radio-pharmaceuticals

Radioisotopes are being used to an ever-increasing extent in medicine for diagnosis and therapy. In this contributed article, Walter Wolf, of the School of Pharmacy, University of Southern California, Los Angeles, USA, and Alexandru T. Balaban, formerly a senior research officer in the IAEA Division of Research and Laboratories and now working in the chemistry section of the Institute of Atomic Physics, Bucharest, Romania, discuss some applications, and consider possible developments.

A labelled compound is a substance in which the natural isotopic abundance of any of its constituent elements has been altered purposefully. This definition includes compounds labelled with radioactive as well as stable nuclides. Radioactively labelled compounds include preparations suitable for human administration, which are known as radiopharmaceuticals. Such preparations fall within the scope of the World Health Organizations's definition of a drug — "any substance or mixture of substances manufactured, sold, offered for sale or represented for use in:

treatment, mitigation, prevention or diagnosis of disease, abnormal physical state or the symptoms thereof in man or animal;

restoring, correcting or modifying organic functions in man or animal." They must, therefore, satisfy stringent requirements with respect to purity, sterility, apyrogenicity and so on.

Radioactive labelling can be achieved by replacing a certain proportion of the stable atoms of an element with a radioisotope, for example as in ^{131}I-hippuran, in which some of the ^{127}I atoms have been replaced by the radioactive isotope ^{131}I ("isotopic labelling"); or a radionuclide can be attached to a molecule such as albumin, to form a new radioactive material, for example ^{99m}Tc-albumin ("foreign labelling").

The forms of use

The applications of radiopharmaceuticals in nuclear medicine fall into four categories: organ visualization studies; dynamic studies; metabolic studies; and therapy. The rationale for the use of radiopharmaceuticals in such procedures derives from three characteristic features of their application — their sensitivity, their selectivity, and the ability they give to "visualize" organs. Thus, when we scan a thyroid, we not only delineate (visualize) the organ; we are also able to identify any abnormalities in it such as cold or hot nodules, that is, zones in which pathology has modified a part of the organ so as to delineate a decrease or an increase in the localization of the specific radiopharmaceutical used. Such information is most useful in diagnosis.

When, in 1946, the Oak Ridge National Laboratory made its first shipment of ^{14}C to the Free Skin Cancer Clinic in St. Louis, Missouri, USA, this event marked the formal beginning of the use of labelled compounds in the diagnosis, investigation and treatment of human diseases. Progress has been extraordinary in the 24 intervening years.

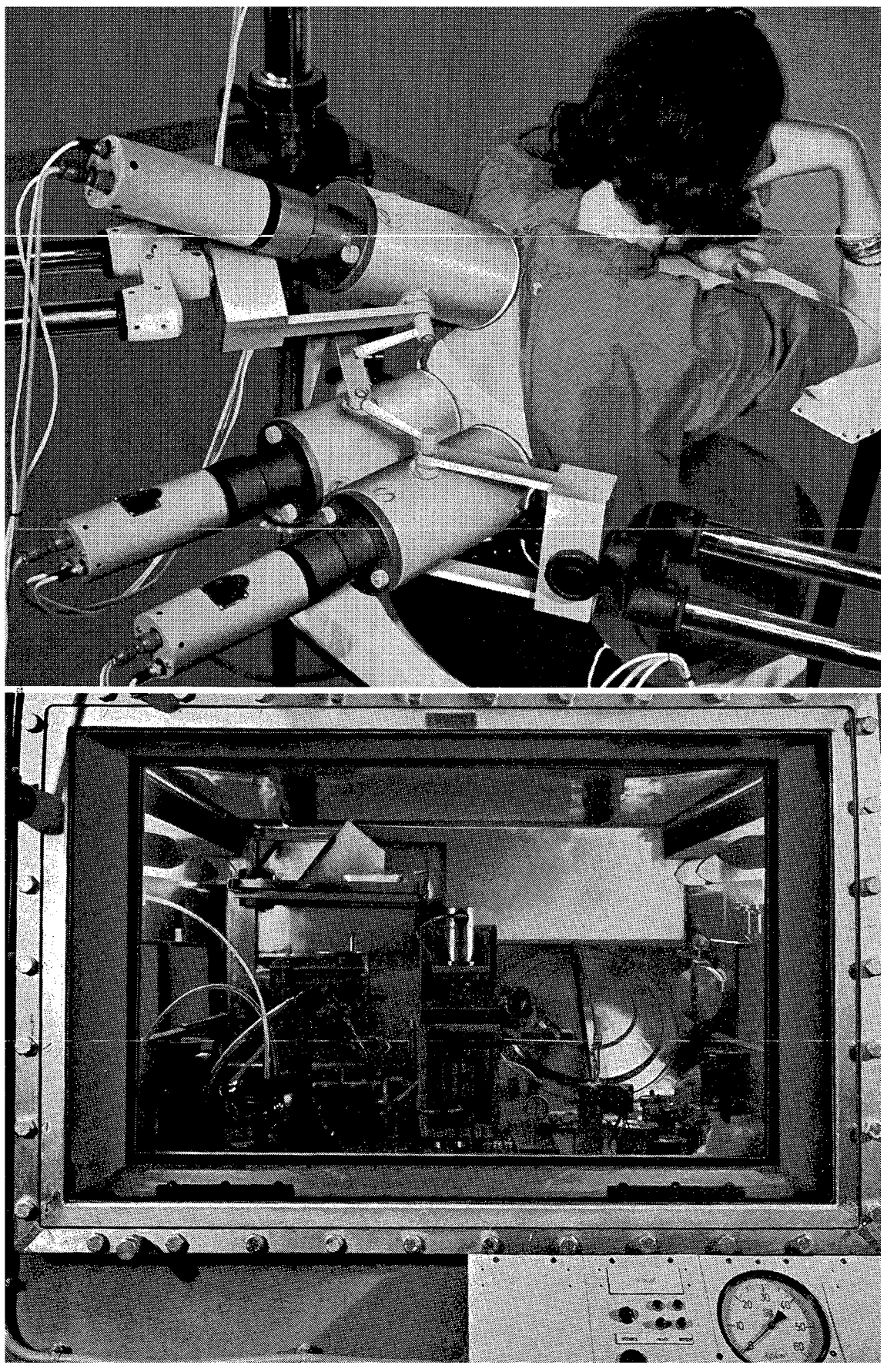
Many of the radiopharmaceuticals first developed were compounds labelled with ^{131}I. This particular radionuclide has a number of substantial advantages. Compounds labelled with it can readily be prepared in large quantities. It is inexpensive, it can be handled easily, and its half-life (8.04 days) is long enough for a manufacturer of radiopharmaceuticals to prepare a labelled compound and deliver it in a pharmaceutically and otherwise acceptable form to a nuclear medicine unit. It emits both beta and gamma rays, its gamma rays making it suitable for use in visualization studies (scanning) and its beta rays for therapeutic purposes.

