Liver scintigraphy of patient in Pakistan's Larkana Institute of Nuclear Medicine and Radiotherapy. (Credit: Pakistan AEC)

Nuclear imaging: Advances and trends

Developments in several fields are influencing future directions

by Gerard van Herk

"One picture is worth more than a thousand words".

The validity of this expression, which is a *leitmotiv* in the publicity sector, is not limited to the strategy underlying advertisements. It certainly also applies to the commanding role images play in diagnostic medicine. To draw lines of development in imaging instruments, one must start where the arsenal of nuclear medicine equipment stands today. In this article, nuclear imaging instruments that are likely to be of interest to the nuclear medicine community of developing countries are emphasized.

The rectilinear scanner was the earliest instrument with which one created an image of a radioactive distribution inside the body. It still is a common — and reliable — piece of equipment in many nuclear medicine centres in the Third World.

The scanner consists of a detector fitted with a lead collimator, which focuses the radiation-sensitive field of view to a narrow spot below it. The detector is being moved along a meandering path over the selected area where a radioactive tracer is distributed — for example, the organ to be imaged in the patient. The amount of radioactivity measured at each position is simultaneously recorded with a printing device attached at the other end of the moving detector assembly. After the total area has been scanned, the total pattern of printed dashes, the "scan", is a life-size presentation of the tracer distribution.

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The type of gamma camera that still is most commonly used is the one designed by Hal Anger in 1959. In the "Anger" gamma camera, the radioactive distribution is projected as a whole through a parallel-hole collimator onto a thin scintillation crystal. The diameter of its field of view can range from 18 to 50 centimetres. Each scintillation event on the crystal is "seen" by an array of photomultiplier tubes (PMTs, typically 19 to 75). The relative outputs of the PMTs are analysed by an electronic positioning network, which produces two position signals per registered photon. When entered into a display monitor, the original "scintillation" is represented by a corresponding light dot on the screen. After accumulating several thousands of those counts with a photocamera, the resulting photograph, the "scintigram", is a projected image of the functioning organ.

Although considered old-fashioned by comparison, the scanner does have a number of advantages over the gamma camera. By its very nature, it provides an undistorted and uniform response over the whole area imaged; it has a satisfactory performance for higher-energy nuclides, some of which are more readily available than technetium-99m, which is mostly used. The scanner offers a superior contrast in deeper structures. Finally, it is usually less vulnerable to adverse environmental circumstances, to unstable power conditions, and to irregular maintenance, situations common in many developing countries.

On the other hand, there are disadvantages of scanners: they cannot be used for dynamic studies, i.e., to image those tracer distributions that are not stationary for the duration of the study. The resolution of a scan is inferior and looks less appealing than the scintigram. The sophisticated gamma camera as such, for that matter, commands more respect than the scanner, the instrument of the pioneer years.

Whatever the nature of the imaging instrument, it is essential to regularly assure that each piece of equipment is functioning properly. This awareness has to translate into a set of quality control (QC) procedures regularly followed. The IAEA supports a number of programmes and projects and has published a technical document on this subject.

Computer applications

In the early 1970s, there was widespread research into applying the computer for processing scintigraph images. It resulted, within the same decade, in an expansive growth of commercial image processing computers.

The use of a computer for static images provides mainly a cosmetic improvement of the scintigram. The contrast in the image may be enhanced by subtracting background activity, or by emphasizing any range in the intensity scale containing significant clinical information. Distortions and artefacts, almost inherent to gamma camera imaging, can be partly corrected for, with the most common corrections for deficient uniformity and linearity. Finally, there are numerous "filtering" programs to improve on the "noise" or unsharp edges of organs in the scintigram.

Apart from its usefulness for visual improvement of images, computer processing is indispensable for analysis of dynamic studies, i.e., in order to assess changes in tracer distribution over time. Immediately following injection of the tracer, a number of consecutive images are recorded in the computer memory. The activity in the organ or selected regions of interest in it are plotted versus the time. These time-versus-activity curves are then analysed using mathematical and physiological models. The quantitative parameters produced are representative for the organ's function. Successful methods have been developed in nuclear medicine for the dynamic analysis of many organ functions: notably brain metabolism, kidney function, stomach emptying, blood flow, and heart contraction. Recent advances in the latter have made "nuclear cardiology" virtually a separate speciality.

