GROWING POINTS

Radioactive Isotopes in Clinical Medicine—I


[WITH SPECIAL PLATE]

A rational understanding of the use of radioactive isotopes must be based on an elementary knowledge of the structure of the atom and of the fundamental particles. To keep this section as brief and as simple as possible we shall first deal with the radioactive particles, and then consider the types of radiation and the measurement of radioactivity.

Fundamental Particles

There are four fundamental atomic particles—the proton, the neutron, the electron, and the positron. The proton has mass and a unit positive electrical charge. The neutron has mass and no charge. The electron has very small mass compared with the proton and neutron, and has unit negative electrical charge. The positron is the positively charged counterpart of the electron, having equal mass and unit positive charge.

The atom is composed of a positively charged central nucleus surrounded by a number of electrons. The nucleus is made up of protons and neutrons. The number of protons determines the positive charge and is known as the atomic number. The number of protons plus neutrons is the atomic mass number and determines the atomic weight. The number of orbital electrons surrounding the nucleus of an atom is equal to the number of protons in the nucleus. Hence the atom is electrically neutral. Since chemical reactions concern only interactions between the outer electrons, the chemical properties of an atom are determined by the number of orbital electrons—that is, they are characterized by the atomic number.

An element is matter consisting of atoms having the same atomic number. The number of neutrons in an atom of an element may vary and therefore its atomic mass number may vary. A nuclide is a species of atom characterized by its atomic number, atomic mass number, and nuclear energy state. Isotopes are nuclides having the same atomic number but different mass number. For example, hydrogen with atomic number one occurs in nature as a mixture of the nuclides hydrogen-1 with mass number one (that is, one proton in its nucleus), and hydrogen-2 (deuterium or heavy hydrogen) with mass number two—that is, one proton and one neutron in its nucleus. Hydrogen-1 and hydrogen-2 are both isotopes of hydrogen and are chemically indistinguishable. The terms isotope and radioactive isotope are frequently used when nuclide and radioactive nuclide would be more accurate. Atomic weight is not quite synonymous with atomic mass number. The atomic weight for a given specimen of an element is the mean weight of its atoms expressed in atomic mass units, for many elements consist of a mixture of different nuclides of that element.

Isotopes may be stable or radioactive. In stable isotopes the relative number of protons and neutrons are found to lie within quite close limits. In radioactive isotopes this balance is upset owing to an excess or deficiency of neutrons, with the result that the nuclei become unstable. They tend to change into stable configurations by processes known collectively as radioactive decay. This involves spontaneous disintegration with emission of radiation. The atomic structure of radioactive carbon, which has six protons and eight neutrons, and that of stable carbon, which has six protons and six neutrons, is illustrated in Fig. 1.

The artificially produced radioactive isotopes may be grouped roughly into two categories, those produced in a nuclear reactor and those produced in a cyclotron. In nuclear reactors the target elements are bombarded with neutrons. The nuclides produced, therefore, are usually isotopic with the stable target elements, and have more neutrons in their nuclei. The radioactive isotope of hydrogen, tritium, has a mass number of three and the ratio of neutrons to protons is 2:1. Isotopes with excess neutrons in the nuclei tend to decay by the emission of beta rays. In the process of producing isotopes in a cyclotron the target material is bombarded with protons, deuterons, or alpha particles. The radioactive products are thus isotopes of a different element from the target. They are deficient in neutrons, and therefore tend to decay by emission of positrons.

Each radioactive substance, whether naturally occurring, produced in a nuclear reactor, or in a cyclotron, is characterized not only by the type and energy of radiation given off but also by the rate of disintegration. The half-life is the time taken for one-half of the original number of unstable atoms to disintegrate. Half-lives of different isotopes vary enormously. For example, carbon-14 has a half-life of over 5,000 years, while silver-109 has a half-life of only 39 seconds. The unit of radioactivity is the curie, which may be defined as that activity in which the number of disintegrations per second is 3.7 × 10¹².

