MEDICAL APPLICATIONS OF RADIO-ACTIVE IODINE

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The development of bulk production of radio-active isotopes has quickened tracer research in biology and opened a new field of medical applications. There is already a large literature dealing with the medical uses of radio-active phosphorus, iron, sodium, carbon and iodine. The two main trends of research today are first, utilization of the labelling property of isotope radio-activity, since they are not distinguished physiologically by the body from the stable forms and yet are quantitatively detectable by their emitted ionizing radiations; secondly, their utilization for selective and local tissue irradiation. Radio-active isotopes can be used in the laboratory and in the body in the synthesis of compounds which then become labelled. Thus, the ingestion of radio-active iron leads to the formation of labelled haemoglobin and the production of 'tagged' red cells. In the field of biochemistry many previous hypotheses have been confirmed using minute quantities of material and many discoveries made. 'Radio-active Tracers in Biology,' by M. D. Kamen, gives a detailed review of work up to 1947.

The atomic weight of stable iodine is 127 (I^{127}). There are now at least eight known radio-active isotopes of iodine. Of these, I^{131} made either by prolonged bombardment of tellurium with deuterons in the cyclotron or with slow neutrons in the uranium pile, is now most used in medicine. I^{131} is unstable, each atom spontaneously giving out simultaneously one beta and two gamma rays to become a stable iodine atom. In any sample it takes 8 days for half the radio-active atoms to become stable. The half-life is measured by the decay of radio-activity which falls to half its initial value in 8 days, one quarter in 16 days, one eighth in 24 days. In other words, any I^{131} atom has a 50 per cent. chance of decaying within 8 days. This half-life of 8 days is most convenient in that it allows time for transit of I^{131} from laboratory to hospital without great loss of radio-activity, it can be traced in the patient for some days and unless given in extremely large doses loses its radio-active sting within a few weeks. The gamma rays emitted enable the physicist to determine its location and quantity within the living body and the beta rays (electron particles) emitted

give rise to an intense local ionizing radiation of the tissues in which it is fixed.

The gamma rays are measured by a Geiger-Muller counter. The movable detector part of this apparatus consists of a partially evacuated argon filled tube through which passes a fine wire. The wall of the tube and the wire, which are nowhere in electrical contact, constitute two electrodes to which is applied a large electrical potential difference nearly but not quite enough to make a current jump across between them. The passage of a single electron ejected from the wall of the tube as the result of the absorption of a gamma ray produces sufficient temporary ionization of the gas to give rise to one electrical impulse across the electrodes. The impulses are amplified and recorded on an electrical counter. One can either measure the number of impulses per minute or the minutes taken for an arbitrary number of impulses to be recorded. A control count away from the material or patient to be tested always shows a background of impulses due to ionizations by cosmic rays and radio-active contaminants in the atmosphere. Therefore one or more background counts are always carried out during a test and are subtracted from the final readings. The background count may vary from about 20 to 80 impulses per minute. A weakly active test object giving out only about 10 impulses per minute must therefore be counted for much longer than a strong one giving out some hundreds of impulses per minute, in order to get significant results. Beta ray measurements are carried out on tissues or tissue extracts in a specially modified detector since they only travel a few millimetres in air. Beta ray measurements are very sensitive and accurate but cannot be applied to structures deep to the skin within the living body.

The radio-activity of these isotopes is measured in microcuries (one millionth of a curie) and millicuries (one thousandth of a curie). One millicurie is given out by 0.008 μ g. (millionths of a gram) of I^{131} . This quantity of iodine contains about 3.7×10^{13} atoms. 15 microcuries of I^{131} suffices for a test dose for an adult human. That is to say that after a patient has been given this dose to drink in the form of a solution of sodium

iodide in water, his urinary output of radio-active iodine can be measured and the amount retained by the thyroid deduced. The test dose needed to get suitable readings from a shielded counter externally placed over the thyroid varies with the sensitivity of the counter but is of the order of 50 microcuries. Therapeutic doses of I^{131} for the treatment of Graves' disease or cancer of the thyroid lie between 1 and 100 millicuries. The samples of isotope can be obtained mixed with 'carrier' stable non-radio-active iodide or, if so desired, practically free of stable iodide—'carrier free.'

