What Can Radioisotopes Do for Man?

Medicine and Biology

by Ralph M. Kniseley

This year marks the 40th anniversary of the first use of man-made radioactive isotopes for medical purposes. In 1934, the first working cyclotron at the University of California had produced small amounts of radioactive phosphorus, iodine, and sodium; but widespread applications appeared only after the second world war when nuclear reactors began making large amounts of radioisotopes, and new detectors and electronic equipment emerged for measuring the radiation that they emit.

To exploit isotopes in biology and medicine, workers use the unique properties of radioactive decay, whereby energy is released in the form of nuclear particles such as electrons, or electromagnetic radiations such as gamma rays. Because the emissions can be detected with great sensitivity and measured with precision, harmlessly small quantities can be administered to delineate organs or tumors, or to measure bodily function or cellular metabolic processes. The destructive potential of the emitted energy must always be reckoned with, and the doses kept to a safe, low level. Yet this same energy can be exploited when a destructive effect is desired.

Among the objectives of the International Atomic Energy Agency, as defined in its Statute, is "to accelerate and enlarge ..... the contribution of atomic energy to peace, health, and prosperity throughout the world". It has a Life Sciences Division to foster advances in medical applications, which, when they reach the routine stage, are turned over where possible to its sister UN organization, the World Health Organization. The Agency's activities include awards of research contracts, modest in amount, and fellowships for professionals in developing Member States. In addition it conducts training courses in topics related to the medical applications of radioisotopes and provides technical experts on request from developing Member States.

TRACER USES IN BIOLOGY

Both the modern biologist and the modern physician find radioactive elements to be an indispensible tool in their laboratories, almost as routine as a microscope or a weighing balance.

The biologist uses labeled compounds in experiments that will reveal how and why the cell and its sub-microscopic parts work, or to understand how amino acids, fats, carbohydrates, vitamins, hormones and so on are used in the body. He may use them to learn how drugs control infection, correct a malfunctioning organ, or quench pain. Space will allow us to give only a few examples.

Consider for instance the world-wide increase in recent years of mercury in our environment — in the air, water, and soil. This metal finds uses in paper manufacturing, fungicides, drugs, and a host of other applications. Comparatively, how susceptible are unborn children or the fetuses of domestic animals to its toxic effects? One group of workers recently has provided some answers. After injection of a mercury radioisotope (mercury-203) into pregnant rats, the brains of the fetuses are found to store mercury in significantly higher concentrations than the mother's brain. Mercury hence passes the placental barrier and the risk of brain damage in fetuses is higher than in adults.

Or take tritium (hydrogen-3), the radioactive form of hydrogen. This is widely used as a label in biological studies. The synthesis of DNA, a main chemical process in cell replication, is assayed in terms of the utilization of tritiated thymidine, a precursor of DNA. Radioactive amino acids labeled with tritium or carbon-14 are customary and convenient for measuring protein synthesis.

As another example of the use of radioisotopes in the biology laboratory we might mention the assay of erythropoietin. This substance, which stimulates red cell production, can be extracted from urine, since it is elaborated in the kidneys. It cannot yet be measured by chemical means, but a bioassay in mice is quite routine now with the radioisotope iron-59. A test dose of iron-59 given to mice treated with the specimen to be assayed provides a measure of its erythropoietin content in terms of the iron-59 incorporated into the red blood cells.

Radioactive iron is also widely used in clinical research. The IAEA, in a co-operative programme with WHO, is completing a research project utilizing iron-59 to study a common world-wide nutritional problem, iron deficiency. Foodstuffs, both animal and vegetable, have been grown with radioactive iron to label the food source. This is fed to volunteers on various dietary regimes. The study has revealed that humans apparently can absorb iron more readily from some foods than others. Ways must now be found to increase absorbable dietary iron.

Recently, an effort has been made to discover why certain women taking combination oral contraceptives show decreased glucose tolerance, in other words show signs of diabetes. By giving rats glucose labeled with carbon-14 after treating them with norethyndrol or mestranol, it was found that the norethyndrol appears, of the two drugs, to be the one causing reduced glucose tolerance and a reduced tissue utilization of glucose.

These examples give only a hint of the many ways radioisotopes serve the biologist seeking answers to important questions about life processes.

