RADIOACTIVE ISOTOPES IN THE TREATMENT OF MALIGNANT DISEASE AND DISEASES OF THE THYROID GLAND

By G. W. BLOMFIELD, M.A., F.R.C.S., M.R.C.O.G., D.M.R.

Medical Director, Sheffield National Centre for Radiotherapy; Lecturer in Radiotherapy, University of Sheffield; Consultant Radiotherapist, United Sheffield Hospitals.

It is difficult to get a balanced picture of any new form of treatment, and much more difficult when new modes of diagnosis and therapy extend into the realms of atomic physics. In this article an attempt will be made to describe the present position of radioactive isotopes as applied to surgery. Without going deeply into the physics of the subject, the author will present the principles underlying their use.

Radioactive elements behave chemically and biologically exactly like their stable isotopes. Radioactive iodine, to take an example, will be metabolized by the thyroid gland along with ordinary iodine without any discrimination on the part of the tissues. But the radioactive atoms are at constant risk of atomic disintegration or rearrangements releasing energy in the form of gamma rays and energetic particles. Each material emits its own characteristic radiation and decays at an equally characteristic rate, and the radioactivity differs widely from one substance to another.

The gamma radiations may be soft or hard X-rays according to the energy released. The energetic particles are usually beta rays which are fast-moving electrons, or alpha rays which are fast-moving helium atoms. In any event, there is ionizing energy emitted which has a biological effect on tissues and is capable of detection by suitable equipment. The gamma rays are of particular value for measurement as they penetrate the body and can be measured externally. The beta rays will only penetrate a few millimeters, the penetration being proportional to the energy released. Consequently, the beta radiation may only be measured by ordinary methods when emitted on the surface or on the skin, and it requires a special type of 'probe counter' for interstitial measurement.

Good examples of different radioactivities are provided by radioactive iodine and radioactive phosphorus. Radioactive iodine (I_{131}) gives off

beta and gamma radiations. Its presence can be measured quantitatively by virtue of the gamma radiation, but its clinical and biological effect is mainly due to beta radiation. By means of a 'directional counter' the concentration in the body can be mapped out quite accurately, and the modern 'scintillation counter' is so sensitive that only minute and quite harmless quantities are required for this. Furthermore, these concentrations can be mapped out and the contours of the thyroid gland can be plotted in different planes with sufficient accuracy to determine the gland volume within reasonable limits of error. This is of particular importance in the treatment of thyroid diseases by radio-iodine. Radioactive phosphorus (P_{32}) gives off beta radiation and no detectable gamma rays. Consequently, its detection and measurement in the tissues, e.g. in a tumour of the brain, cannot be estimated by external counters. It can, however, be measured by a 'probe counter' pushed into its substance. Its concentration in the blood or in body fluids can be measured by taking appropriate samples.

Equipment Necessary

The amount of laboratory equipment required depends entirely upon the nature of the work undertaken. Very little equipment would be necessary for the use of radioactive isotopes as a substitute for radon seeds. A great deal of equipment, including a 'hot laboratory' for therapeutic measurements and a 'tracer laboratory' for the very much smaller diagnostic measurements, would be necessary for the more extensive use of isotopes in large hospitals. The assistance of a physicist will be advisable, if not indispensable, as the handling and measurement of these substances is a highly technical matter and the hazards associated with radioactivity are very real when radioactive solutions are handled. But these difficulties should not deter us from their judicious use.

Diagnostic Use of Radioactive Isotopes

The diagnostic value of the isotopes depends upon the detection of tracer quantities and their accurate measurement by physical means. Good examples of routine tests are given below.

(1) *Radioactive Iodine*

As a clinical test for thyrotoxicosis, radio-iodine has the immense value of separating hyperthyroidism from the anxiety states, non-toxic goitre and other disturbances simulating hyperthyroidism. Various tests can be used. All depend upon the fact that in hyperthyroidism the gland quickly takes up a large percentage of the ingested iodine and rapidly converts it into thyroxine, which is absorbed by the blood in a protein-bound form. Only a very small quantity is required for this test. The simplest test, which can be carried out as an out-patient, is to give a measured tracer dose of the radio-iodine as a drink and measure the quantity which goes to the gland during the next few hours. A much more reliable test is to measure the percentage of ingested iodine as protein-bound iodine in the plasma two days after the drink. In thyrotoxicosis the gland usually takes up more than 50 per cent. of the iodine, and the presence of more than 0.2 per cent. of protein-bound iodine per litre of plasma at 48 hours is diagnostic of thyrotoxic gland function. The presence or absence of retrosternal thyroid tissue can be directly verified by plotting the radioactivity in the neck and over the sternum.