Within the nucleus the particles are in constant motion, and therefore they collide frequently. In these collisions energy transfers take place, so that all particles do not have the same kinetic energy. In a stable nucleus no particle ever acquires sufficient energy to overcome the potential barrier and to escape from the nucleus. In an unstable nucleus, owing to the presence of an excess number of neutrons, there is an excess of energy among the particles, so that there is a probability that one particle will acquire.

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sufficient kinetic energy to overcome the barrier and to escape from the nucleus.

Types of Radiation

The type and energy of radiation given off by radioactive substances is the same for any one nuclide. The primary radioactive decay process is always either the emission of a charged particle (alpha particle, beta particle, or positron) or the capture by the nucleus of an orbital electron. These processes alter the charge on the nucleus, giving rise to a chemically different element. Any one of these may be accompanied by gamma rays or x-rays. In medical diagnosis the beta particles and gamma rays are the most commonly encountered forms of radioactivity.

Beta particles are electrons and have limited tissue penetration dependent on their energy. Even energetic beta particles are able to penetrate about only one centimetre of tissue, so they are not suitable for the study of deep organs. Gamma rays are not particulate, but are electromagnetic radiations of the same nature as light, though of much shorter wavelength, and therefore of much higher energy. They may be considered as being made up of discrete amounts of energy or photons. They have a much greater power of penetration than beta particles, and this power is dependent upon their energy.

Isotopes having an excess of neutrons usually decay by emission of negative beta particles. Decay of an isotope by emission of a beta particle may be thought of as the conversion of a neutron into a proton and electron, with the immediate ejection of the electron from the nucleus (Fig. 2). The loss of a unit of negative charge means that the nucleus has effectively gained a proton in place of a neutron, and the resulting nucleus is that of the next highest element in the periodic system. To maintain electrical neutrality the atom must acquire an extra orbital electron. The decay of radioactive isotopes has thus fulfilled the dream of the alchemist. Radioactive carbon decays by emission of a beta particle and becomes stable nitrogen (Fig. 2). Similarly phosphorus-32 disintegrates with the emission of a beta particle, and thereupon becomes stable sulphur. This may be represented by the equation:

\[ ^{14}\text{P} \rightarrow ^{14}\text{N} + e^- + \beta^- \]

Application of Radioactive Isotopes to Diagnosis

The use of radioactive isotopes in diagnosis is based on the fact that it is possible to tag many of the substances normally present in the body with a radioactive label. Because it is possible to detect minute quantities of radioactive material, only very small doses need be given. The body pool of the material is therefore not appreciably altered, and metabolism is not disturbed. Thus in studies of iodine metabolism the ratio of radioactive atoms administered to stable atoms in the body pool is of the order of 1 to 1,000 million. By measuring radioactivity in the body, in blood samples, or in the excreta it is possible to gain information about the fate of the labelled substance, and hence of the chemically identical inactive material. Hence it is theoretically possible to trace the absorption, distribution, and excretion of any substance normally present in the body, provided that it can be tagged with a suitable radioactive label.

If the investigation necessitates tracing the path of the material through the body by means of external counting over the body surface it is obviously essential to use an isotope that emits gamma radiation or positrons. If, however, only measurements on blood samples or excreta are concerned it is possible to use pure beta emitters. Recently whole-body counters have been introduced which measure the total radioactivity in the body, and these are of great value in absorption studies. Another development has been that of more sensitive scanning devices, which are used in studying the distribution of radioactive isotopes in various organs and tissues. Furthermore, the recent production of isotopes with shorter lives has made it possible to give higher radioactive doses without increasing the radiation hazard. This is of particular advantage to the scanning techniques, which now enable most organs of the body to be visualized.

Metabolic Studies

The use of radioactive materials in metabolic studies is based on the fundamental property that all isotopes of an element are chemically identical. The radioactive isotope is used as a true isotope tracer—that is, when introduced into the body (in whatever form) it behaves in the same way as the inactive
element. Thus isotopes of iodine are used to measure thyroid function, and isotopes of calcium enable kinetic studies of bone formation and destruction to be performed. The distribution of iron-59 from the serum to the bone marrow, liver, and spleen may be followed and its incorporation into the haemoglobin of the red cell used as a measure of bone-marrow function. Orthiodohippurate (Hippuran) labelled with iodine-131 may be used to assess renal vascularity and to detect differences in renal blood supply due to such conditions as renal artery stenosis.

