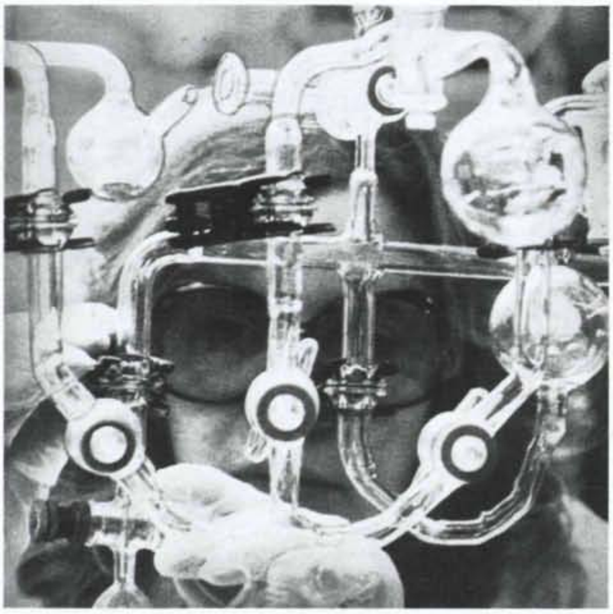
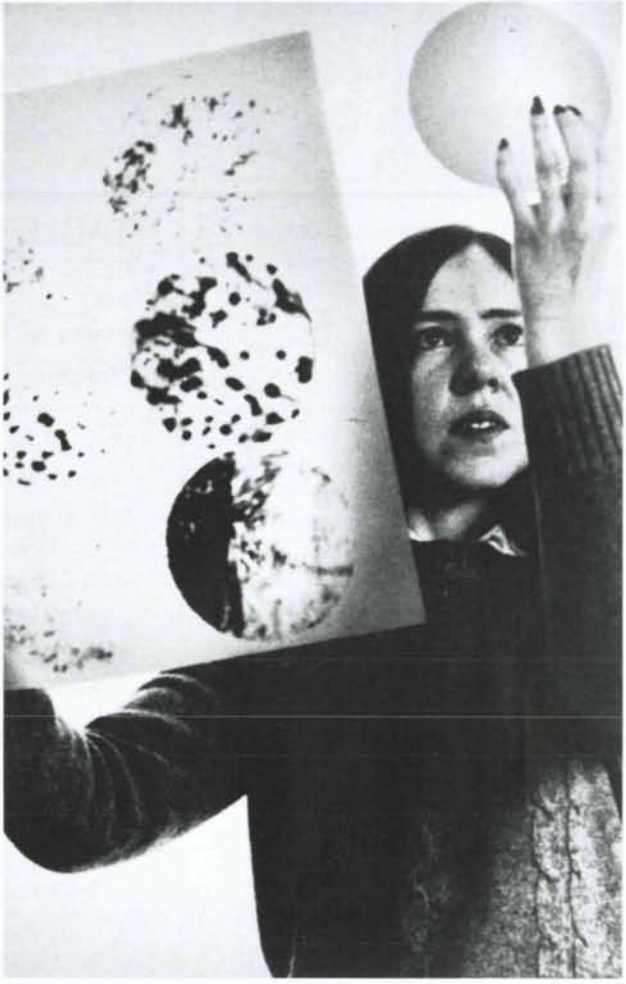
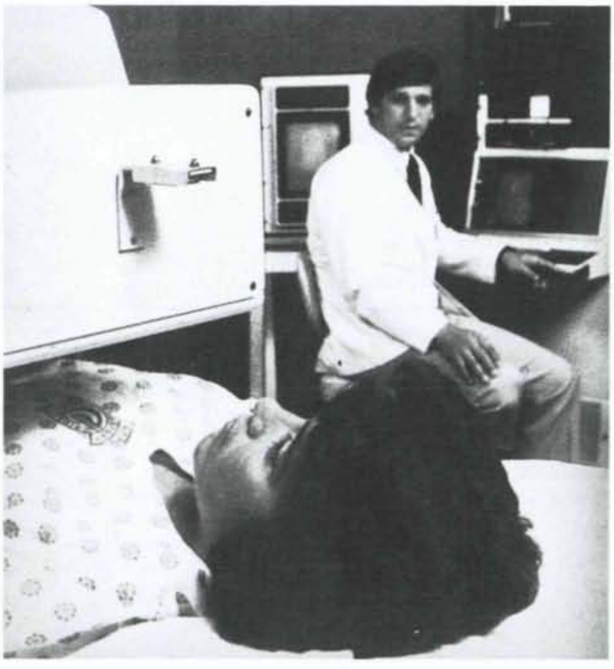
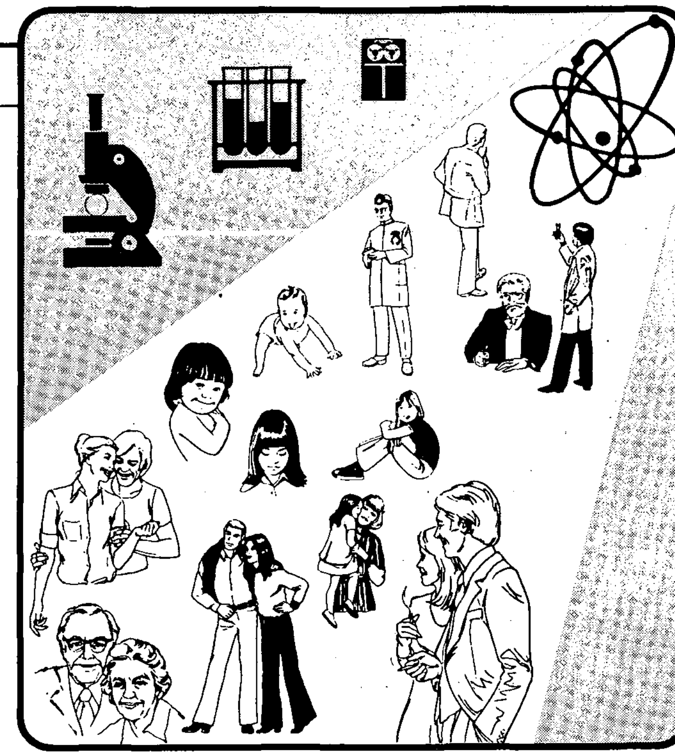






