# ISOTOPES IN MEDICINE

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Isotopes have an established place in medical research, diagnosis and therapeutics. The understanding of complex problems connected with intermediary metabolism and metabolic products in health and in disease has been, in many ways, bound up with the application of tracer techniques, dilution analysis and kinetic studies involving isotopes whilst irradiation of unhealthy tissue by radioactive isotopes has afforded a major line of treatment in many forms of new growth.

## What are Isotopes

The atomic nucleus is built up of particles of unit mass (nucleons); some of these are positively charged (protons) and others are uncharged (neutrons). The number of protons, which is equal to that of electrons of negligible mass in the surrounding negative charge-cloud, is known as the *atomic number* and characterises a particular chemical element. Carbon with six protons has an atomic number of six; similarly cobalt with twenty seven protons is distinguished from any other element by its atomic number twenty seven.

## Variation in the Number of Neutrons

The number of neutrons is in no way a constant characteristic of an element. This variation gives rise to atoms of the same element possessing different masses since each extra neutron carries with it one additional mass unit. These different types of atoms are referred to as isotopes. Every element exists in nature as a mixture of isotopes. Oxygen, for example, has three known isotopes:

$^{16}O$ (read oxygen sixteen) has 8 protons and 8 neutrons,

$^{17}O$ has 8 protons and 9 neutrons.

$^{18}O$ has 8 protons and 10 neutrons.

## Radioactive Isotopes

Some combinations of protons and neutrons are unstable. Spontaneous nuclear changes involving emission of radiation reflect this and these changes take place so that a stable nuclear configuration is eventually attained. Three types of radiation are usually described.

1. *Alpha-emission* or high-speed emission of two protons and two neutrons (the equivalent of a stable helium nucleus) is associated with a decrease in atomic number of two units.

2. *Beta-emission* of an electron of *nuclear origin* or of a positron (a positively charged electron) likewise brings about a unit change in atomic number. These two types of radiation are accompanied by atomic transmutation.

3. The third type or *Gamma-radiation* is a penetrating electromagnetic radiation consisting of waves of very high frequency (i.e. smaller in wavelength than X-rays).

Nuclear bombardment by alpha-particles, protons, deuterons, neutrons and high energy gamma rays in cyclotrons produces isotopes with unstable unclear configurations. Most of the commercially available radioactive isotopes (for example from the Radiochemical Centre, Amersham, Bucks, England) are *artificially* produced in nuclear reactors.

### Detection of Radioactivity

Radioactivity produces a number of effects in the medium in which it is occuring. Most important is the ionisation (or the stripping of the outer electrons) of the atoms of the medium. Instruments such as the Geiger-Muller, proportional and scintillation counters, and ionisation chambers are available and they are capable of counting or automatically recording the number of these secondary ionisations and hence afford a means of determining the 'activity' of any radioactive isotope.

### Period of Half-Life

The time taken for half the radioactive atoms of an isotope to decay is called its half-life and is characteristic of the isotope. The rate of radioactive decay depends on the concentration of unchanged isotope present. The rate equation

$$\frac{dN}{dt} = -\lambda N$$

expresses this concisely. ($dN/dt$ is the instantaneous rate of change or 'activity' of the specimen, $\lambda$ is a proportionality constant known as the decay constant, and N is the number of unchanged nuclei at time t). The equation can be solved:

$$t = \frac{1}{\lambda} \log_e \frac{N}{N_o}$$

where $N_o$ is the initial number of nuclei. When the ratio $N/N_o = 0.5$, t is known as the time of half-life, $t_{\frac{1}{2}}$, and becomes equal to $1/\lambda \log_e 2$. This means that t, is independent of the initial concentration of nuclei. $^{131}I$ with a half-life of 8 days or $^{24}Na$ with a half-life of fifteen hours, both isotopes of short life can be introduced into the animal organism without fear that their activity will persist beyond the time when harmful secondary effects can take place.

The standard used for measuring the activity of an isotope is the *curie* which is the activity of 1 g. of radium for which $dN/dt = 226$ and $t_{\frac{1}{2}} = 1622$ years. It represents $3.7 \times 10^{10}$ disintegrations per second. A more useful unit is the millicurie.

### Stable Isotopes

It must be borne in mind, however, that most combinations of protons and neutrons as found in nature are stable and remain so indefinitely. Such nuclei are not easily detectable (except by mass spectrography). In certain instances, where appreciable mass differences obtain, detection is possible. The nucleus of hydrogen, in particular, consists of a single proton without any accompanying neutrons. Deuterium, D, is an isotope of hydrogen and since its nucleus is made up of a proton and a neutron, it is twice as heavy as hydrogen. $D_2O$ concentration in ordinary water can be estimated by specific gravity determinations and thus deuterium can be incorporated in any compound containing hydrogen and the labelled compound may be detected provided it may subsequently be made to react to give $D_2O$. Tritium, another isotope of hydrogen has 1 proton and 2 neutrons but is also a gamma emitter.

### Isotopes in Medical Diagnosis and Research

The use of isotopes in this ever-widening field depends essentially on the fact that chemical behaviour is a function of the atomic number and not of the atomic mass. Small amounts of detectable isotopes do not in any way interfere with the metabolic pathways of food and substances with specific pharmacological properties introduced into the living organism. The particular element or compound so introduced is thus labelled and its history within the organism can be followed at times with bewildering precision. While tracer techniques allow complex paths to be followed, the rate of a particular step in a metabolic sequence can in many cases be studied and a lot of insight into the actual chemical mechanism can be obtained. Finally, the extent to which a labelled compound, introduced into the organism at a known concentration, is diluted on recovery, gives an estimate of the amount of the original unlabelled substance present, a technique widely used in chemical analysis in industry known as isotopic dilution analysis.