**Absorption and Distribution Studies**

The fate of labelled substances given by mouth can be followed to assess their absorption, utilization, and excretion. In most of these studies the isotope is a true isotope tracer. For example, iron absorption can be measured with radioactive iron; vitamin-B₁₂ absorption may be investigated with vitamin B₁₂ tagged with radioactive cobalt. In studies of fat absorption, on the other hand, triolein labelled with iodine-131 may be used, but this is not a true isotopic tracer.

**Body Composition by Dilution Studies**

By introducing an isotope into a compartment, such as the blood or extracellular space, it is possible to measure the volume of that compartment by determining the dilution of radioactivity when equilibrium has been reached. In this way iodine-131-labelled human serum albumin is used to estimate the plasma volume; chromium-51-labelled red cells to measure the red-cell volume; and bromine-82 to determine the extracellular water. The total body exchangeable potassium can be measured with potassium-⁴², and total exchangeable sodium with sodium-²⁴ or sodium-²².

**Physical Tracing Studies**

In this type of study the isotope is not necessarily used as a true isotopic tracer. In other words, it does not trace the path of the corresponding inactive isotope. For example, xenon-¹³³ is used in measurements of blood flow in muscles, and in lung-function studies; krypton-⁸⁵ is used to detect intra-cardiac shunts. Neither of these elements is normally present in the body. The survival of red cells may be followed and the organ of sequestration revealed by labelling red cells with radioactive chromium. Though chromium is normally present in the body, it does not take part in the metabolic process of the red cell, and the labelling of cells with chromium-⁵¹ is simply used as a convenient tag to trace their fate.

**Scanning of Organs and Tissues**

Scanning is a technique which is used to determine the distribution of radioactive isotope within the body or within one particular organ. In the conventional scanner the radiation detector, which is a scintillation counter, "sees" only a small cross-sectional area of the body at a time. The activity "seen" at each point is registered, and a "map" of the activity seen over the scanned area is recorded. Various methods of presentation have been used, and the most recently introduced display systems present the information gathered by the scanner more effectively. Mechanical printing of black marks, which are closer together for higher count rates (Fig. 3), has been followed by photoscanning and by "colour print-outs," where the colour of the mark is selected by the count rate. A pictorial representation of the degree of radioactivity is thus achieved (Special Plate, Fig. 4). This is advantageous, as the eye can detect quite small variations in colour pattern from point to point much more easily than in monochrome. More recent developments are stationary detectors such as the gamma camera, autofluoroscope, and other devices which can view the whole of the area simultaneously. Thus when selective concentration of an isotope in a tissue occurs it is possible to examine the distribution of that isotope by means of scanning. A toxic nodule in the thyroid may be identified by its selective concentration of iodine-¹³¹ (Fig. 3). Areas of absent function on the radioactive scan ("cold" areas) suggest the presence of tumours, abscesses, and similar lesions. Iodine-¹³¹ may be used to localize tumours of the thyroid, and chloromerodrin labelled with mercury-¹⁹⁷ to delineate tumours of the kidneys. Of even greater practical application is the localizing of brain tumours with chloromerodrin labelled with mercury-¹⁷⁷, with human serum albumin labelled with iodine-¹³¹ or with radioactive technetium.

**Metabolic Studies**

**Iodine Isotopes**

Isotopes of iodine are the most commonly used isotopes in clinical medicine, and, as they have also thrown considerable light on the physiology of the thyroid gland, they will be considered at some length. Iodine is present in the diet as iodide and is readily absorbed from the gut into the blood stream, being trapped by the thyroid and excreted by the kidneys. In the plasma, iodine exists partly as inorganic iodide (less than 1 μg of iodide per 100 ml.) and partly as protein-bound or hormonal iodide (4 to 6 μg per 100 ml.). The average daily diet contains 100 to 200 μg. of iodide and about 55 μg. are taken up by the normal thyroid each day.

