and radioactive isotopes to study immunochemistry and some problems of chemotherapy and cancer, and, where possible, this work is closely linked with investigations made by our clinical colleagues.

The varied nature of this relatively new application is well illustrated by reference to some of the ways in which isotopes have been used to label inorganic and organic compounds, and also organisms, both pathogenic and non-pathogenic. Penicillin, sulphydryl, and vitamin B₁ have been labelled with radio-sulphur; amino-acids and antibodies with heavy nitrogen; and red cells, leucocytes, bacteria, viruses, trypanosomes, tsetse flies, and mosquitoes with radio-phosphorus and other radioactive isotopes. In other fields of investigation the isotopes have been used to "date" the Egyptian tombs and to calculate the age of the earth. For scientific detective work they offer a most attractive new tool.

It is obviously impossible to review the whole of this extensive field in one lecture, but I shall attempt to outline the more theoretical side of this new technique and say something about its historical development. A few typical examples of the use of isotopic tracers will be given.

Historical Development

This story would, of course, be incomplete without reference to the pioneer workers on nuclear physics. Lord Rutherford, who has been described as the founder

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