## Intermediary Metabolism

A simple example is the biosynthesis of ascorbic acid from glucose or galactose. Glucose, uniformly labelled with $^{14}C$, is found to produce labelled acid. Another example is concerned with the proof that tissue proteins are in a continuous state of flux. Experiments with amino-acids labelled with $^{15}N$ show that the nitrogen is quickly incorporated in the tissue proteins — a process requiring the rapid formation and breakdown of peptide bonds.

## Iron Metabolism

The radioactive isotope $^{59}Fe$, with a half-life of 45 days, has been used to determine the average life of the red cell. It has been possible to follow the movement of the ingested iron from its initial high concentration in the bone marrow, through its appearance in the systemic circulation and its final accumulation in the spleen. In this way the life of the red blood corpuscle has been found to be 16 weeks. Moreover it has been found that the iron can be used over and over again. This means that iron depletion occurs slowly in health. It is thus possible to study the chemistry of iron storage disease, where, for example, it has been shown that the brown paches over the skin of the lower limbs in elderly persons are due to the deposition of ferrous iron.

## Iron and the Thyroid Gland

The application of isotopic techniques in this connection is generally familiar. $^{131}I$, the isotope commonly employed, is convienently produced by the irradiation of tellurium in the nuclear reactor. A small dose of the isotope is found to be concentrated over the thyroid reaching its maximal activity within two days after which renal exeretion starts. Urinary excretion rates measure thyroid function and are normally useful as a preliminary test in out-patient practice. More elaborate tests give (a) thyroid activity / time and (b) blood activity / time curves and (c) thyroid activity / thigh activity ratios which can be correlated with thyroid dysfunction. It is also possible to outline the borders of the thyroid and functional thyroid carcinoma and its metastases can be accurately diagnosed and located.

## Measurement of Blood Volume

Dilution analysis with $^{32}P$ enables the blood volume to be estimated. Blood is withdrawn from the patient and labelled with radio-phosphorus by letting it stand in a solution of this isotope. A known quantity of this blood is re-injected so as to mix with the circulating blood. The radioactivity in a second sample of withdrawn blood enables the extent of dilution and hence the blood volume to be determined. By applying tourniquets blood volumes in limbs can be similarly estimated.

## Miscellaneous Applications

Space does not permit the discussion of other uses of isotopes in medical science such as the following:

1. The metabolism of Vitamin $B_{12}$ and the diagnosis of pernicious anaemia by means of cobalt-sixty.

2. The diagnosis of haemolytic anaemias by the radiochromium red blood cell

survival test and the estimation of the red cell mass.

3. The study of electrolytic diffusion through cell membranes with reference to digestion, renal excretion and the placental barrier by means of radiosodium and radiopotassium. These isotopes are also used to determine exchangeable sodium and potassium.

4. The use of $^{45}Ca$ in the study of bone and teeth formation.

5. The study of the biochemistry of diseases such as diabetes with labelled insulin.

6. The estimation of the efficiency of limb circulations by means of $^{24}Na$.

7. The confirmation of the establishment of an efficient circulation in skin and bone grafts using radiophosphorus.

8. The location of brain tumours by labelled diiodofluoroscein and phosphorus.

9. The use of radioactive isotopes in pharmacological research.

10. The use of tritium in the estimation of the body water content.

11. The application of isotopic techniques in the study of viruses, bacteriophages and immunology.

## Radiotherapy

Unhealthy or rapidly growing tissue in benign or malignant growths is often destroyed by smaller doses of radiation than are normally required to kill healthy cells. X-ray radiation demanding high-voltage tubes has been used extensively in the past but nowadays it is also convenient to use radioisotopes as sources of radiation. The use of radium in this connection is well known.

Radioisotopes can be used either as external agents (teletherapy) or internally. Important external sources are $^{60}Co$ in the form of the Cobalt Bomb for deeply seated tumours such as carcinoma of the oesophagus or of the fundus of the uterus, $^{137}Cs$, $^{90}Sr$, $^{137}Ba$ and $^{192}Ir$. Isotopes can also be given internally. Thus $^{131}I$ is useful for functional thyroid carcinoma whilst a colloidal suspension of $^{198}Au$ has been employed with success in the treatment of pleural effusions and ascites secondary to malignant growth; it is administered directly into the appropriate cavity after withdrawal of fluid. The radiotherapy of cancer is on the whole a palliative measure though early small tumours of the skin, tongue, larnyx, cervix uteri and bladder can be completely cured. On the other hand it is ineffective in many instances such as primary malignancy of the gut and pancreas.

Radiosotopes are not exclusively employed for treating malignant disease. Intravenous radiophosphorus has been employed in polycythaemia vera and has increased the survival time. $^{131}I$ has been effective in Grave's Disease and for the symptomatic relief of intractable angina pectoris by induction of myxoedema. Keloids and various skin lesions such as warts and verrucas are routinely treated by radiotherapy.

## Radiography

In conclusion two other applications may be mentioned.

Thulium-170 can be inserted in the mouth (in the centre of hollow sphere) and a good radiograph of all the teeth can be taken after a few minutes exposure. For bone radiography good contrast pictures are not obtained but this low-energy gamma ray emitter can be employed as a convenient portable 'X-ray machine'.

## Sterilisation

Gamma-rays are capable of killing bacteria and as such provide provide an extremely useful means for sterilising heat-sensitive materials. Cheap polyethylene syringes, catheters, scalpels, sutures and dressings can be reliably sterilised by means of a radioactive cobalt sources. Disposable syringes and other aseptic commodities have nowadays become a reality.