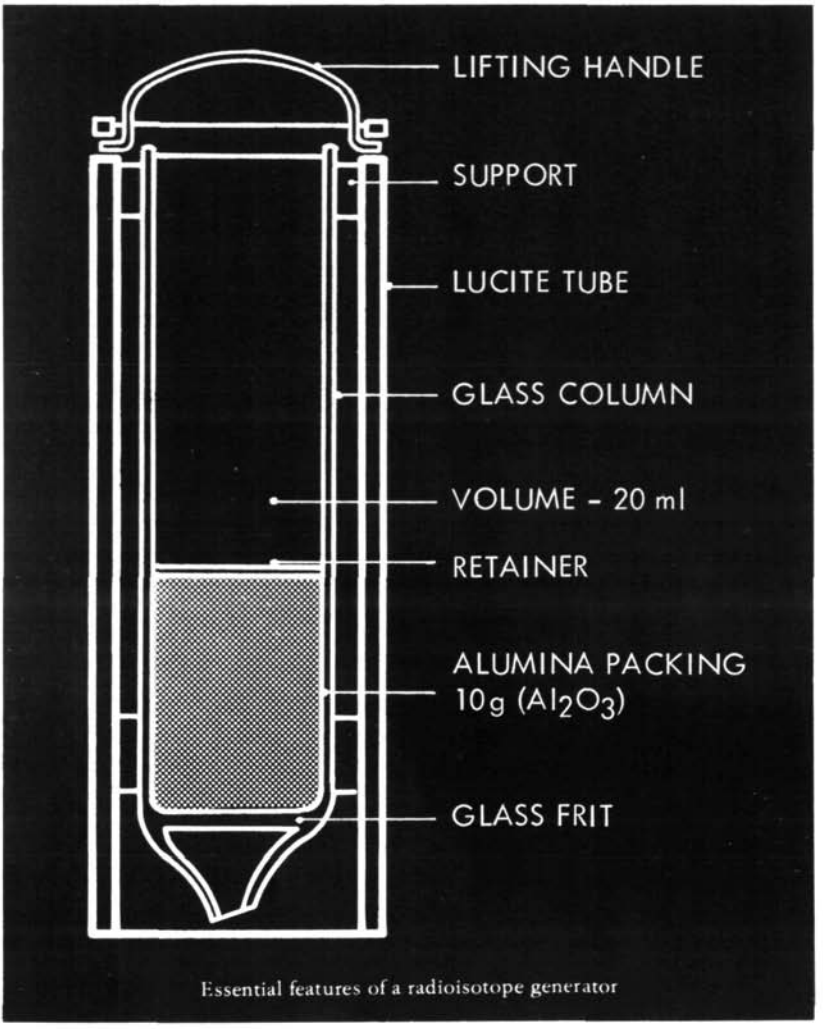
But the radiopharmaceutical selected is only one feature of any procedure in nuclear medicine. To provide optimum service to the patient, we need an ideal conjunction of three factors: instrumentation, radiopharmaceuticals and personnel — the nuclear medicine triangle.