Conventional scintigraphy provides an image of functioning organs, as a projection over the full thickness of the body. The activity in all planes parallel to the detector are superimposed in the final image. Until recently the only way to view selectively a single section inside the body was by means of surgical tomography. In the last decade the new imaging modality of "computer-aided tomography" (CAT or CT) reached maturity as a product of the intimate relationship of a highly advanced imaging instrument and a high-capacity computer. The principle of CT is based on the mathematical reconstruc-

Basics of nuclear imaging

Originally nuclear medicine was not concerned with imaging, but with the quantitive assessment of a certain biomedical substance at a certain time and place. The concept of tracer kinetics is that physicians "label" a biomedical compound with a radioactive "isotope" and follow the path and fate of this "tracer". Since the added substance is small in quantity and equivalent to the substance to be traced in its chemical behaviour, there is little interference with normal physiology. Tracers used in nuclear medicine are often called "radiopharmaceuticals".

The close co-operation of scientists, such as biochemists, physiologists and pharmacologists, has produced a large selection of radiopharmaceuticals. For most organs and for various organ functions there is a specific tracer that plays a particular role in the metabolism or in transportation mechanisms. As a radioactive "label", the nuclide technetium-99m is mostly used because of its convenient physical and chemical properties. It has a short half-life, limiting the radiation dose to the patient and avoiding problems with waste management.

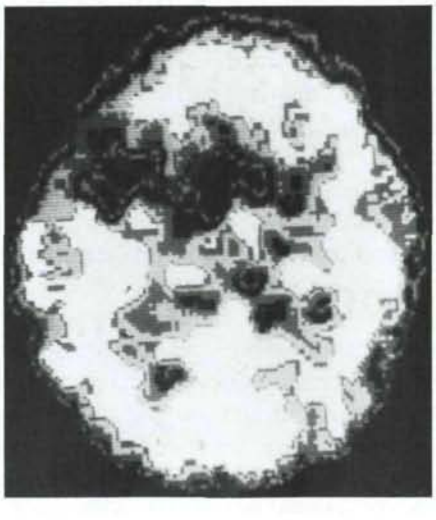
One characteristic advantage of nuclear medicine is that the tracers behave as "functional probes". Other diagnostic imaging modalities, such as radiology and ultrasound, visualize the static properties of tissue, such as its density. Nuclear medicine images, on the other hand, reflect the functioning biochemistry. The seemingly stationary distribution of a tracer represents the momentary uptake of the labelled compound, a snapshot of a highly dynamic process.

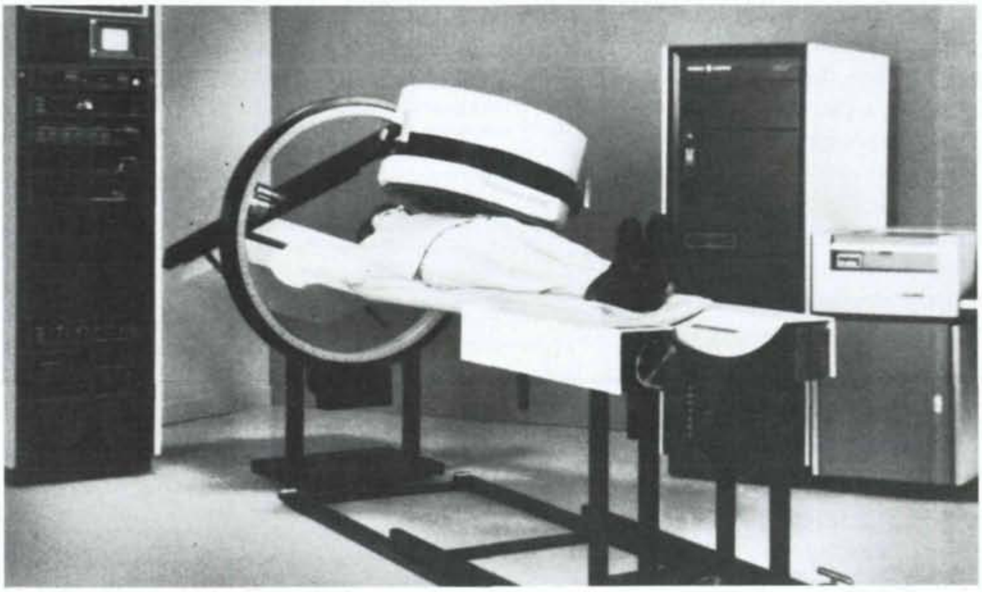
Most imaging techniques apply light or other radiation in such quantity that its intensity is measured as a total flux of radiation. The gamma radiation applied in nuclear medicine is handled in its smallest indivisible units, as single distinct packages of light, called "photons".