Most of the pioneer observations on humans of investigations with radio-active iodine have come from J. G. Hamilton and E. O. Lawrence and their colleagues at Berkeley, California, and from Robley D. Evans, S. Hertz and A. Roberts and their colleagues at Boston.

It has long been known that the thyroid gland has a high degree of selective affinity for iodine and that after a large dose most of the iodine which is not taken up by the thyroid is promptly excreted, much of it in the urine. Studies on thyroid uptake and urinary excretion of radio-iodine seemed at the outset likely to be fruitful.

Iodine Metabolism

Hamilton (1942) reviewed his findings with Soley on the uptake of labelled iodine by the thyroid gland in a series of normal controls, cases of toxic goitre and cases of hypothyroidism without goitre. Patients were given a solution containing 24 to 100 microcuries of radio-iodine to drink and the radio-activity of the thyroid determined by placing a Geiger counter tube against the neck directly over the isthmus of the gland. Frequent counts were made over periods varying from 5 days to 4 weeks. The total oral dose appeared to be absorbed from the alimentary tract within one hour. Normal thyroids showed radio-activity within a few minutes, the peak of activity being reached within 1-2 days and thence was maintained for a few days. 74-89 per cent. of the administered dose was excreted in the urine during the first 5 days, 53-81 per cent. appearing during the first 24 hours. Cases of hypothyroidism showed a very much lower and flatter uptake curve, those of non-toxic goitre a steeper and higher uptake curve. The thyroids of patients with toxic goitre showed the greatest uptake of iodine which was three to four times that of normal controls, and more rapidly accumulated. When the test dose of iodine was given together with a large amount of carrier (14 mgm. sodium iodide) the peak in the normals reached only 3.5 per cent. of the dose administered and in the toxic goitre cases 14 per cent. Whereas when the amount of

carrier was very small (0.1 μ g.) the uptake in all groups was higher; 20 per cent. in the normals, 60 per cent. in the thyrotoxics. Not only does a large amount of carrier lower the percentage uptake of labelled iodine but so does previous treatment with stable iodine compounds. This is very important to remember since 15 minims of Lugol's preparation contains, from the point of view of saturating the thyroid, the enormous dose of 120 mgms. of total iodine.

Using similar methods Quimby and McCune (1947) found in 34 normal infants and children that after 48 hours the thyroid gland had taken up 12 per cent. (± 3.6) of a tracer dose of I^{131} . Four cases of sporadic cretinism took up less than 1 per cent. after 48 hours, two cases of Graves' disease 34 and 60 per cent. They studied various dwarfs and cases of enlarged thyroid and found the method a useful indicator of thyroid function in children.

Similar findings have been described in adults by other workers (Hertz *et al.* 1942, Rawson *et al.* 1943 and 1944, Keating *et al.* 1947), who have also carried out detailed studies of the urinary excretion of tracer iodine. Provided there has been no previous recent iodine therapy, normals excrete a total of about 80 per cent. in the urine of an administered tracer dose, cases of myxoedema over 90 per cent., toxic goitre very much less (16 per cent. in one series). Thiouracil treatment leads to urinary excretion of the major part of the tracer dose.