(2) *Radioactive Di-iodo Fluorescein*

Radioactive di-iodo fluorescein has been tried as a diagnostic test for cerebral tumour. This has not as yet proved satisfactory, as the specific concentration in the tumour is seldom sufficient to give a positive result, and even less likely to give a lead as to its position when present. It has largely been replaced by the P_{32} test described below.

(3) *Radioactive Phosphorus*

Anaplastic tumours have a tendency to take up slightly more phosphorus than normal tissues. The white matter of the brain takes up very little phosphorus. Consequently solid neoplasms in the brain have a high differential absorption of P_{32} relative to the white matter. The range of the radiation is only a few millimeters. Consequently a probe counter will register a higher counting rate when pushed into a cerebral tumour than it will in the white matter. These probes are now produced commercially in a size convenient for exploring the brain, and their use in searching for cerebral tumours and particularly

in the final location has been of proved value (Morley and Jefferson, 1952). It will not differentiate between granulomatous lesions and other neoplasms as these also have a relatively high take-up.

(4) *Radioactive Sodium*

Radioactive sodium, which has a short half-life (15 hours), gives off a very penetrating gamma radiation in addition to beta radiation and has been used extensively as a research tool in tracer work. Clinically it can be of value in determining the circulation rates (Farmer, 1953) and this has been applied in plastic surgery for the assessment of circulation in skin flaps. A small amount of Na_{24} is injected interstitially into the flap and its rate of diffusion will give a very good indication as to its viability. This may effect a very considerable saving in time between the various steps taken in plastic operations.

Therapeutic Use of Radio-isotopes

The therapeutic use of radio-isotopes depends upon the biological effects of the radiation emitted. Radio-gold in the form of a radioactive colloid solution, for example, can be used in the treatment of malignant pleural or peritoneal effusions by virtue of the beta radiation emitted and wherever the colloid is in contact with the tissue the biological effect will be maximal.

Diseases of the Thyroid Gland

Thyrotoxicosis can be effectively treated with radioactive iodine however severe the disease may be. In these cases a high proportion of the radio-iodine is taken up by the gland. It gives off its beta and gamma radiations there without affecting the skin or the trachea, the dose being almost entirely limited to the gland. One hundred cases have been treated and followed up for over one year at Sheffield and the impression gained is that this is a most powerful and effective method of treatment. Details of technique and reports on cases treated have been given by Wayne, Macgregor and Blomfield (1952). Special attention has to be given to physical measurements of 'take up' and dosage. The great advantages of radio-iodine therapy lie in its immediate safety and the practical certainty of controlling the hyperthyroidism if sufficient or repeated dosage is given. It is of particular value in cases failing to respond to thiouracil or relapsing after surgery. Contraindications are pregnancy and the presence of a large toxic adenoma, the latter being best dealt with surgically on account of the tumour. Treatment can at present be carried out only in specially equipped hospitals where the necessary physical measurements can be made and where

FIGS. 1 and 2.—Functioning secondary glands from carcinoma of thyroid gland. Isodose contours plotted after thyroidectomy showing take-up by secondary deposits. Fig. 1: Right lateral aspect of neck.

the radio-iodine can be properly dispensed. The possibility of inducing malignant change in the gland is still held out as a remote hazard sufficiently important to limit the use of this treatment to the older age groups or to those for whom it offers special advantages. The possibility of causing hypothyroidism is one reason why special attention has to be given to dosage, and this complication arises, at present, in about the same proportion of cases as in surgery.

Ablation of Thyroid Gland

For complete ablation of thyroid function, which is sometimes indicated as a therapeutic measure, e.g. in cardiac failure or angina pectoris, a single large dose of radio iodine is all that is necessary. A drink of 30 to 40 millicuries of radio-iodine will usually cause cessation of thyroid function.

Malignant Disease of the Thyroid

A great deal has been written on the treatment of malignant thyroid tumours by radioactive iodine, but the fact remains that less than 10 per cent. of thyroid carcinomas are suitable for such treatment. It does not replace surgery, but it may be used along with total thyroidectomy in

suitable cases where the tumour concentrates the iodine. For effective radio-iodine therapy the tumour must concentrate iodine and must therefore be a functioning growth. The best response is therefore obtained in follicular and alveolar carcinomas. Papillary carcinomas show but little tendency to concentrate iodine and anaplastic growths show no effective concentration. Unfortunately even the well-differentiated growths are patchy and uneven in their function, and sometimes one secondary growth may function whilst another is completely idle. The so-called aberrant thyroid in the neck, associated with a malignant gland, shows the best response of all. In one such case met with by the author, thyroidectomy and removal of the main mass of the tumours was carried out surgically, but was followed by recurrences in both sides of the neck. These functioned so well (see Figs. 1 and 2) that only one single dose of radioactive iodine was necessary to effect a complete clearance. They have not returned in three years, but the patient is hypothyroid and requires thyroxin. There can be no doubt that surgical ablation of the thyroid along with the main mass of the primary is indicated in the first instance in order that the thyroid-stimulating hormone should be boosted as much

FIG. 2.—Anterior aspect of neck. There is practically no take up in the region of the thyroid gland. Contour lines are marked in counts per second.

as possible before the radioactive iodine treatment is given. The preliminary physical tests using tracer quantities of radio-iodine should be carried out thoroughly so as to locate the presence of functioning secondaries and estimate the effective dosage which will be possible. An example of functioning metastases in the chest is illustrated in Fig. 3. But here a metastasis in the femur failed to function, although the metastases in the chest took up iodine very well. Repeated doses of radio-iodine will be necessary in the majority of cases, as the treatment is usually a matter of control rather than cure.