For the detection of gamma radiation, scintillation detectors are widely used. In a scintillation crystal each incoming gamma ray creates a tiny light flash. A photomultiplier (PMT) subsequently converts this scintillation into a small electronic pulse. The pulse height or amplitude is proportional to the "gamma energy" (and inversely to the wavelength) of the incident photon. The total number of detected photons, or "counts", accumulated in a given time represents the number of radioactive tracer, the "activity" present in the field of the detector. It is this characteristic of single-count measurement that makes nuclear medicine suitable for quantitative investigations.

An inherent complication of the limited amount of photons used, and of the random character of the radioactive disintegration process in itself, is the statistical imprecision of a measurement. This imprecision results in irregular fluctuations of "noise" in the measured intensity and the undesired patchiness in nuclear images.

Scintigram of brain. (Credit: CEA)





An ECT (emission computerized tomography) system. (Credit: GE)

tion of three-dimensional (3-D) image information collected in a number of single views taken from various sides around the object. The 3-D image information obtained is viewed by selecting planar sections in frontal, lateral, and also in transversal projections from the computer memory. Particularly the possibility of visualizing structures in the latter view, perpendicular to the body axis, has contributed to a significant widening of the anatomical horizon.

PET and SPECT

The rapid and successful introduction of X-ray CT as a routine tool in clinical diagnosis has further stimulated the development of nuclear medicine CT or "emission computerized tomography (ECT)". Incidentally, ECT had been conceived and developed long before X-ray CT, but was not considered a feasible standard imaging method for long. Two distinct modalities of ECT exist in nuclear medicine: positron emission tomography (PET) and single photon ECT (SPECT).

The 3-D image information in PET is derived through the counting in coincidence of the two simultaneous photons that accompany positrons. Positrons in turn are emitted by certain, mostly short-lived, radioactive nuclides. The imaging instrument for PET, having detectors at either side of the patient, allows a relatively high sensitivity, i.e., detection of a large fraction of the emitted radiation. Positron ECT has been very successful, particularly as a research tool in physiology and microbiology. The atoms composing organic compounds have mostly radioactive isotopes that emit positron radiation. Impressive results have been published quantifying and imaging metabolism and oxygen consumption in the brain and the heart muscle.

The success of PET in turn has stimulated the quest for a tomography instrument, with which conventional — single photon — nuclides could be applied. At least three categories of instruments for SPECT may be distinguished. These collect necessary views from different angles through a multi-pinhole collimator, a rotating slant hole collimator, and a rotating camera respectively. The latter one has been most promising because it is least affected by unwanted artefacts and allows imaging in the transversal planes, too.

The additional efforts spent for SPECT over conventional scintigraphy are repaid by a modest but significant improvement of diagnostic accuracy. The tomographic image offers a superior contrast because it eliminates overprojection of overlying structures. Thus, deeper structures are visualized with better contrast.

It was only after the first wave of enthusiasm over SPECT had subsided that the image artefacts were discovered. The artefacts could be hot spots, streaks or circles in the final image. It appeared that they were caused either by significant activity that remains partly outside the field of view, or by maladjustments of the gamma camera. Defects in uniformity, non-linearities and misalignment of the rotating camera, while insignificant for conventional scintigraphy, are blown up in the reconstruction process and may suggest serious abnormalities in the final tomographic image. Rigorous QC procedures for test and calibration are essential if the advantages of ECT are not to be turned into drawbacks.