Rectilinear scanners, using sodium iodide crystal scintillation detectors, work very well with ^{131}I, but a scan may take from 20 to 40 minutes, depending on the size of the organ and the amount of radioactivity administered. An important development was that of the Anger camera, an instrument incorporating a large (10 to 12 inch diameter) thin crystal with multiple phototubes, which allows for the imaging of an entire organ in a short time and also allows for the performance of dynamic studies. The thin crystal, necessary for good resolution, is most efficient at gamma energies of 150 keV, and is considerably less sensitive at the 364 keV of the principal ^{131}I gamma photon. Furthermore, most procedures in nuclear medicine require from a few minutes to 24 hours for completion; the use of a compound labelled with ^{131}I often results

Apparatus used in one English hospital in studies of kidney function. Detectors are placed one over each kidney and one over the heart. The patient is then given an intravenous injection of ^{131}I-labelled hippuran; the output of the detectors is used to prepare a graph, or renogram, representing the amount of radioactivity in each kidney and in the blood passing through the heart plotted against time. Photo: UKAEA

A view of equipment used in the preparation of the radioisotope caesium-137 at the Saclay nuclear research centre, France. Photo: Commissariat à l'Energie Atomique/Sudre





Essential features of a radioisotope generator

in a radiation dose to the patient greater than is necessary for a given procedure.

The radioisotope cow

Recognition of these factors has led to efforts to reduce the dose received by the patient. One of the most successful solutions has been the use of radionuclides with a shorter half-life, such as ^{99m}Tc which has a half-life of six hours. This radionuclide has two added advantages: it behaves chemically as a pseudo-halogen, hence the techniques developed for iodine-labelled compounds can be extended, by and large, to compounds labelled with technetium; and it emits gamma rays with an energy of 140 keV, very near to the optimum for the Anger camera. This has led to a tremendous use of this radionuclide.

While most radionuclides are obtained from target bombardment in either a reactor or a cyclotron, a small number of them are "daughters" of longer-lived radionuclides. The daughter can be obtained from the

"parent" in a system called a generator, such as that illustrated in the figure. The longer-lived radionuclide, in this case ^{99}Mo, is loaded to the column and absorbed on a binding agent in such a way that an eluant solution will dissolve only the daughter radionuclide — not the parent. Such a generator is also called a "cow" because elution mimics "milking the cow." The advantage of such a system is that fresh, very high specific activity radionuclides can be obtained in the hospital repeatedly, for as long as the generator lasts.

The use of such generator systems has increased significantly since their introduction in the 1960s. The full impact of such developments, and what we can see of future developments, is demanding some reappraisal of the different elements composing the nuclear medicine triangle. While in earlier times it was perfectly feasible for most radiopharmaceutical companies to manufacture, verify the purity of and deliver a radiopharmaceutical to any department of nuclear medicine anywhere in the world, the present emphasis on short-lived radionuclides has decreased this ability and has increased the demand for *in situ* preparation and quality control of radiopharmaceuticals. It has become increasingly difficult to prepare compounds labelled with a short-lived radionuclide such as ^{99m}Tc and to deliver it to the customer when and where he needs it. Such commercial operations are limited to very local distribution. Among attempts which have been made to circumvent this problem is the development of "kits" for the in-house production of radiopharmaceuticals. While this approach has been reasonably successful, its main limitation is that the kits are expensive and, most of all, the quality control of the finished product is limited.

Functions of the Radiopharmacist

A different approach has been the development of a new profession, that of the radiopharmacist. Such a person is required, as a part of the nuclear medicine team, to fulfill the following functions:

Responsibility for preparation and administration of radiopharmaceuticals:

(a) Synthesis of radiopharmaceuticals;
(b) Compounding and dispensing radiopharmaceuticals;
(c) Advising on dosage form and incompatibilities;
(d) Overseeing radiation safety procedures;
(e) Improving and maintaining radioisotope facilities;
(f) Handling legal and pharmacopoeial aspects of radiopharmaceuticals.

Involvement in research and development:

(a) Improving existing preparative and dispensing techniques;
(b) Studying syntheses and metabolism of new radiopharmaceuticals;
(c) Assisting with research involving labelled compounds.

Participation in teaching:

(a) Educating the patient;
(b) Training nurses and technicians;
(c) Lecturing to interns and residents;
(d) Instructing pharmacists in radiopharmacy.

And the future?