Treatment of Hyperthyroidism

In a three to five year follow-up Hertz and Roberts (1946) described the results of radio-active iodine therapy in 29 cases of hyperthyroidism. The patients had had no previous iodine therapy and were given a mixture of iodine isotopes over 90 per cent. of whose radio-activity was due to 12.6 hour half-life I^{130} the remainder of the 8 day I^{131} . The total dose administered varied between 0.7 and 28 millicuries (1 dose in each of 19 cases, divided doses in the rest). The carrier iodide was always kept below 2 mgm. Routine administration of stable iodine, 5 minims of Lugol's iodine twice daily, was begun at periods varying from one day to several weeks after the radio-active iodine dose. Basal metabolic rates, weights, pulse rates and physical findings were recorded. There were no adverse effects (no fever, nausea or leucopenia) and no increase in degree of thyrotoxicosis. In most cases the B.M.R. fell to normal limits within four or five weeks. Routine iodine therapy was stopped when an essentially normal B.M.R. had been maintained for a few weeks. Failure of the B.M.R. to rise on this withdrawal of Lugol's iodine was then inter-

puted as positive evidence of remission of the disease. 20 cases were considered to be cured and at the time reported had been followed up from 2 to 4 years. Of the remaining 9 cases, 5 who were doing very well were discounted because subtotal thyroidectomy was performed. All 5 developed post-operative hypometabolism. Two failed to respond in spite of receiving total dosages of radio-iodine (3.4 and 5 millicuries) which had proved adequate in other cases. A third failure was attributed to too small a dose of radio-iodine (0.7 millicuries). And the final case was discounted as a 'special ophthalmoplegic' patient whose cure could not be uniquely attributed to the effect of the radio-iodine. The authors concluded that radio-active iodine given in a dosage range of 5 to 25 millicuries to uniodized patients with hyperthyroidism possessing goitres of 60 to 75 grams was highly effective as a cure of the disease in about 80 per cent. of cases. They devised a formula for calculating the total thyroid irradiation in Roentgen units. The rate of delivery from the I^{130} was much more rapid and thus more effective than that from the I^{131} . Among the successes the total thyroid irradiation from the I^{130} varied from 350 to 2,000 roentgens.

Chapman and Evans (1946) treated 22 cases of hyperthyroidism with larger doses of a similar mixture of I^{130} and I^{131} ; 14 to 79 millicuries, some patients receiving repeated doses over a period of months totalling 100 to 150 millicuries. They dispensed with postradiation Lugol's iodine therapy which they considered unnecessary. They thought that in Hertz and Roberts' series such therapy made it difficult to decide whether the patients who improved were responding to the ordinary iodine, to the radio-active iodine or to their combination. 14 patients responded well to a single dose of radio-iodine. The B.M.R. came down to normal in about seven to eight weeks (this was longer than the time required for the response to iodine or thiouracil). The remaining 8 patients required further dosages; 2 responded well, 4 developed myxoedema and 2 remained mildly hyperthyroid. Reactions resembling roentgen-ray sickness were observed in 6 patients following large doses of radio-iodine. Fibrosis of the thyroid was seen in the biopsies of 2 patients after treatment.

Treatment of Cancer of the Thyroid

Seidlin, Marinelli and Oshry (1946) described in great detail the successful treatment with radio-active iodine of a case of hyperthyroidism due to functioning metastases of adenocarcinoma of the thyroid. 15 years following thyroidectomy for a 'malignant adenoma' at the age of 30, a man came to hospital because of the recent develop-