Owing to its content of specific enzymes the thyroid gland is able to trap these small amounts of circulating iodide into its substance. The iodide is then converted to iodine and bound to organic compounds of tyrosine to form the thyroid...
hormones thyroxine and tri-iodothyronine, which are then either secreted into the circulation or stored in the gland as thyroglobulin. The initial trapping of iodide is blocked by substances such as perchlorate and the subsequent organic binding of iodine is inhibited by drugs such as the thionaurics and carbimazole.

The most commonly used isotope of iodine is iodine-131, which has a half-life of 8 days and emits both beta particles and gamma rays. The beta particles are completely absorbed within the thyroid gland and cannot be measured externally. It is therefore the gamma emission that is important for diagnostic purposes. In certain situations another isotope of iodine, iodine-132, is advantageous. This has a half-life of only 2.3 hours, so that the radiation dose to the thyroid is only 1% of that with iodine-131. This may be of importance when repeated studies are necessary or when radiation must be kept to an absolute minimum, as in pregnancy or in children. Furthermore, if the isotope studies are to be repeated a few days later the short half-life is a great advantage, as no appreciable remaining radioactivity will be present after a day or two (only 0.05% remains after 24 hours).

Tests of Thyroid Function

Tests of thyroid function depend, firstly, on the rate of uptake of the iodine isotope by the gland, and, secondly, on the proportion that reappears in the circulation as labelled hormone bound to the plasma proteins. The functional activity of solitary thyroid nodules can also be assessed by special scanning procedures. Nevertheless, it must be remembered that the clinical state of the patient depends on the amount of stable iodide taken up by the thyroid which is converted into thyroid hormone and secreted into the circulation.

The most commonly used diagnostic test of hyperthyroidism is the uptake of iodine-131 by the thyroid gland after an administered dose of the isotope by mouth. The value of this depends on the fact that the rate of trapping of iodide by the thyroid gland in general parallels the rate of secretion of thyroid hormone into the circulation. A few exceptions exist. If the thyroid store of iodine is low the uptake of iodine-131 will be high. When stores are low most of the iodide derived from the peripheral degradation of thyroxine is reutilized, and little is allowed to escape in the urine. The thyroid hyperfunction to maintain a normal output of thyroid hormone by trapping a greater proportion of the circulating iodide from the blood. This gives rise to the hyperplastic, non-toxic goitre of iodine deficiency, puberty, and pregnancy, in which the increased uptake of iodine-131 is not associated with an increased secretion of thyroxine.

The normal range of uptake varies from 20 to 55% of the administered dose of iodine at 24 hours. Values exceeding 55% are suggestive of hyperthyroidism, and values less than 20% of hypothyroidism. The test is more reliable in overactivity than underactivity of the thyroid, and the chemical estimation of the protein-bound iodine concentration in the serum is a better test of hypothyroidism. Though in euthyroid patients the uptake by the thyroid gland is maximal at 24 hours, in many cases of hyperthyroidism the maximum uptake is reached earlier, and by the time the 24-hour reading is taken the level has fallen, because some of the isotope has been secreted into the blood as labelled thyroxine. This accounts for the fact that one in ten patients with hyperthyroidism shows a normal 24-hour uptake. Readings should therefore be taken at four and six hours after administration of the isotope as well.

It is also advisable that the 24-hour uptake should be combined with some other test of thyroid function, and this usually takes the form of a measure of the iodine-131, which has reappeared in the circulation as labelled hormone bound to plasma proteins. In hyperthyroidism a high concentration of protein-bound iodine-131 is present in the serum after the dose of isotope, and this reaches a peak at about 48 hours. The normal value does not exceed 0.3% of the administered dose per litre of plasma. An alternative measure is the proportion of total plasma radioactivity that is bound to protein at 24 hours. The unbound portion represents the administered dose that has not been taken up by the thyroid. The protein-bound fraction represents that which has been taken up by the thyroid and which has reappeared as circulating thyroxine bound to protein. Normally the proportion of the protein-bound fraction is less than 35%, while in hyperthyroidism it is usually greater than 50%.