Trends in imaging instrumentation

The thrust of the development in nuclear medicine imaging equipment comes, at least partly, from what commercial suppliers of instruments select to manufacture. Research in nuclear medicine is characterized by rapid innovation, particularly in the field of instrumentation. The process of actually implementing these appears to have slowed down recently, due to a number of factors. While engineers and physicists are ready to embark on ever new designs, the medical world sometimes shows much more inertia in its acceptance of new methods and instruments into clinical routine.

That may explain the typical two-stage growth and acceptance shown with new developments, such as with nuclear cardiology and emission tomography recently. First there is an enthusiastic wave of innovative ideas, published and presented at annual scientific meetings. This high time is followed by a comparative lull on the subject, which may last as much as half a decade. Then, a sudden rise in general acceptance, supported by finished products marketed by industry, indicates that the new development has matured and will serve as a new tool for clinical imaging studies.

With the impressive expansion of other imaging modalities, and the generally tightening budgets for research and development, industrial innovation in imaging instruments for nuclear medicine has lost some of its impetus in recent years. For instance, a significant number of companies marketing computers for nuclear medicine have discontinued their business in the last years. Furthermore, the market in the developed world is reaching a saturation level. An estimated 10 000 gamma cameras are presently installed all over the world with a turnover rate of roughly 1000 per year.

Electronic developments

Development of new instruments is facilitated and stimulated to a great extent by advances in electronics. A recent trend is miniaturization, leading to increasingly large-scale integration of components, and consequently a dramatic fall in the costs of those "chips". The introduction of microprocessors in place of hardware circuits is rendering instruments more powerful and more versatile, but for a lower price. The emphasis of design efforts appears to be shifting away from hardware towards software development. Extensive processing power can now be stored into ever more compact chips. Software so condensed is sometimes referred to as "firmware".

Trends in gamma cameras and SPECT

The principle of the Anger camera has its inherent limitations, which forces the designer into some compromise between, for instance, sensitivity and spatial resolution (resolving power in the image). Compared with other imaging methods, such as X-ray radiology and nuclear magnetic resonance (NMRI), nuclear medicine is constrained by the limited number of photons available, since radiation exposure to the patient has to be restricted.

Any approach to improve spatial resolution (by using a thinner crystal or a finer collimator) is paid for by a loss in sensitivity and consequently an image with more "noise". Some research is done in applying other scintillation crystals, such as caesium-iodine or pure germanium, instead of sodium-iodine, which is generally used. However, this has not yet resulted in a viable new product. The use of more photomultipliers on the crystal has pushed the spatial resolution only slightly more towards its theoretical limit. At the same time, however, the instrument becomes more susceptible to breakdown, since every added component contributes to the probability of instrument failure.

Considering its price and relative reliability, however, the Anger camera is likely to remain the accepted and practical imaging instrument for nuclear medicine.

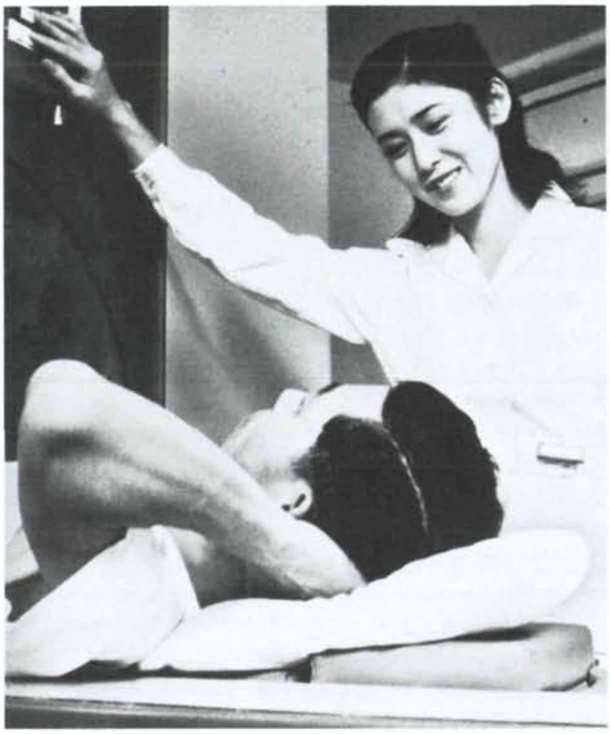
Rather than significant changes in gamma camera design as such, there is a definite trend toward specialization. The inevitable trade-off in camera design may be tailored to the specific clinical application, leading to dedicated systems. There are, for instance, small field-of-view cameras capable of handling high count rates, applied for nuclear cardiology; there are camera systems, rotating very closely around the body, designed to optimize tomographic imaging; cameras are specialized for mobile use, and others for whole-body scanning.