Activation analysis as a tool in biology also deserves more than a brief mention. The measurement of a number of elements can be carried out by neutron bombardment in a reactor and measuring the emissions of the radioisotopes thereby produced. For instance, the IAEA laboratories at Seibersdorf have access to a reactor and are thus able to provide analytical services with this tool. It is now being applied in a joint WHO/IAEA co-ordinated research programme on trace elements in cardiovascular disease, searching for clues to this widespread health problem.

USES IN CLINICAL DIAGNOSIS

In nearly all medical specialities one finds radiopharmaceuticals of use in one or another diagnostic problem. In some situations the tests in which they are used are screening procedures nearly as routine as a blood count; in other instances they may be supplementary procedures. Here it might be noted it is the labeled compound, and not the radioactive element with which it is labeled, that is usually of interest. For example, when one uses cyancobalamin (vitamin B-12) labeled with a radioisotope of cobalt, one wishes to study not the fate of the cobalt metal but the vitamin.

IN VITRO TESTS

In clinical chemistry, the emergence of *in vitro* tests with radioisotopes is particularly noteworthy, significantly changing the nature of this laboratory sub-discipline. The special attractiveness of such tests is based not only on their great precision and sensitivity, but also on the advantage that the patient himself is not exposed to any radiation. The general procedure, which has many variations, is called by several names. A sample of the patient's blood is withdrawn from a vein and the plasma or serum separated from the blood cells. In the test a measured amount is interacted with a specific binding agent equilibrating with a known quantity of the compound to be measured, labeled with a suitable radioisotope. Depending on the compound to be measured, the specific binding agent used may be a natural protein, a prepared antibody, antigen, enzyme, or reagent. The ratio of bound to unbound radioactivity then provides a means to quantitate the amount of the compound present in the patient's blood plasma.

Consequently, a wide variety of compounds which occur only in small amounts, previously analyzed with great expense and difficulty, are now in reach of many more physicians (Fig.1). Hormones of the thyroid, pituitary, adrenal, and gonads, vitamins, trace elements, and certain drugs, digitoxin for instance, are now all assayed by this method. Because of the fact that the methods are inexpensive they offer great potential for developing countries previously denied access to the more cumbersome methods. In this connection the IAEA through its research contract programme is fostering projects in fifteen countries, with emphasis on intercomparison and standardization of techniques.

IN VIVO TESTS

Radioisotopes have also found their way into many *in vivo* procedures, where the injected radiopharmaceutical is measured in the body of the patient by a variety of detection instruments, or in samples of body fluids and tissues. Customarily, these procedures are classified as one of three main types: a) imaging procedures, b) dynamic studies, c) measurement of compartments and spaces. These of course are at times artificial divisions and in truth do melt into one another.

IMAGING PROCEDURES

Elegant and expensive devices are commercially available to delineate body organs or tissues with a variety of radiopharmaceuticals. Almost every organ or tissue can be visualized, though it must be admitted, not with the fine detail of a radiologic

FIGURE 1. PARTIAL LIST OF SUBSTANCES CURRENTLY MEASURED BY RIA*

Peptide hormones	Non-peptide hormones	Non-hormonal substances
Insulin	Aldosterone	Intrinsic factor
Growth hormone (GH)	Testosterone	Digoxin/Digitoxin
Adrenocorticotrophic hormone (ACTH)	Dihydrotestosterone	Morphine
Parathyroid hormone (PTH)	Oestradiol	Cyclic - adenosine monophosphate (cAMP)
Glucagon	Oestrone	Cyclic - guanosine monophosphate (cGMP)
Thyroid-stimulating hormone (TSH)	Oestriol	Cyclic - inosine 5′ phosphate (cIMP)
Human chorionic gonadotrophin (HCG)	2-Hydroxyoestrone	Cyclic - uridine monophosphate (cUMP)
Follicle-stimulating hormone (FSH)	Prostaglandins	Hepatitis B - antigen (Australia antigen, HBA)
Human chorionic somatomammotrophin (HCS)	Triiodothyronine (T3)	C_1 esterase
Prolactin	Thyroxine (T4)	Fructose 1,6 diphosphatase
Secretin	Progesterone	Carcinoembryonic antigen (CEA)
Luteinizing hormone (LH)	Medroxyprogesterone	Rheumatoid factor
Vasopressin	17-Hydroxyprogesterone	Human immunoglobulin IgG
Angiotensin		Folic acid
Oxytocin		Neurophysin
Bradykinin		Thyroxine-binding globulin (TBG)
Thyroglobulin		
α-Melanocyte-stimulating hormone (α-MSH)		
β-Melanocyte-stimulating hormone (β-MSH)		
Gastrin		
Calcitonin		
C-Peptide		
Pancreozymin-cholecystokinin (PZ-CCK)		