It is important to remember that the protein-bound iodine-131 is not a true measure of the plasma-thyroxine concentration. The former depends not only on the rate of secretion of thyroid hormones but on the size of the iodine pool within the thyroid and the proportion of the isotope dose that has accumulated within the thyroid. In hyperthyroidism the isotope pool within the thyroid is usually normal, and a raised protein-bound iodine-131 concentration reflects an increased hormonal secretion rate. If, however, the thyroid iodine pool is reduced, which will happen if the patient has had a previous thyroidectomy or previous iodine-131 therapy, and also if the patient has lymphocytic destruction of the gland (Hashimoto's disease), a raised radioactive protein-bound iodine level may mean no more than a reduced iodine pool. Moreover, if the amount of stored thyroid (thyroglobulin within the acini of the gland) is reduced radioactive thyroxine will be present in greater concentration, and the same hormone output will contain more radioactive protein-bound iodine.

Nevertheless, a combination of the 24-hour uptake by the gland and some measure of the rate of reappearance of labelled thyroxine enable most cases of hyperthyroidism to be diagnosed accurately. If doubt remains in differentiating a simple goitre from a toxic gland a suppression test with tri-iodothyronine may be performed. This depends on the fact that normally 120 μg. of tri-iodothyronine daily for one week will suppress pituitary thyrotrophic hormone and considerably reduce the amount of isotope taken up by the gland (usually to less than 35% of the uptake at 24 hours). In hyperthyroidism, on the other hand, the activity of the thyroid gland is usually unaffected by administered tri-iodothyronine. Hence a measure of iodine-131 uptake before and after treatment with tri-iodothyronine is often helpful in difficult cases.

In pregnancy the administration of iodine-131 is contra-indicated. The most satisfactory test for hyperthyroidism in pregnancy is measuring the iodine-132 uptake and the effect of tri-iodothyronine suppression. The protein-bound iodine and basal metabolic rate are raised in normal pregnancy, and therefore of little help.

Thyroid Scanning

The distribution of iodine-131 in the gland may be investigated by scanning techniques (Fig. 3). If a solitary nodule takes up iodine more freely than the rest of the gland it is likely to be benign, whereas if it does not take up any isotope the nodule is likely to be a cyst or possibly neoplastic. Subsuntial extension of the gland and ectopic thyroid tissue may also be identified by scanning, while this technique is also of use in detecting metastases from those carcinomas of the thyroid which are metabolically active.

All these isotope investigations, as well as the chemical estimations of plasma-iodine concentrations, will be affected by alterations in the inorganic iodide pool of the body, such as may occur in states of iodine deficiency or as a result of increased dietary intake of iodine. It is the total amount of iodide trapped by the gland, converted to thyroid hormone, and secreted into the circulation that determines the clinical state of the patient. It is therefore important that the inorganic iodide pool should be normal if the isotope measurements are to be significant. As
increase in the size of the pool will decrease the uptake of isotope, and a decrease in the size of the pool will increase the uptake of isotope. It has been shown that a single dose of 1 mg. of stable iodide by mouth will reduce the isotope uptake of a hyperthyroid patient to normal, and that 10 mg. will reduce it to inappreciable levels. One millilitre of Lugol's solution contains 130 mg. iodine, which is equivalent to a normal iodine requirement for 1,000 days. The iodine pool would thus be increased tremendously if such doses were taken. Many cough mixtures contain a large amount of iodine, and organic iodide is contained in compounds used as radiographic contrast media. These will suppress the radioactive-iodine uptake and invalidate the test. Though the kidney rapidly excretes the dyes used for pyelography, the contrast media used for cholecystography, bronchography, and myelography may continue to release iodide for many months or even years. Hence it is of the utmost importance that patients referred to hospital for investigation of thyroid function should not receive iodine therapy before coming. The taking of antithyroid drugs will also suppress the isotopic iodine turnover.

Though iodine-131 tests are less reliable for the diagnosis of hypothyroidism, they provide a useful distinction between primary and secondary hypothyroidism when undertaken before and after the administration of thyroid-stimulating hormones.