Nuclear medicine procedures and tools play a vital role in health care and medical research, but not all countries have been able to benefit. Efforts of IAEA, WHO, and other organizations are aimed at helping developing countries to overcome problems in setting up nuclear medicine units in more of their own hospitals and laboratories. Shown here (from top left) is a medical researcher in radiopharmaceuticals; a hospital technician performing radioimmunoassay tests in the laboratory; nuclear imaging; and a cancer researcher analysing an autoradiogram, whose black areas show radioactive DNA (deoxyribonucleic acid) fragments. (Credit: NEN)



Promoting nuclear medicine in developing countries

An overview of the field and IAEA's role

by Ramanik Ganatra and Mohamed Nofal

Nuclear medicine, as described in a technical report of the World Health Organization (WHO), covers all applications of unsealed radioactive materials in diagnosis and treatment of diseases or in medical research. It includes not only *in vivo* diagnostic procedures, but also radioimmunoassay (RIA) and related *in vitro* procedures.

In medical research, applications of radionuclides are too numerous to be included comfortably in such a definition of a basically clinical discipline of medicine. A comprehensive term, such as "medical applications", often is used to combine the clinical and several research-oriented applications of radionuclides. A distinction is thereby made between two types of medical applications of radionuclides: (1) where they relate directly to the care of the patient; and (2) where they help in understanding the nature of the disease. In actual practice, a large part of nuclear medicine is diagnostic in nature.

Although radionuclides were used in medicine before World War II, a variety of them only became widely available for medical purposes later, when newly built reactors started producing radionuclides in adequate quantities. In a way, it can be said that the medical profession was introduced to the monstrosity of atomic energy first and then only gradually realized the mitigating medical benefits of the monster. The primal driving force in nuclear medicine development was not its impact on health care, but a desire to look for more and more that could be done with atomic energy — for as many tales of good deeds as possible, as if looking for that elusive other side of the coin.

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Nuclear medicine applications

Whatever its evolutionary path, nuclear medicine has grown in about 40 years to such an extent that there is not a single clinical speciality that has not gained by one or another medical application of a radionuclide.

A diagnostic application of nuclear medicine has three facets: (1) a clinical problem; (2) a radiopharmaceutical that is administered to the patient; and (3) an instrument that is used to detect radioactivity either externally *in vivo*, or *in vitro* in blood, urine, or cerebrospinal fluid. In a purely *in vitro* procedure, no radioactivity is administered to the patient but a radiolabelled substance is added to a clinical specimen, such as blood, in a test tube.