ment of signs and symptoms of hyperthyroidism. In addition, he complained of severe radiating pains associated with a small pulsating tumour in the midline of the back at the level of T.₁₂. His B.M.R. was + 40. A laminectomy was performed and a metastatic well differentiated carcinoma of the thyroid removed in November, 1939. A thyroid crisis developed post-operatively. Nil was found in a further exploratory operation in the region of the thyroid. Symptoms and signs of hyperthyroidism increased during the next two years. In December, 1941, X-ray examination revealed numerous circular almost certainly carcinomatous deposits in the left lung, destructive lesions of the right upper femur, second left rib and left ilium. He was given a course of high voltage X-ray therapy to the spine and femur without symptomatic improvement. By April, 1942, evidence of a new metastasis was seen in the left intraclavicular region in addition to confirmation of all the previous ones. The symptoms of hyperthyroidism were marked; weight 38 kg., B.P. 128/50, pulse rate 100-110, B.M.R. + 36, plasma cholesterol 114 mg. per 100 cc. blood. He was given Lugol's iodine for 9 months and, as the lesions of bone continued to grow, another course of X-ray therapy to the right upper femur and left pelvis, without any relief. In March, 1943, a tracer dose of radio-active iodine was administered orally. Geiger counter measurements revealed iodine uptake by all the known metastases and revealed two previously unsuspected ones, one in the skull and one in the region of the ischium. He excreted only 30-40 per cent. of the tracer dose in the urine. Between May and August, 1943, 102 millicuries of I^{130} and 20.5 millicuries of I^{131} were given him as a first course of radio-active iodine therapy. It was estimated that the radiation dose to each of the tumours was roughly equivalent to 16,000 r units. The clinical picture definitely improved. He gained 7 kg. in weight, his B.M.R. dropped to + 20. In November, 1943, following a 5 millicurie dose of I^{131} , a dissection biopsy of the rib metastasis was made and revealed partially necrotic well differentiated thyroid adenocarcinoma. Estimation of the radio-iodine content per gramme of tumour tissue in this biopsy gave the extra data needed for calculation of the total tumour tissue present in the body based on iodine uptake. The result came to 312 grammes, assuming the iodine to be localized and evenly distributed in tumour tissue. From January 23 to February 21, 1944, the patient was submitted to a course of treatment with thiouracil in order to check further on the functional nature of the metastases. This produced a striking but only temporary remission of the symptoms of hyperthyroidism. By April, 1944, the patient had

reached a state of equilibrium; weight 48 kg., B.M.R. + 10 per cent., no detectable changes in the various metastases. He was given a second therapeutic dose of 55.4 millicuries of I^{131} on April 28, 1944. 13.8 millicuries were extracted from a 21 hour urine collection and readministered on April 29. A second fraction of 6.3 millicuries was similarly extracted from the urine and readministered on April 30. The patient's weight rose to 53 kg. by January, 1945, the B.M.R. fell to zero and remained at this level until March, 1945. A temporary circumscribed alopecia appeared over the area corresponding to the skull metastasis. From February 8 to 25, 1945, he was given intramuscular injections of thyrotropic hormone without any rise in B.M.R. On March 3, 1945, a third therapeutic dose of 41.6 millicuries of I^{131} plus 16 millicuries recovered from the urine was administered. The patient's weight increased and his B.M.R. dropped to -27 per cent. At the time of the report his general condition was good. Over a period of 3 years he had received nearly 40,000 equivalent r units to each of his tumours. Further tracer studies still showed localization of radio-active iodine in the lesions, so that continuation of the therapy was proposed until a state be reached when the patient would show a lack of iodine pick-up by the metastases.

Franz *et al.* (1942) described a case of thyroid carcinoma one of whose metastases was well differentiated, the rest poorly differentiated. The former showed a considerable uptake of radio-active iodine, the latter nothing appreciable. Following 10 millicuries of radio-active iodine the former metastasis was the only one which temporarily ceased to grow. Later it grew again and the patient succumbed with widespread carcinomatous deposits.

It would appear that in cases of well differentiated carcinoma of the thyroid, tracer doses of radio-iodine will help in the detection of well differentiated metastases; very large repeated therapeutic doses will help to arrest their further proliferation and possibly destroy them. Unfortunately, less than 15 per cent. of all thyroid cancers are likely to fall into this category.