* Partial list of in vitro radioimmunoassay procedures from "Standardization of Radioimmunoassay Procedures", Report of a Panel of Experts of the IAEA in: J. Applied Radiation & Isotopes 25 1974, p. 147.

study. Even the tiny parathyroid and the small, well-hidden adrenal gland have been visualized with special agents, though these have not yet gained a place in common practice.

One main application has been in tumor localization. Depending on the organ in question, one or more radiopharmaceuticals are available which yield, in some cases, a negative or "cold" spot surrounded by the radioactivity in the organ, or a "hot" spot of radioactivity concentrating in the tumor. Brain imaging is virtually routine in any neurological workup, and imaging for cancer which has spread to liver and bone is also a daily procedure in any nuclear medicine laboratory. Of great promise is the emergence of new agents which preferentially are taken up in a variety of cancers. The citrate form of gallium-67 has remarkable affinity for some lymphomatous tumors, especially Hodgkin's disease, and also for lung cancer **(Fig.2)**. Better agents and refined instruments are still needed and most likely will appear in the coming years.

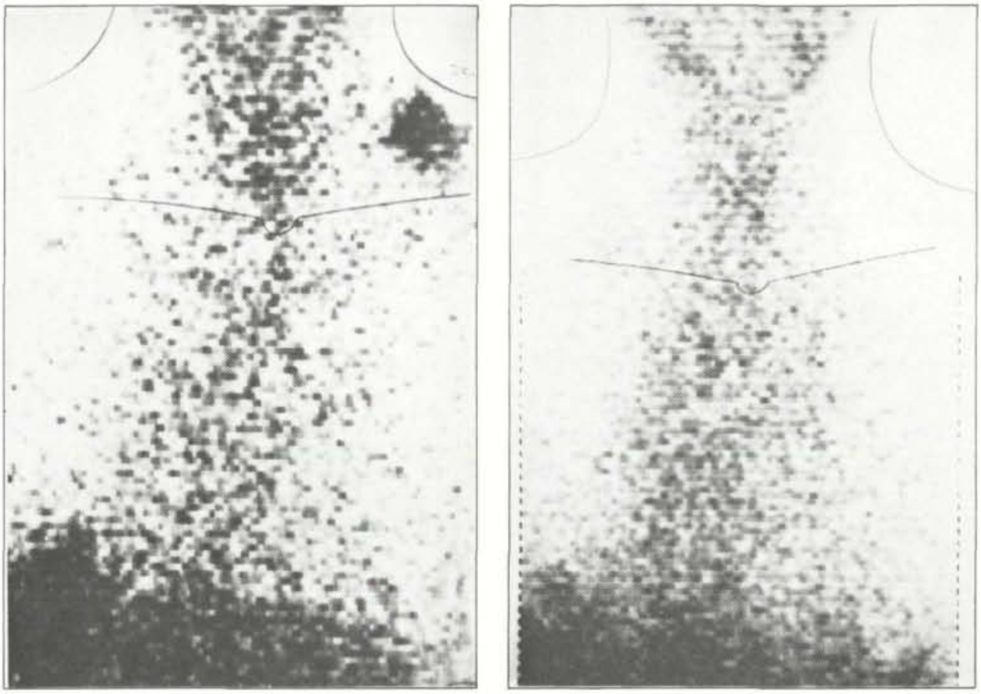
Great interest and work is focused on the use of computers in imaging procedures, to collect and store the data and also to process it for the optimum display of the image. A number of institutions have research agreements with the Agency to make intercomparisons on computer-assisted scintigraphic techniques, the Agency serving in a co-ordinating function.