Bone-marrow Function

The utilization by the red blood cells of iron-59 given intravenously can be used as a measure of bone-marrow function. Daily measurements of radioactivity in the red cells will demonstrate the rate of incorporation of iron into the haemoglobin molecule, and this provides a measure of effective erythropoiesis—that is, erythropoiesis which results in the production of viable red cells that survive an appreciable time in the circulation. The amount of iron leaving the plasma can be calculated from a knowledge of the rate of disappearance of iron-59 from the plasma and the concentration of the serum iron. This is called the plasma-iron turnover, and it measures the total erythropoietic activity, which includes both effective and ineffective erythropoiesis. Ineffective erythropoiesis includes erythropoiesis which does not result in viable red cells because the red-cell precursors are destroyed within the bone marrow or because the red cells produced are so defective that they survive only a few minutes or hours in the blood. Plasma-iron turnovers are of little value as a measure of bone-marrow activity, and they are largely used for research studies of iron metabolism. Scanning over the body surface will reveal the distribution of radioactive iron in the bone marrow, liver, and spleen, and may be of help in determining whether extra- medullary haemopoiesis is taking place in such organs as the spleen. The presence of extramedullary haemopoiesis can be assumed when iron-59 curves resembling those seen by scanning the bone marrow are found also to occur over the liver or the spleen. When the bone marrow is aplastic most of the iron goes to the liver. These patterns of iron metabolism may be of help in diagnosing disorders of the bone marrow.

A disadvantage of the iron-isotope test is that it cannot measure any increase in bone-marrow function. Thus the bone marrow may increase its output sixfold in chronic haemolytic states, but the red cell uptake of radioactive iron will be reduced because the rapid destruction of labelled red cells leads to a loss of iron-59 from the blood. In both haemolytic anaemia or iron deficiency, for example, the marrow curve of iron-59 uptake will fall more rapidly than normal, as the iron leaves the bone marrow in the red cells at an enhanced rate.

Kidney Function

Iodine-131-labelled orthiodohippurate (Hippuran) may be used to study renal function. An initial rapid rise in isotope concentration over the kidneys following intravenous administration represents the filling of the renal blood vessels. Differences in the rate and degree of this initial uptake between the two kidneys may permit the detection of renal artery stenosis in the assessment of patients with hypertension. A subsequent slower rise in isotope concentration represents active tubular transport, and the final stage of rapidly decreasing concentration coincides with the excretion of the dye into the bladder. Non-functioning kidneys show a slight initial uptake, followed by a flattening of the curve. Ureteric obstruction will be characterized by a normal uptake with a delayed excretory phase.

(To be concluded next week.)

FORENSIC MEDICINE AND TOXICOLOGY

Medical Aspects of Divorce and Nullity of Marriage

BY A QUEEN'S COUNSEL

There are few suits for divorce or nullity of marriage in which the court may not require to be assisted by expert medical evidence. The particular aspect upon which such assistance may be required depends, of course, on the legal ground upon which relief is sought in each suit. An attempt is here made to indicate the sort of questions on which a medical practitioner is likely to be called upon to give evidence of his expert opinion in suits in which different matrimonial offences are alleged.

Cruelty

Cruelty has for long been a matrimonial offence, though not until the Matrimonial Causes Act, 1937, did it become by itself a ground for dissolution. Cruelty may be defined as conduct of such a character as to have caused danger to life, limb, or health (bodily or mental), or as to give rise to a reasonable apprehension of such danger.

Evidence is not normally required of a doctor to establish that a bone has been broken or that a bruise has been inflicted. But the evidence of a layman will carry much less weight than that of a qualified man when it is sought to prove injury to general health. Not only will the doctor be able more accurately to assess and describe the matters of which his patient complains (e.g., headache, loss of weight, depression) but his expert evidence may be essential to inform the judge of any causal connexion between the condition observed by him and the conduct on the part of the other spouse which is alleged.

The role of the expert witness is to state factually what he has observed as a result of examination, and to give his opinion of the possible causes of the symptoms found by him to be