Autoradiographs

Radio-active material in histological sections will produce a photographic image of its position when placed in close contact with a photographic emulsion. The photograph and slide can be compared under the microscope. Hamilton was the first to make autoradiographs of human thyroids. He showed that the radio-iodine accumulates inside the follicles. In various conditions the concentration of iodine was roughly proportional to the secretory activity of the follicles. No

autoradiographs could be obtained from undifferentiated thyroid carcinoma sections. Seidlin obtained positive autoradiographs of the rib metastasis biopsy in the case of cancer described above. This technique has been mostly applied to animal thyroids. It is becoming much more refined (Bélanger and Leblond, 1946, Evans, 1947). The earlier method is being superseded by coating or fixing to the actual section a fine layer of photographic emulsion. After suitable time of contact, the slide is developed, fixed and stained so that the exact relation of darkened particles in the emulsion to the underlying section can be determined under the microscope. Working with specially prepared emulsions Pelc (1947) in this country has prepared autoradiographs of rats' thyroids giving a resolution of about 5μ . It seems likely that the technique will improve sufficiently to allow cytological studies of iodine distribution and will play an important role in general in biological research.

Assay of Antithyroid Drugs

It appears from experimental work (Vanderlaan and Vanderlaan, 1947), that there are two clear cut stages in the absorption of iodine by the thyroid. First, the thyroid tissue concentrates the iodide ion which, secondly, is converted to organically bound iodine (di-iodotyrosine and thyroxine). The second process accounts for the major quantity of iodine accumulated in the thyroid and is the stage inhibited by thiouracil whose administration consequently greatly decreases the accumulation of iodine by the thyroid in normal individuals. Stanley and Astwood (1947) have recently applied this iodine blocking property of thiouracil to the assay in humans of antithyroid compounds using radio-iodine. They fed 0.1 millicuries of I^{131} to normal volunteers and measured the rate of iodine uptake by the thyroid by serial counts with an externally placed Geiger counter. They found that when the thyroid radio-activity registered in counts per second was plotted against the square root of the time in minutes elapsed from taking the iodine, a straight line graph resulted for about the first 10 hours. There was variation between subjects in the gradient of the straight line. The gradient was determinable in most cases in about one or two hours, the rate of iodine accumulation for about the next eight hours was then predictable along the straight line graph. Once the straight line relationship had been established, subjects were given a dose of thiouracil or other antithyroid compound by mouth and the inhibition of iodine accumulation by the thyroid, i.e., degree of deviation from the straight line graph, was determined. Within one hour of taking 500 mgm. of

thiouraea by mouth the thyroid showed a complete cessation of any further uptake of iodine for 24 hours. The effects of varying doses of the same compound were also noted and showed a nice gradation with degree of response. The same dose of the same compound given to different subjects with varying gradients produced remarkably similar quantitative effective inhibition of iodine accumulation. In all, 32 compounds were assayed and their antithyroid activity compared with that of thiouracil as the reference standard. They found this elegant method of assay to give on the whole a closer agreement with clinical trials than the hitherto standard method of assay by goitrogenic potency on young rats and chicks.

Non-toxic Goitres

The effect of therapeutic doses of radio-active iodine has not yet been described in cases of non-toxic goitre. It would appear from chemical and autoradiographic studies (Leblond, 1946), that the more solid ('foetal') types of adenoma hardly take up radio-iodine. Beta rays from surrounding thyroid tissue would only penetrate a millimetre or two into these adenomas. Functioning adenomas might take up enough radio-iodine to prevent further cell activity. But there is always the hypothetical possibility that radio-active iodine might be carcinogenic to an already adenomatous thyroid. The carcinogenic potencies of radio-iodine have yet to be worked out and until more experimental data are established will stand as a dim bogey behind all this work.

It is not within the scope of this article to review the animal experimental work already carried out. A precise knowledge is accumulating on the fate and turnover of administered iodine, upon the rate and mode of formation of di-iodotyrosine and thyroxine (Taurog and Chaikoff, 1947) and the effect of various drugs and physiological states upon iodine metabolism. We are only at the beginning but enough has already been done to show how useful radio-iodine promises to be in the diagnosis and treatment of diseases of the thyroid gland.

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