It seems probable that the years to come will be characterized by the use of radionuclides of shorter and shorter half-lives, and will see small cyclotrons and neutron sources in hospitals generating radionuclides almost at the patient's bedside. Among the radionuclides whose importance will increase considerably are ^{11}C (half-life 20 minutes), ^{13}N (half-life nine minutes), ^{18}F (half-life 108 minutes) and ^{123}I (half-life 13 hours).

Perhaps it would be sensible at this time to recall that for the use of such nuclides a team effort is necessary. For example, ^{11}C, with its half-life of only 20 minutes, must be produced in a cyclotron in high yields and released from the target in an acceptable chemical form — for example, $^{11}CO_2$. The radiochemist or radiopharmacist must then take this gas and make another compound, such as ^{11}C-benzoic acid, whose radiochemical, radionuclidic, chemical and pharmaceutical purities have to be controlled; and the certified product must then be delivered to the physician for administration to the patient for use, for example, in kidney studies. The time between production of this radionuclide and use must be as little as one hour.

Another development to be expected is the synthesis of new types of radiopharmaceuticals, related to a greater extent to physiological functions. The use of ^{11}C and ^{13}N will certainly be helpful in this regard, and the development of biochemicals labelled with short-lived radionuclides (for low radiation dose) for metabolic functional studies or studies in clinical pharmacology may usher us into a whole new era of nuclear medicine.

All of these developments require a careful appreciation of the relationship illustrated by the nuclear medicine triangle: instrumentation, radiopharmaceuticals and the professionals. It demands, especially of the latter, a very substantial team effort. There must be close cooperation between the members of the nuclear medicine team — the physician, the radiopharmacist and the technician and, in a more extended sense, the radiochemist, the nuclear engineer and the nuclear physicist.

Such new developments will obviously require new concepts, and it is at this point that the roles of the national and international agencies become most significant. Agencies such as the national atomic energy commissions and the public health services occupy key positions in such work.

The activities of IAEA

Commonly, one of the first and most rewarding activities of a newly-commissioned research reactor is the production of radioisotopes and their incorporation into radiopharmaceuticals. To encourage developing countries in this connection, the IAEA has organized regional study group meetings on radioisotope production (at Lucas Heights, Australia, in 1968 for the Far East, and at São Paulo, Brazil, in 1969 for Latin America), and has published technical reports on this topic. The emphasis was placed first on production, and more recently on quality control. A *Manual of Radioisotope Production* published by the IAEA in

1966 included recipes only for 15 reactor-produced radioisotopes; an expanded and up-to-date version, *Radioisotope Production and Quality Control,* which is to appear early this year, is to contain recipes for 22 radioisotopes produced by use of a reactor and, in addition, chapters and recipes on special techniques (sealed sources, production of radioisotopes by secondary nuclear reactions and by Szilard-Chalmers effects), radioisotope generators, accelerator-produced radioisotopes, labelled compounds and radiopharmaceuticals.

The first IAEA meeting to deal explicitly with radiopharmaceuticals was held in Vienna in July, 1969. This panel, and the ensuing monograph *Analytical Control of Radiopharmaceuticals,* made specific proposals on the role of international organizations in the subject field, and on the organization of centres for control of purity in laboratories producing radiopharmaceuticals. With the shift towards shorter-lived radionuclides, a part of the production and quality control must be done in medical units. To review the problems connected with such radioisotopes, derived from longer-lived "parent" radionuclides, a panel was held in Vienna in May 1970 to consider the preparation and control of radiopharmaceuticals from generator-produced radionuclides in medical radioisotope laboratories. In 1971 another panel is to be held to assess the preparation of compounds labelled with accelerator-produced radionuclides.

To assist in the dissemination of specialist information in developing countries, a regional demonstration course on radiopharmaceuticals was held in October 1970 in Trombay, India, for the Far East. In November-December this year an inter-regional training course on the production and quality control of radiopharmaceuticals is to be held in Prague, Czechoslovakia; further regional training courses are contemplated.

A coordinated research programme on radiopharmaceuticals was initiated in 1970 jointly by the Chemistry Section of the IAEA Division of Research and Laboratories and by the Medical Applications Section of the Division of Life Sciences. During 1971, this coordinated research programme aims at devising rapid methods for the purity control of radiopharmaceuticals incorporating radioisotopes derived from a "parent-daughter" nuclear sequence.

All of these activities are being undertaken in close collaboration with the World Health Organization. The results of the coordinated research programme referred to above, together with those of investigations carried out at the Agency's laboratories at Seibersdorf, near Vienna, on related topics are being made available to WHO; it has been agreed that, within this framework, the Agency will provide technical information to WHO and that that organization will draft specifications on radiopharmaceuticals for inclusion in the International Pharmacopoeia published by it. Monographs on most of the major radiopharmaceuticals have been already or are being drafted, constituting useful guidelines for national or multi-national pharmacopoeias which may have the force of law.