Below are four major categories of the applications of nuclear medicine. Note that only one example is given for each classification, since a full listing for each would be very extensive.

- *In vivo* external detection of radioactivity after internal administration of a radionuclide. This includes (1) imaging of organs — for example, liver imaging; and (2) non-imaging functional studies — for example, renogram, which is a graphical description of the course of a renal excretion of a radioactively labelled substance.
- *In vitro* measurement of radioactivity in a clinical eluate after internal administration of a radionuclide. This includes (1) absorption studies — for example, vitamin B-12 absorption; (2) studies of body composition — for example, total body water; (3) metabolic studies — protein turnover; and (4) hematological applications — for example, red blood cell survival.
- *In vitro* assays where no radioactivity is administered to the patient — for example, radioimmunoassays (RIAs) of hormones.
- Radioisotope therapy — for example, radioiodine for thyroid cancer.

A basic concept underlying all these diagnostic investigations is that radioisotopes are used as tracers in all of them. They are trying to trace some physiological phenomenon by behaving in a way that is indistinguishable from a natural physiological substance in the body. The radioisotopes are like spies tracing biological events in the body. A camouflaged radiolabelled tracer relays information about what is happening in the body at different points of space and time. The emissions from radioactive substances can be detected by highly sensitive and precise modern electronic machines. One can thus trace quantity (how much, as in thyroid uptake), volume (as in blood volume), rate (as in renogram) or mode of a biological reaction (as in biochemical applications).

Some special consideration may be given to two investigations that dominate all others, namely imaging and radioimmunoassays (RIAs). (See accompanying boxes.)

The relevance to medical care

As nuclear medicine is primarily diagnostic, its reputation is based mainly on its all-pervasive and non-invasive characteristics. A set of basic instruments can serve the needs of various disciplines, unlike, for example, the electro-encephalogram that would help only neurologists and no one else. These techniques, although sensitive, may not be always specific. They may not establish a diagnosis but may exclude several possibilities, thereby eliminating the need for many other costly investigations — for example, the presence of a space-occupying lesion in a brain image does not establish the nature of the lesion. It would, in fact, necessitate a number of other investigations to arrive at an unequivocal diagnosis. On the other hand, a negative brain scan will exclude the possibilitiy of a space-occupying lesion, making it unnecessary to do further neurological investigations, which are liable to be expensive and occasionally traumatic.

Let us visualize from this perspective the utility of current nuclear medicine procedures:

- Procedures that help establish a positive specific diagnosis — for example, thyroid function tests.
- Procedures that may exclude diagnosis of a particular nature — for example, scintigraphy for space-occupying lesions.
- Procedures helpful in follow-up of patients — for example, nuclear cardiology. Once a positive diagnosis is reached and a definite therapy given, the non-invasive character of radionuclidic procedures make them eminently suitable for the follow-up of patients.

Nuclear medicine in developing countries

Nuclear medicine developed as a spin-off from the overall growth of nuclear technology. As a result its present techniques have evolved in advanced countries that had the resources to develop instrumentation and the requisite radiopharmaceuticals. A variety of instrumentation is now readily available from commercial sources. Radiopharmaceuticals also are available in forms that can be supplied to different countries from a few international sources.

Nuclear medicine can no longer be considered an esoteric and exotic discipline of medicine. A variety of medical applications of radionuclides have established that it has the ability to save lives, restore health, predict the cause of disease, and alleviate suffering. There is no branch of medicine that has not felt the impact of nuclear medicine techniques in some way or other. This multidisciplinary spread in the medical uses of radionuclides makes it desirable that adequate facilities are provided for nuclear medicine in the overall plan for health care of a developing country, wherever a proper infrastructure exists for the practice of nuclear medicine.

Developing countries do face several problems in setting up nuclear medicine in their milieu. To be viable as a medical service in a hospital, the nuclear medicine unit should have a wide repertoire of tests, should cater to a large number of patients referred to it from diverse clinical disciplines, and should be able to provide sensitive and specific answers to a large number of diagnostic questions in a non-invasive way.

This kind of service needs sophisticated equipment, regular uninterrupted supply of radiopharmaceuticals, and, above all, trained staff. All these are not readily available in developing countries. Equipment is costly and difficult to maintain for optimum performance. Radiopharmaceuticals have to be imported from abroad and their supply is capricious for a variety of reasons. Personnel usually are trained in developed countries but find it difficult to work under local conditions after their return to the homeland. Radioimmunoassays are relatively simple *in vitro* procedures requiring inexpensive instruments, but here, too, to maintain precision and quality for a large number of samples for a variety of assays is often beyond the means of hospitals in the Third World.

