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The impact of W. K. Röntgen's discovery on the use of internalizable sources of ionizing energy in diagnostic and therapeutic nuclear medicine

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Abstract. The early history of cathode rays, X-rays and a third kind of natural radiation from several minerals and atomic fission is described. In this way the fundamental concept of radioactivity, laws of decay and atomic models were developed. With artificial radioactive isotopes, new tailored radiopharmaceuticals could be introduced into metabolic research, medical diagnostics and therapy. Von Hevesy's concept of the dynamic state of body constituents led to examination of the locations and movements of labelled atoms and molecules as a function of time. That was the birth of nucler medicine. The principles and value at the molecular level of several specific tracer studies in research and diagnostic or therapeutic use are explained. Typically, diagnostic tests with tracer agents are non-invasive and have low radiation exposure. Competing with other diagnostic and therapeutic modalities, nuclear medicine is a speciality in its own right. But there are moves to classify it as a subspecialization of other organ-oriented clinical disciplines. That is a misunderstanding of the radiologist's role and does not answer the question: What is the best way of woking for the patient? New horizons in diagnostic modalities, biochemistry, immunology, imaging and the use of immunogenic therapeutic agents demand a continuous cooperation within interdisciplinary teams. That is as necessary with radiologic departments, participating in changed organizational structures, as with other clinical departments.

Key words. Nuclear medicine; natural and artificial radioisotopes; tracer techniques; location diagnostics; radiopharmaceuticals; radiation measurement.

History

The 'new class of rays' which Wilhelm Konrad Röntgen reported on 8 November 1896 were part of a hitherto unknown aspect of nature. His discovery was the result of only one month's intensive studies of cathode rays, forsaking some previous work in quite another field of physics.

However, his discovery was not just a godsend of a bright idea to a brilliant scientist. Hermann von Helmholtz (1821–1894) and James Clerk Maxwell (1831–1879) had predicted the existence of invisible electromagnetic waves. Those with a wavelength longer than light (the radio waves) had just been described by Heinrich Hertz (1857–1894). Techniques helpful in generating rays of shorter wavelengths were made available over the preceding 50 years. The technician Sprengel had invented the mercury air pump to produce a high vacuum in a short time (1830); the glass-blower Geissler had filled his evacuated tubes with small amounts of rare gases and subjected them to an electric discharge. Photo-techniques were available since Nicéphore Niepce and Daguerre 1838, and films to register cathode rays were easily at hand. Plücker and Hittorf had compiled early information on the nature of these 'Kathodenstrahlen', a term that was coined by Eugen Goldstein, who was the first to observe photo plates blackened when placed inside the tube. Sir William Crookes let his chance slip away, when he observed some of his 'defective' photo plates blackened. W. Hittorf, G. F. Varley and W. Crookes had succeeded, however, in recognizing cathode emanations to consist of charged particles, because they were deflected by a magnetic field. Philip Lenard, a student of Heinrich Hertz and his coworker, observed the penetrating power of the cathode rays and realized that these invisible rays even blackened film outside the tube. He also measured absorption, when he made the rays pass through a wedge of nine aluminium layers.

Nevertheless, these pioneers were far from a comprehension of possible consequences. Was it the lucky idea occurring to Röntgen to use fluorescent screens (of barium platinocyanide) in order to trace these rays, or was it the circumstance that these detectors responded even at a distance of a meter from the source, which led him to open the door into the unknown? It was in any case his prepared mind which realized an unknown factor caused fluorescence and film-blackening, and which produced shadows of lead as well as of the bones of his wife's hand[37] on screens and films (see Roth and Elke in this issue).

With his first publication, Röntgen was able to report on absorption in various materials and his inability to refract these rays by a prism or deflect them by magnetic fields, just the features associated today with his X-rays (although they also characterize another kind of ray emitted by a selection of ordinary fluorescent sub-

stances). The way was paved: less than two months after Röntgen's communication, Antoine Henri Becquerel (1852–1908) communicated to the Paris Academy of Science his discovery of phosphorescent rays emitted from compounds of uranium (4 February 1896). He gave apparent reality to the authochthoneous nature of this penetrating emanation: he had systematically eliminated stimulating sunlight when he exposed his well-wrapped film to pieces of uranium salt. He saw dark spots at the positions of the mineral: the rays were spontaneously and continuously given off by uranium[6] (see Reinhardt and Gast in this issue). Röntgen had recognized the potential value of X-rays in medicine, and the news media immediately publicized them as an aid to medical diagnosis, particularly to identify broken bones and foreign objects. In January, i.e., less than one month after Röntgen's invention, the very first deliberate applications were done by a Viennese surgeon, followed, like an avalanche, by worldwide use of medical radiography and its continous technical improvement. Not so with Becquerel's discovery and his exhibition of a new and unexpected property of matter; newspapers and magazines took little or no notice of the uranium emanations. However, in 1897 a 30 year old Polish scientist, excited by the publication of Becquerel, started studies on radioactivity as the topic of her doctoral thesis. Maria Sklodowska-Curie's first publication (17 December 1897), dealing with piezoelectric measurement of the radiation of uranium, was followed by a second one, six months later, a cooperative paper together with her husband, Pierre Curie. They confirmed the existence of thorium, which had been independently discovered by G. C. Schmidt a few weeks earlier, and they reported on a new element, which they called polonium in honour of Maria's native land. The word 'radioactivity' appeared for the first time in the literature of science. In 1898 they reported on radium, the second new radioactive element. In 1902 and after 4 years of herculean work, Marie Curie succeeded in the preparation of 100 mg of radium chloride. Elementary radium was not obtained until 1910, now by Marie Curie alone, after her husband had died in 1906 in a street accident. It was she alone who earned her second Nobel Prize, the first person to be so honored[37].