DYNAMIC STUDIES

This class of procedures embraces many quite diverse types of studies, having in common the time-related patterns of uptake, metabolism, clearance, or excretion of administered radiopharmaceuticals. The function of an organ, or the flow of blood to a region, or the metabolic conversion of a labeled test compound are quantitated in the context of seconds, minutes, or even days. For example, the flow of blood through the heart or lungs occurs in seconds, the function of kidney or liver is assessed over minutes, while the turnover of calcium in bone disorders is observed over a span of days. Here, as in imaging procedures, the assistance of the computer is becoming inextricably entwined as part of the data storage, analysis, and display systems.

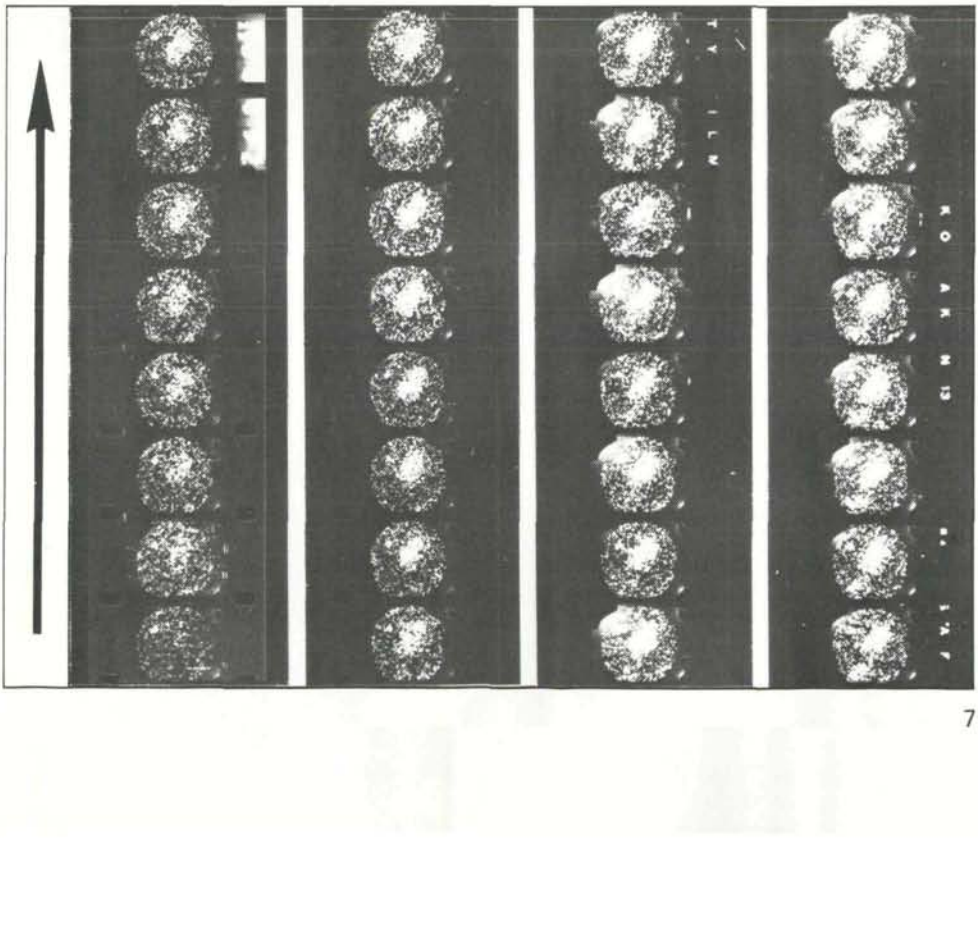
As one new trend, kidney transplants are an increasingly common procedure for persons suffering from irreversible renal failure. Unfortunately, a variety of complications such as thrombosis of a transplanted vessel, leaking of the urine, or rejection of the foreign tissue by the host's immune system can beset the patient. The injection of a radiopharmaceutical labeled with technetium-99m or iodine-131 gives us a safe and inexpensive method for monitoring the new kidney's function, not only in the post-operative period but in later months. In this instance a scintillation camera can provide sequential images, which can also be interpreted along with the numerical data collected during the 30 - 45 minute time course of the study **(Fig.3)**.