Frequency of procedures

The frequency of nuclear medicine procedures in the United States is currently reported to be 33 per 1000 population per year.* This must be far higher than the frequency prevalent in the developing countries.

Although no direct estimates are available for nuclear medicine, one may consider the situation somewhat analogous to that of radiological examinations. In the world as a whole there is one X-ray machine per 5000 inhabitants, but in the developing countries of Africa and Southeast Asia there is only one machine per 60 000 or 100 000 population. There is a reported frequency of 1000 radiological investigations per 1000 population per year in advanced countries against an

* See "Trends and utilization of medicine in the United States", by F. Mettler, A. Williams *et al.*, *Journal of Nuclear Medicine*, 26, 201 (1985).

average frequency of less than 10 examinations per 1000 population per year in the developing countries, reports Mr N. Racoveanu of the World Health Organization's Radiation Medicine Section. As far as nuclear medicine is concerned the situation could not in any way be better. The comparable ratios for nuclear medicine may be far worse than that for radiology.

Ways and means of IAEA's support

The IAEA's present efforts in the field of nuclear medicine are directed towards helping developing countries to set up nuclear medicine capabilities in their hospitals. This is part of the Agency's major goal related to transplanting technology from the developed to the developing countries. These efforts fall into the following pattern:

- *Technical support.* From the technical assistance funds during 1985, US$ 3.18 million was spent on health-related projects to assist 41 countries. This constitutes 9.5% of the overall technical assistance budget. Most of the assistance is towards setting up *in vivo* and *in vitro* nuclear medicine facilities. The practice of nuclear medicine requires costly electronic equipment and a regular supply of radiopharmaceuticals. Most often, these are not indigenously available and, therefore, good airline connections and smooth customs clearance procedures are needed. The instruments need to be kept in an optimum environment and need appropriate facilities for maintenance and repairs. All these constraints should restrict setting up nuclear medicine to a relatively few countries, which have the proper infrastructure, and in a few of the major hospitals in urban centres of these countries.
- *Training courses.* For more than a decade, the Agency has organized an annual interregional training course and study tour in nuclear medicine for participants from developing countries. At present the practice is to select mostly medical doctors for this course, which provides a basic introductory overview of current clinical nuclear medicine techniques. Participants are provided with theoretical and practical training in the common diagnostic and therapeutic applications of radioisotopes, safe handling of radioisotopes, general principles of radiopharmacy, analysis, interpretation and quality control of *in vitro* and *in vivo* nuclear medicine procedures, organizational aspects of nuclear medicine service in a hospital, and a general background education in physics related to radiation and radioactivity. In addition, the Agency's Division of Life Sciences frequently organizes various short-term training courses and workshops throughout the year in different parts of the world on special topics in nuclear medicine — for example, quality control of imaging instruments, radioimmunoassays, and maintenance of nuclear medicine equipment.
- *Expert assistance.* One of the most vital aspects of training is on-the-spot instruction in a developing country by a recognized expert. The expert may cover some or all aspects of nuclear medicine. A mission may be of a few months duration or may extend to a whole year. When complex equipment is supplied to a country, the project usually includes the visit of an expert to train the staff in the operational and technical aspects of the instrument. During 1985, 72 man-months of expert time was provided within 69 projects for assistance in the field of nuclear medicine.
- *Training fellowship.* The ultimate aim of setting up nuclear medicine facilities in any country is to have a fully trained local person to take up the clinical and technical responsibilities of the nuclear medicine unit. For this purpose a local person with requisite academic credentials is sent abroad for comprehensive training to a suitable institution for periods ranging from a few months to a few years. For instance, during 1985, 388 man-months of fellowships were provided in nuclear medicine.
- *Conferences, symposia, seminars.* These meetings are designed for exchange of ideas between scientists from various countries. In 1985, the Agency organized an international symposium on "Nuclear medicine and

Radioimmunoassay: Insights to health

The achievement of radioimmunoassays (RIAs) is a glorious chapter in nuclear medicine — aptly recognized by the award of the Nobel Prize to Rosalyn Yalow in 1977 for her work on RIAs. These assays provide means of quantitatively and specifically measuring a large number of biologically important substances in a specimen of clinical sample (for example, blood) withdrawn from the patient. Here, as in nuclear imaging, the underlying principle is that of a tracer. A radio- labelled hormone is trying to trace the bound and the unbound fractions of a hormone in the presence of a binding agent in the blood sample.