Carcinoma of the Bladder

The scope of effective local irradiation to the bladder has been increased by three new methods:

- (1) The intravesical use of radioactive isotopes in solution.
- (2) The use of a very high intensity source of radioactive cobalt, placed centrally in the bladder, within a balloon.
- (3) The implantation of radioactive tantalum wire which can be pulled out later per urethram.

Radioactive Isotopes in Solution

This method gives an entirely new approach; it makes possible the delivery of an evenly distributed radiation over the whole of the bladder mucosa or over a portion of it. The isotope first used was Na_{24} . This has a very short half-life (15 hours) and gives off strong beta and gamma radiations. Bromine (Br_{82}) has proved more suitable. It has a slightly longer life and delivers a relatively higher ratio of gamma to beta radiation and is more penetrating.

As pointed out by Dukes and Masina (1949), the gross characters, histology and extent of spread are the three most important pathological factors in bladder tumours, and the choice of treatment depends upon clinical and pathological considerations. Superficial growths which are confined to the bladder without extending to paravesical fat or adjacent tissues, and particularly the early superficial but rather widespread papillomata, are best suited to treatment by intravesical radioactive solutions. They are too diffuse for interstitial treatment which is limited to small areas, but they are not so deep as to be beyond the range of the radioactive solution. A latex or

FIG. 3.—A case of haemoptysis from metastatic thyroid tumour in the chest. Note heavy concentration of iodine in the right upper mediastinum. Regression of growth and relief of symptoms followed I^{131} therapy. Figures show counts per second.

acrylic bag is inserted in the bladder per urethram in the female or through a perineal stab in the male. It is then filled with radioactive solution, which is allowed to remain in place for an hour or so according to the strength of the solution. Walton (1952) advocates three treatments to give a total of approximately 6,000 r. (maximum) beta radiation and 1,500 r. gamma radiation. The calculation of the dosage is best left to experts. Wallace (1953) reports 58 cases treated by this means with very promising results. Half the bladder can be radiated by using a mixture of liquid paraffin with the aqueous solution of isotope. The liquid paraffin floats to the top, allowing the lower half to be irradiated.

Radioactive Cobalt

This is dangerous in solution on account of its long half-life (5.3 years). It has, however, been used as a high-intensity source of radiation, and this is illustrated in Figs. 4 and 5. In this method

the radio-cobalt has to be accurately centred in the bladder, and a special balloon catheter has been produced for this purpose (Cones and Gregory, 1952).

Tantalum Wire

Tantalum wire in a thin sheath of platinum which is drawn over it can be activated in the atomic pile. It then gives off gamma radiation almost identical with radium. It has a half-life of 120 days. The wire can be introduced into a bladder carcinoma by open cystotomy, in the form of 'hairpins' which are then attached to the catheter by silk threads and withdrawn with the catheter after irradiation is completed. This method is suitable for a lesion which has not infiltrated very far. Deeply infiltrating lesions extending beyond the bladder wall cannot be adequately irradiated excepting by external irradiation, preferably by supervoltage X-rays.

FIGS. 4 and 5.—Central radio-cobalt source used in the treatment of diffuse papillomatosis of the bladder. Balloon filled with radio opaque medium in order to position the radioactive source at the centre. (Photograph by courtesy of Dr. D. M. Cones, Mount Vernon Hospital, Middlesex.)

Malignant Ascites and Malignant Pleural Effusion

Radioactive gold colloid in a solution of gelatin has been used with considerable success in the palliation of malignant effusions. Here the object is to irradiate the malignant process, multitudinous minute papillomata and malignant deposits which may cover the visceral or parietal peritoneum. The Au_{198} gives off beta and gamma radiation, but it is the beta radiation which accounts for most of the irradiated energy, i.e. for most of the dosage. This will penetrate one or two millimeters into the intestinal coat, but it will not penetrate deeply into large masses of growth. There is a tendency for the colloid particles to be absorbed at the surface and ingested by histiocytes (Fig. 6). This will increase the radiation locally and actual dosages are difficult to compute. Essentially this treatment provides us with a useful means of reducing the rate of effusion and between one-third and one-half of all cases treated by this method receive effective palliation for some months (Walter, 1953). Excessive dosage leads to intestinal damage and the formation of a pathological exudate on the surface, which is descriptively referred to as 'sugar icing.' About 100 to 150 millicuries of gold colloid is used at a time and is injected into the peritoneal cavity after preliminary withdrawal of most of the ascitic fluid. It is necessary to