SPECT is likely to become more important in the near future. This is helped by a concomitant rapid improvement in computer hardware and software, together with an increasing number of accepted clinical applications. Along with PET, its more sophisticated counterpart, SPECT is developing to allow quantification of tracer distribution. A crucial condition to quantify reliably is accurate correction for tissue attenuation. This is generally achieved by measuring the actual attenuation with a transmission scan. A drawback of any image correction using measured radioactivity is the increase of the "noise" or statistical fluctuations, and consequent degradation of the resulting image. Another approach is to determine the body contour or assume an allipsoid shape and apply a theoretical correction. This does not degrade the image quality, but may represent a less accurate approximation of the real situation.

Improving visualization of depth

However attractive insight may be into deeper sections cut through deeper planes within the body, the drawback is that one ends up with a multitude of selective pictures. Much of the advantage of tomographic imaging depends on the visualization of the 3-D image in a compact and comprehensible way. There are a number of methods presently being explored by which the impression of depth is added to the display of tomograms.

Normal photographs that only suggest a 3-D structure have the advantage of being practical and transportable. They are obtained from the screen, whereby successive deeper sections are displayed with decreasing contrast or with edges removed, thus having the same effect as the wings on a theatrical stage. Other, more elaborate methods are stereoscopic pictures, holograms, and the "vibrating mirror", where the three dimensions are clearly "seen" when one is seated at the display station of the image-processor computer. A simpler way to suggest depth at the computer screen is to display all origi-



Competitive imaging systems, such as computer-aided tomography, are influencing the future of nuclear medical imaging. (Credit: Tech-Ops)

nal views in rapid succession, just as they were taken from around the patient. This "rotating view in movie mode" leaves it to the observer's perception system to smooth out the noise in images and to visualize three dimensions in body organs.

A number of different designs of cameras for PET are being developed. Some have become available commercially. However, the world of PET seems to dissociate itself further from the SPECT imaging field. PET requires the availability of a nearby cyclotron and a staff of highly skilled scientists, whereas SPECT uses conventional radiopharmaceuticals. Moreover, the benefit of clinical applications using PET have turned out to be limited, in relation with the costs involved. While a very sophisticated tool *per se*, positron tomography is being applied predominantly in advanced physiological research.

Integrating computers and cameras

The trend towards more compact, more powerful, and less expensive computer hardware, combined with the need for fast signal and image correction, has led to an integration of the computer with the camera. The analogue position signals, originating from the PMTs on the detector crystal, are converted to digital data at an earlier stage, thus reducing the distortion of the image information. These so-called "digital cameras" have a more stable performance, since they are less susceptible to disturbances or a gradual drift of the analogue signals. On the other hand, since the gamma camera is controlled by the digital electronics, any failure of the computer would cripple operation of the whole system.

For the reconstruction algorithms in ECT and, for example, Fourier filtering in nuclear cardiology, extensive "number crunching" has to be carried out, normally consuming considerable computer time. Parallel processors, such as the array processor, can perform a number of operations simultaneously. With the price for hardware falling, array processors may well become an integral part of computer systems for image processing.

In general, a major contribution to nuclear medicine soon will come from the development of software. Together with the trend to "freeze" computer programs into chips, this may indicate that more image analysis protocols will become standard features of the imaging instruments. Presently software is freely accessible for personal and customized modifications, which hampers the standardization of procedures. One attractive application that deserves mentioning is the "functional image". In the functional or "parametric" image the intensity or colour of each picture element ("pixel") represents the value of a parameter, e.g., the result of the mathematical analysis of a dynamic study for that particular point of the image. Functional images of the phase and amplitude of the heart contraction, after Fourier analysis, and of kidney function, after "factor analysis", are gradually gaining acceptance.