Life is made possible by the balanced interaction of thousands of complex organic molecules, whose sizes range from a few to many thousands of atoms, and whose concentrations in biological fluids range from parts per hundred to parts per billion. Many differ from each other almost negligibly, yet nevertheless they have very different functions. Before the advent of radioimmunoassay, the assay of most of these substances was difficult or impossible, and insight into biochemical processes was correspondingly restricted.

Radioimmunoassay brought two key innovations. First, it introduced as a highly specific and sensitive "reagent" a particular class of biological molecule, namely antibodies, to segregate the particular substances of interest. Second, it made use of radioactive tracers to permit quantification of minute amounts of these segregated molecules.

RIA is one medical application of radionuclides that can be carried out at the lowest level of technical complexity. RIA and related techniques have come to play an enormous role in medical diagnosis and research. Today hundreds of different substances are assayed by these methods, including hormones, vitamins, pharmaceuticals, drugs, products shed by infectious viruses and by parasites, substances released by malignant tumours, and many others. The yearly investment in these techniques worldwide must exceed US$ 1 billion, and the techniques play some part in the diagnosis of perhaps 10 to 20% of all patients hospitalized in developed countries. It is natural that developing countries are eager to introduce these methods into their own health systems.*

* See "The promotion of RIA in human health", by R. Dudley, in the *IAEA Bulletin*, Vol. 25, No. 2 (June 1983).

Expert assistance is a vital aspect of the Agency's training programme in nuclear medicine. (Credit: NEN)

related medical applications of nuclear techniques in developing countries" in co-operation with WHO.* Proposed for the future is a symposium on "Dynamic function studies in nuclear medicine" and a seminar on "Training in nuclear medicine".

● *Research contracts*. Many clinical nuclear medicine protocols currently accepted in various countries may not be suitable for the developing countries. There is a necessity to simplify the procedures and work with relatively less sophisticated instruments and with easily obtainable radiopharmaceuticals. This process of adaptation of techniques to suit the needs of the laboratories in developing countries is what the Agency programmes encourage. The approach recognizes the fact that advanced methods cannot be adopted *de novo* but need to be adapted to existing realities in developing countries. With this kind of adaptive process in mind, the Agency has set up Co-ordinated Research Programmes on the following subjects: (1) optimization of nuclear medicine procedures for the diagnosis and management of thyroid disorders; (2) quantitative evaluation of nuclear imaging procedures for the diagnosis of liver disease; (3) investigation of the impact on the performance of quality control procedures of nuclear medicine instruments; (4) formulation and implementation of maintenance plans for nuclear laboratories; (5) radionuclide applications in the diagnosis of parasitic diseases; (6) external quality assessment of radioimmunoassay of thyroid-related hormones.

The Agency's research contract has to be tuned to nuclear medicine's current trends in the world and to the perception of what future role it will be playing in the overall management of patients — vital components in the development of the Agency's future programmes.

* Proceedings now are available from IAEA. See *Keep Abreast* section for ordering information.

Trends and new directions

Nuclear medicine started as a tracer investigation for the study of function and flow. The advent of scanners and the development of new radiopharmaceuticals localizing in various organs directed the attention of nuclear medicine physicians to imaging of various organs. For years, apart from radiology, nuclear medicine was the only technique available for such imaging. Now that no longer holds true. Various competing imaging modalities are available, such as ultrasound, computerized axial tomography (CAT), and nuclear magnetic resonance. Each one has its own virtues and limitations. A hospital administrator is faced with alternatives. What kind of imaging services should be established in his hospital? A physician also is faced with a similar dilemma as to what is the most appropriate investigation for which he should refer the patient.

There is a gradual awakening of an awareness that the primary role of nuclear medicine is not to seek anatomical defects or search for structural abnormalities. Its main forte is the study of function with respect to time or, in other words, to study a radiopharmaceutical's changing distribution in the body during a certain time period. This kind of study yields important information about the function of various organs. This realization has led to special attention to the study of cardiovascular and cerebral functions, where in the last few years nuclear medicine has brought about a dramatic surge of new data. So far, such data has been obtained with the use of special instruments and cyclotron-produced radiopharmaceuticals. Now it appears that new cerebral and myocardial radiopharmaceuticals labelled with technetium-99m are just around the corner and that it would be possible to do *in vivo* functional brain and heart studies with conventional gamma cameras.