In July the Agency sponsored its second Symposium on Dynamic Clinical Studies in Knoxville, USA, bringing together workers in the field from many parts of the globe. (A report could not be included in time for this Bulletin.) The first Symposium was held in 1970 in Rotterdam, Netherlands.



Gallium-67 scans before (left) and after (right) deep X-ray therapy to the left neck region in a patient with Hodgkin's disease.

Fundtional study of a renal transplant as recorded on motion picture film.



COMPARTMENTS AND SPACES

The use of radioisotopes has made a great advance possible in understanding the various so-called compartments, pools, or spaces in the body. These are conceptual terms, rather than simple anatomically defined boundaries. They are a way of describing the amount of water, electrolytes, protein, and other substances which are equilibrates among the intravascular, extravascular, and intracellular sites of the body. With a variety of radioisotopes of normally occurring elements as well as labeled compounds one can measure the size of these so-called spaces by means of the dilution principle. For instance, if a patient has lost a significant amount of blood by hemorrhage, or is being prepared for major surgery, a knowledge of the red blood cell volume may greatly assist in the scientific management of the patient. The usual blood values of hemoglobin, red cell count, and packed cell volume may mislead in estimating the total amount of red cells within a patient's circulatory system. A small sample of the patient's own red cells are labeled with chromium-51 and a precisely measured quantity is re-injected. The physician then can calculate, on the basis of the radioactivity in the blood a few minutes after complete mixing of the labeled cells within it, the total size of the circulating red cell pool. Using this same dilution principle, doctors can measure the sodium and potassium spaces, intracellular water and other substances.

USE OF LARGE RADIATION SOURCES IN BIOMEDICAL PRACTICE

The destructive or killing effect of large doses of radiation is a great resource to the cancer therapist. Radioisotopes provide basic tools widely used in addition to the more conventional X-ray machines and radium sources. Cobalt-60, with high-energy gamma emissions, and a long half-life, is the most usual radioisotope for beam therapy; large sources of several thousand curies activity can be housed in a lead shield. To obtain a beam of the required shape and size for a certain tumor, the radiotherapist selects an appropriate collimator from an array, and aims it at the patient's tumor for the number of minutes calculated to give the correct daily fraction of a total treatment dose. Since precise doses are a life and death matter, the IAEA has several programme components to assist institutions in Member States on this aspect of radiation therapy **(Fig.4)**. In co-operation with WHO it offers an intercomparison service to check and improve the accuracy of radiation dosimetry, thereby increasing the effectiveness of radiotherapy. As an outgrowth of this effort Secondary Standards Dosimetry Laboratories are being set up in regions or countries to take over this task eventually. Hope continues also for further improvement in radiation cures of cancer; research in radiation biology suggests that the radiosensitivity of cancer can be enhanced by several approaches.

Radioactive needles or capsules, called brachytherapy devices, can be inserted directly into tumors for specified periods to destroy or control certain cancers, for example uterine cervical cancer, or cancer of the head and neck. In selected cases these have advantages over external beam therapy, sparing sensitive normal tissues that would lie in the pathway of the beam.

The use of radioactive medicines either ingested or injected was earlier thought to have great potential for cancer therapy. Physicians hoped that many radioactive substances might be found which would concentrate in specific tumors, yet not remain in other

FIGURE 4
REGIONAL AND INTERREGIONAL SHORT-TERM TRAINING PROJECTS*

Project	Place and dates	Total number of participants	Source of funds
Interregional training course on the use of radio-isotopes and radiation in entomology	Gainesville, Florida United States 2 July to 24 August 1973	18	Regular programme and the United States
Interregional training course on the use of tracer techniques in industry and environmental pollution studies	Raleigh, North Carolina, United States 9 July to 3 August 1973	21	Regular programme and the United States
International training course on the theoretical principles and practical techniques of isotope hydrology	Heidelberg, Federal Republic of Germany 14 August to 14 December 1973	8	Regular programme and the Federal Republic of Germany
Study tour on radiation dosimetry in medicine and biology	Soviet Union 20 August to 14 September 1973	28	Regular programme
Interregional training course on the maintenance and repair of nuclear electronic equipment	Turin, Italy 3 September to 30 November 1973	15	UNDP
Interregional training course on the use of nuclear techniques in animal parasitology and immunology	Zemun, Yugoslavia 1 to 26 October 1973	20	SIDA
Regional seminar on the use of isotope techniques in water resources inventory, planning and development	Mexico City 12 to 23 November 1973	27	UNDP

* Figure 4: from IAEA Division of Life Sciences 1973-4 Annual Report.