Radiopharmaceutical developments

Since nuclear medicine is an intimately multidisciplinary endeavour, its future is not only determined by instrument trends, but also by developments in radiopharmacy. Ultra-short-lived radionuclides, in combination with gamma cameras capable of handling high count rates, will lead to new applications in blood flow studies and nuclear angiography.

The present trend in development of tracers that are more organ- or function-specific may open up a whole new area of functional imaging. Particular mention should be made of monoclonal antibodies, highly tumour-specific compounds presently used in radioimmunoassay. If this application would expand into the *in vivo* field, a totally new imaging modality could evolve ("radioimmuno-imaging"). If these antibodies were to be labelled with the widely available technetium-99m, the nuclear medicine physician would have a new and powerful tool in his combat against cancer.

Growing competition

Apart from these developments, there is significant external influence on the future of nuclear medicine — increasing competition of other imaging modalities, such as (digital) radiology, ultrasound, and NMRI. This competition, together with the growing similarity among their needs for image processing and computer use, may dictate establishment of integrated imaging departments in hospitals of the future. Similar to the development in the *in vitro* laboratory, this may even lead to a gradual end to isolated nuclear medicine departments as such.

For the developing world it may take 5 to 10 years longer before a new development in nuclear medicine becomes commonplace. Among other causes, this is inevitably due to the shortage of financial resources.

Administrative procedures and political pressures sometimes appear to set the time-frame for the transfer of technology. The generally extensive bureaucratic procedures add a considerable delay to the procurement of new equipment. In addition to all this, there are pertinent problems in coping with the more adverse circumstances in many developing countries. Notably insufficient climatic- and power-conditioning create an unsuitable environment for increasingly sophisticated and vulnerable equipment. An inadequate infrastructure and lack of foreign currency hamper the regular supply of short-lived radiopharmaceuticals and the prompt availability of repair and maintenance services. And last of all, insufficient pay and training of engineers, together with a considerable "brain drain" does not stimulate growth of motivation, knowledge, and experience. On the whole, for the developing world, the pace of development is much slower than in the developed world, and consequently the gap in accepted (nuclear medicine) technology continues to widen gradually.

Future directions

Trends in nuclear medicine and imaging instruments seem to lead to different futures for the developing world and for developed countries. There are significant differences in the disease patterns and clinical questions in both worlds. Moreover, resources available for sophisticated medical facilities differ in absolute and relative terms. It is a risky and unrealistic endeavour to even try and predict the future of a development, which, in its short history, has proved to be capricious, rapid, and directed by unexpected events and inventions.

In more advanced parts of the world the rate of expansion and innovative designs in nuclear medicine equipment may well slow down in the years to come. The competition with other imaging modalities involved in clinical diagnosis and the changing public attitude towards nuclear applications may dampen the force which drove nuclear medicine to its present level of sophistication.

Integration of more powerful computers in the Anger gamma camera is likely to continue, allowing on-line image optimization and efficient analysis of dynamic studies. With the further implementation of fast array processors, single photon tomography may mature to a routine and accurate imaging modality. A major contribution to new clinical studies will come from the development of highly organ-specific radiopharmaceuticals.

While rectilinear scanners are gradually being replaced by gamma cameras in the developing countries, there is a definite trend towards attaching computers to existing gamma cameras. This will allow access to new applications, such as nuclear cardiology. SPECT systems are only beginning to be installed among the more advanced of the nuclear medicine centres in that part of the world.

The acquisition of new equipment is, in general, a goal aspired with much more fervour than the maintenance of existing instruments. Nevertheless well-organized repair and maintenance facilities will prove of prime importance both for a continued development of clinical nuclear medicine services and as a means of training for electronics engineers. Apart from the obvious saving of financial resources, the strengthening of local expertise will help countries to become more self-supporting.

However challenging nuclear medicine developments may appear, it is important to justify spending the manpower and other valuable resources in view of the specific clinical questions posed and of their contribution to public health in general. Only when the quality of the investigations is constantly and rigorously assured, and when the expenditures are evaluated against their social impact, may nuclear medicine imaging maintain its role as a useful and attractive application of atoms for peace.