Radiopharmaceuticals

Nuclear medicine's future is intimately tied up with developments in the field of radiopharmaceuticals. In all other imaging modalities, one needs only the instrument and the patient. In nuclear medicine one also needs a suitable radiopharmaceutical. This weakness of nuclear medicine is also its virtue. It is possible to develop a wide variety of new radiopharmaceuticals each tracing one or another function of the body. This enhances the versatility and the virtuosity of nuclear medicine. It appears that a large number of radiopharmaceuticals are on the anvil and many more useful diagnostic applications of nuclear medicine will be forthcoming.

Another new direction — also related to radiopharmaceuticals — is the development of specific monoclonal antibodies labelled with an appropriate radionuclide and targetted towards an antigenic site either for imaging or for therapeutic purposes. Radiopharmaceuticals targetted to such specific antigens or receptors are likely to combine the specificity of immunology and sensitivity of radioisotopes in a single investigation.

At the same time, there would be a gradually increasing recognition of the vast extent of information offered by *in vitro* assays, such as RIAs. One does not have to visualize the disease as a lesion or the affected organ as an image of some kind. It is possible to detect "footprints in the sands of time" in the form of biological markers of the disease in the circulating blood. Tumour markers for the diagnosis and management of cancer patients and detection of antigens and antibodies in infectious diseases are two of the most potentially fertile areas in this respect.

The most crucial application of nuclear techniques in medicine is towards providing insight into the pathophysiology of diseases. The Agency in this respect seriously promotes use of radioisotopes in the management of communicable diseases common in developing countries. In the last decade, RIAs were devoted towards the understanding of endocrine disorders, and, over the next decade, the direction is towards the understanding of infectious diseases.

Just as all RIAs are not diagnostically useful in endocrinology, all RIAs related to infectious diseases may not be diagnostically significant at the present stage. However, each contributes towards better understanding of host and parasite relationships. This kind of coverage of nuclear techniques in parasitic diseases is unusual for a nuclear medicine department and the encouragement of this novel departure on the part of the Agency is noteworthy. (See a related article in this issue of the *IAEA Bulletin*.)

Reverse flow of research

There is at the same time evidence of a reverse flow of research. The research is continuously progressing from more complex to more simple technology. Complex cardiovascular investigations can be done with a gamma camera attached to a dedicated computer. But in a simpler, though less sophisticated way, a single probe with a small microprocessor-based device (a kind of "nuclear stethoscope") can generate the same kind of diagnostic information. There is a reverse trend from cyclotron-produced radiopharmaceuticals to those labelled with technetium-99m, from gamma camera to single probes for dynamic functional information at the predetermined sites, from automated conventional RIAs to innovative novel RIAs done with "homegrown" antibodies and simple manual counters. This is a healthy sign because simplification of technology would lead to a wider spread of nuclear medicine techniques instead of its monolithic growth in few institutions.

What is most gratifying is the general realization of what nuclear medicine is about. It is basically a tracer investigation of regional physiology and biochemistry. Imaging is incidental to it. What matters is that in each procedure a specific biological process is being traced.

Nuclear imaging

Radioisotope imaging started as point-by-point *in vivo* mapping of the distribution of radioiodine in the thyroid gland. The manual mapping was replaced by an automatically moving sensitive detector criss-crossing over a preselected region. Pretty soon, it was no longer necessary for the detector to move over an organ for point-by-point viewing. A large detector can look at the entire organ at the same time and it was possible to map out electronically what the detector sees at each point in front of it. This kind of instrument, called a gamma camera, makes it possible to do dynamic studies in temporal terms because images of the whole or a part of the organ can be obtained sequentially at different points of time.

Radioisotope imaging is a functional image in an anatomical framework. For the organ to be visualized, it is first of all necessary for a radiopharmaceutical to localize in that organ. In the presence of a normal function, such localization has a characteristic pattern. In case a region has pathological function, the concentration of the radiopharmaceutical at that site is abnormal.

Although apparently similar, there is a gross difference between X-rays and nuclear imaging. In radiography, the tissue is a passive intermediate in the passage of a X-ray beam through the body, and what is being visualized is the alteration in the beam of X-rays because of the intervening tissues. The image has no reference to the function of an organ and it will be the same whether the subject is dead or alive.