FIGURE 4 cont.

Project	Place and dates	Total number of participants	Source of funds
Regional survey and briefing course on the technical and economic aspects of nuclear power projects	Bangkok 3 to 18 December 1973	37	UNDP
Interregional training course on the use of isotopes and radiation techniques in research on soil-plant relationships	New Delhi 4 March to 26 April 1974	13	SIDA
Study tour on the utilization of nuclear research reactors	Democratic Republic of Germany and the Soviet Union 13 May to 11 June 1974	..	Regular programme

vital normal tissues. The enthusiasm based on the beneficial effect noted with iodine-131 (which has had great success in controlling hyperactive thyroid glands and certain functioning thyroid cancers) has been unfounded. In special instances phosphorus-32 has been effective, particularly in the treatment of polycythemia vera and some leukemias; for a time people injected gold-198 into body cavities or certain cancers as a palliative measure. But no other major significant advances in cancer therapy by radioactive drugs have yet emerged.

The killing effect of ionizing radiation has come to be a tool in other aspects of medicine, indirectly related to the patient.

For instance, many medical products can be sterilized by irradiation in specially designed equipment rather than by autoclave or gas. The IAEA has been active in fostering this development and has elaborated a recommended code of practice, and also has published a working manual on the topic.

Similarly, radiation provides an alternate way of attenuating certain pathogenic micro-organisms, particularly parasites. The application of heat or chemicals at times alters the immunizing capacity of some microbes, while radiation does not. Current research work supported jointly by WHO and the IAEA is being extended to parasitic infestations of major importance, hoping to produce effective vaccines which will protect against these debilitating and sometimes fatal infestations.

Another potential application, only superficially explored till now, is the high-level radiation treatment of sewage to render water polluted with pathogens sufficiently safe for re-use in agricultural irrigation. Many technical questions must be answered before this novel idea is proven to be feasible.

In summary, radioisotopes have been a valuable gift to many branches of medicine and biology. Many fundamental questions about the nature of life and human disease are being answered with this tool. The technological advances in computer science and electronics interlaced with newly developed radioactive substances are changing the face of modern medical diagnosis. With the growing number of radiotherapy machines more cancer victims have access to improved management of their disease. There is a basis of hope that further major improvements in radiation therapy may come from research in radiation biology, for instance by increasing radiosensitivity, but a cancer killing "atomic cocktail" is remote and unrealistic at present.

References

Fig. 2. from McCready et al. in: Vol. II, Medical Radioisotope Scintigraphy (1973) p. 578. Proceedings of an IAEA Symposium.

Fig. 3. from Rejali et al. in: Dynamic Studies with Radioisotopes in Medicine (1970) p. 116. Proceedings of an IAEA Symposium.

The Growing Need for Analytical Quality Control

by O. Suschny and D.M. Richman

Technological development in a country is directly dependent upon its analytical chemistry or measurement capability, because it is impossible to achieve any level of technological sophistication without the ability to measure. Measurement capability is needed to determine both technological competence and technological consequence. But measurement itself is insufficient. There must be a standard or a reference for comparison. In the complicated world of chemistry the need for reference materials grows with successful technological development.

The International Atomic Energy Agency has been distributing calibrated radioisotope solutions, standard reference materials and intercomparison materials since the early 1960's. The purpose of this activity has been to help laboratories in its Member States to assess and, if necessary, to improve the reliability of their analytical work. The value and continued need of this service has been demonstrated by the results of many intercomparisons which proved that without continuing analytical quality control activities, adequate reliability of analytical data could not be taken for granted.

Analytical chemistry, lacking the glamour of other aspects of the physical sciences, has not attracted the attention it deserves, but in terms of practical importance, it warrants high priority in any developing technological scheme, because without it there is little chance to evaluate