dilute the gold colloid solution with a pint or so of ascitic fluid which is purposely left behind. After injection the patient is placed in different postures to ensure good mixing of the radioactive solution, otherwise the result would be one of local radiation only and dangerous 'high spots' of local radiation would follow, with overdose effects. Measurement of the radioactive distribution by Geiger counter should follow in order to check up the dose and the distribution of the radiation. Considerable success has been reported in palliation of malignant effusions by this method.

Widespread Growths

A few cases have been reported where P_{32} has been of some value in the treatment of widespread malignant tumours of exceptional radiosensitivity, such as multiple myelomata. The rationale is similar to the treatment of thyroid tumours and depends upon a sufficiency of the element being concentrated in the growth. Successes have been very few and far between, and mostly control or palliation is all that can be expected.

Irradiation by Local Injection

Gold colloid and other substances have been used by local injection and infiltration of the tissues; two objects have been in view, viz.:

FIG. 6.—Photomicrograph illustrating fibrinous reaction by the intestinal peritoneum and absorption of colloid gold grains by histiocytes. Treatment by radioactive gold colloid.

- (1) The treatment of local tumours such as carcinoma of the uterine cervix.
- (2) The treatment of lymph glands.

Difficulties are encountered owing to the local infiltration being uneven and uncertain. So far, these measures have not been reported as particularly successful. It has recently been reported that hyaluronidase is useful in gaining an even distribution.

Radioactive Isotopes as a Substitute for Radium and X-rays

Radioactive cobalt, tantalum, iridium and other substances can be used as substitutes for the natural radioactive substances already used in well-established radiotherapy. This is purely a matter of substitution in radiotherapy and does not, as a whole, alter the policy of treatment in the same way as radioactive isotopes given by mouth, by injection and by radioactive solutions in the bladder. Seeds of radioactive gold, sheathed with a thin layer of platinum to filter off the beta radiation, are used instead of radon seeds and have the advantage of being smaller. They can therefore be used very effectively for ocular work and offer particular advantages in the treatment of glioma of the retina and small tumours involving the eye. Radio-strontium is now available as a high-intensity beta-ray source for ocular use or other purposes. The basic principles of radiotherapy are, of course, quite unaltered by the application of radio-isotopes as substitutes for radium and X-ray therapy, and they merely provide convenient or more powerful sources of radiation which offer certain practical advantages.

BIBLIOGRAPHY

- CONES, D. M. T., and GREGORY, C. (1952), *Brit. J. Radiol.*, **25**, 597.
 DUKES, C. E., and MASINA, F. (1948), *Brit. J. Urol.*, **21**, 273.
 FARMER, F. T. (1953), *Proc. Roy. Soc. Med.*, **46**, 235.
 MORLEY, T. P., and JEFFERSON, G. (1952), *Brit. med. J.*, **1**, 575.
 WALLACE, D. M. (1953), *Proc. Roy. Soc. Med.*, **46**, 240.
 WALTON, R. J., and SINCLAIR, W. K. (1952), *Brit. med. Bull.*, **8**, 158.
 WAYNE, E. J., MACGREGOR, A. G., BLOMFIELD, G. W. (1952), *Ibid.*, **8**, 148.
 WALTER, J. (1953), *Proc. Roy. Soc. Med.*, **46**, 466.

CARDIOLOGY

A series of papers reprinted from the Postgraduate Medical Journal,

Price : 3s. 3d., post free

Contents :

The Trend of Cardiology

By William Evans, M.D., D.Sc., F.R.C.P.

Cyanotic Congenital Heart Disease

By James W. Brown, M.D., F.R.C.P.

The Surgical Treatment of Congenital Heart Disease

By O. S. Tubbs, F.R.C.S.

Advances in the Treatment of Heart Disease

By Graham W. Hayward, M.D., F.R.C.P.

Radiology in Cardiac Disease

By G. Simon, M.D., F.F.R.

Angiocardiography

By Frances Gardner, M.D., M.R.C.P.

The Contribution of Venous Catheterization and other Circulatory Techniques to Cardiology

By Professor E. P. Sharpey-Schafer

Phonocardiography

By Aubrey Leatham, M.B.(Cantab.), M.R.C.P.(Lond.).

The Social Welfare of Cardiac Patients

By D. M. Thornton, M.A.(Oxon.), A.M.I.A.

Published by

THE FELLOWSHIP OF POSTGRADUATE MEDICINE

60 Portland Place, London, W.1