In nuclear imaging, active biological transport of a radioactive substance through an organ is visualized with reference to time. The difference is as much as in a photograph and a mirror. A photograph shows a physical image in which time is static. A mirror can show a continuously varying physical form.

For nuclear imaging, it is necessary to have a specific radiopharmaceutical with a high degree of concentration in the organ of interest. To visualize a small region of interest in an organ at time intervals of few seconds, it is necessary that a large amount of radioactivity is injected into the patient so that electronic signals emanating from the region of interest are strong enough to register on the display in a statistically significant way. This is possible without causing harm to the patient only if short half-life radiopharmaceuticals are used, which usually can be obtained from "laboratory generators". Technetium-99m and indium-113m are two radionuclides produced by generators that are widely used in nuclear medicine today. A laboratory generator is a device where a long half-life radionuclide, the "parent", produces a short half-life progeny that can be then used conveniently in various formulations for different clinical imaging procedures.

For more information about nuclear imaging advances and trends, see a related article in this issue of the *IAEA Bulletin*.

Future programmes

In developed countries, nuclear medicine has turned towards new directions. There is increasing reliance on cyclotron-produced radionuclides. Positron emission tomography (PET) using ultra-short-lived radionuclides of this origin has shown remarkable achievements in neuro-physiology, and new biotechnology has contributed by way of monoclonal antibodies to both *in vivo* and *in vitro* investigations. Many of these new developments are yet beyond the reach of the developing countries. The present practice of nuclear medicine in developed countries is a kind of expensive high-technology medicine. There is an attempt even in these countries to simplify the technology to contain the cost.

On the other hand, simpler and reliable technology is sought for developing countries because resources available to set up new techniques are limited. There is a natural process of bridging the gulf between what is current and what should be desirable for the future. The Agency's efforts over the next few years should be towards bridging the present gulf and assisting in the natural process of evolution towards simplification and containment of costs.

The level of technical assistance will have to be augmented because many countries now would be ready to discard their old slow rectilinear scanners and would be eager to acquire gamma camera/computer complexes. This would need forward planning for creating maintenance facilities for this kind of equipment at the hospital level. Many nuclear and non-nuclear non-invasive investigational modes now are available. With various competing diagnostic modalities available to a physician, it is necessary that a proper scientific cost/benefit study or efficacy studies are done for each of the diagnostic tests. Apart from decision-making about individual patients, these studies would help the developing countries in deciding their priorities as to what technology they should develop and what they can relinquish.

Enthusiasm for new technology is likely to make physicians forget the important aspects of quality control. In nuclear medicine, quality control is at various levels: of instruments, of radiopharmaceuticals, of *in vitro* assays, of training of technicians and physicians. This also is an area that an international organization such as the IAEA should encourage and support.

Appropriate technologies

What was earlier described as the "reverse flow of research" really means development of "appropriate technology". This process should be encouraged by stimulating research of this kind, making it possible to show that what is available at large hospitals at the apex can also be provided to a large number of smaller hospitals with lesser means and poorer resources.

The study of infectious diseases with RIA and other similar technology offers hope of new insight into interaction between basic immune processes and pathogens. Apart from diagnostic information, it can lead to newer understanding of the biological course of the disease. Research in this field should be appropriately funded and supported in developing countries.

Functional studies are the strength of nuclear medicine and these, of course, require a computer of some sort. As computers become more widely established in developing countries — in airports, hotels, banks — the means to support them are bound to become more widespread. If we were to introduce the internal combustion engine into developing countries today, people would say it is not possible. Yet look at how the trucks and lorries are kept going in the most primitive conditions in the developing countries. What is needed is the will to recognize, accept, and amalgamate nuclear medicine in the hospital programme. The Agency has to support this ongoing process of evolution and facilitate the wheels of progress.

In the field of nuclear medicine, the interests of international organizations, such as the IAEA and WHO, overlap. Many Agency activities in nuclear medicine are in co-operation with WHO and many future activities of these two bodies will have to be in close collaboration when they relate to nuclear medicine.

If the target is "health for all by the year 2000" — as WHO has pronounced — we cannot afford to neglect the growth and nourishment of this "20th century technology" so important in the diagnosis and treatment of diseases. One objective of the IAEA is "in accelerating and enlarging the contribution of atomic energy to peace, health and prosperity throughout the world". Promotion of nuclear medicine is one step forward in this direction.