Marie Curie and her husband consolidated their discoveries publishing some pioneering work on radioactivity between 1899 and 1902. Their work became one of the most publicized stories in the history of science. There came many honors from outside France, and remarkable aid from the greatest French scientists; but also rebuffs by the French scientific community solely because of her sex. It is hardly understandable today. The Curie's engagement was heroic: 5 years after their first Nobel Prize in 1903 (together with Becquerel), both were still working in an unheated shed, and they worked, of course, freely exposed to the abundant gamma-rays. Marie Curie was to die of aplastic anaemia in 1934 (see Fritz-Niggli in this issue).

Ernest Rutherford, A. Ramsay and F. Soddy substantiated the theory of radioactive disintegration in 1902, based on their own experience with the isolation of more than 20 radionuclides. They proposed the 'radioactive (decay) constant' and hence formulated the fundamental law of decay[37,78]. Radium mining (see Reinhardt and Gast in this issue) started on a commercial basis in 1902; after some use in quackery, its application in cancer treatment began in 1910 following progress in dosimetry. Out of the discovery of radioactivity therapeutic radiology grew rapidly, as diagnostic radiology did out of the discovery of X-rays.

Radioactivity and biology

Improvements in medical diagnosis have often been related to the development of new instruments. Milestones in medical progress are marked by inventions in the field of technical engineering. The microscope, especially its decisive improvements in the early 19th century, made invisible organisms and their interactions understandable. The ophthalmoscope (Helmholtz 1851) allowed direct investigation into hitherto concealed pathologies of the living organism. Röntgen himself knew about the biological importance of his discovery; he observed that X-rays made organic matter translucent. Absorption occurred dependent on specific features of biological matter: bones were less transparent than soft parts of his wife's hand. A broad spectrum of techniques rapidly improved in vivo anatomical diagnostics. Becquerel's discovery of spontaneously phosphorescent elements, on the other hand, paved the way for non-invasive physiological studies. Thus, Georg von Hevesy was well prepared to enter this field of 'bio-engineering', as one is tempted to call it in retrospect. During his scholastic year in 1911 with Ernest Rutherford in Manchester, he became involved in investigations of valence changes and of the 'displacement law', i.e the rules governing the new position in the periodic table an element occupied after the emission of radiation[48]. Two years later he had the idea that radioactive elements which are chemically inseparable from non-radioactive ones could be used as 'indicators' for the latter. He proclaimed the concept of isotopy (F. Soddy had proposed the name 'isotope' in 1913) and 'chemical identity' and was able to convince a critical audience that the atomic number determined the chemical properties of an element rather than the atomic weight. But it was Niels Bohr, then also working with Rutherford, who had the first clear-cut idea of the orbital structure of the atom.

Von Hevesy, together with Fritz Paneth, used a naturally occurring radioactive lead (RaD, a decomposition product of radium and thorium) to follow non-radioac-

tive lead through diffusion and exchange processes[67], and in 1913 he reported more generally on the 'tracer technique' in analytic chemistry[75]. Ten years later, when he obtained information regarding certain aspects of calcium metabolism in plants, he introduced the tracer principle into biological sciences. He made experiments on the absorption and translocation of lead and bismuth ('RaF') by plants[13].

The next important steps in the application of radioisotopes to biology were again preceded by technical innovations. In 1929 Ernest O. Lawrence and M. S. Livingstone invented the cyclotron. They were able to produce iodine-128, and when asked for a radioisotope with a more suitable half-life, iodine-131, too[44]. Three years later Enrico Fermi reported on radioactivity which he had observed after neutron bombardment[20]. In 1938 Otto Hahn and F. Strassmann proved that the union of a neutron with a uranium atom caused that element to split into two major fragments. In their experiments this resulted in the splitting off of a barium atom, which subsequently decayed to lanthanum[23]. Lighter elements contain a smaller proportion of neutrons than uranium; thus, this nuclear fission provides a ready source of neutrons, and a spreading type of chain reaction can be initiated, which, if controlled in a nuclear reactor, can be a major source of useful radioactive elements. Fission fragments were made available with mass numbers from about 70 through 160, many of which are building blocks of life. Radioactive isotopes of iodine, to give an example, are available as the most suitable agents for biological studies, but also as a danger in nuclear accidents. By neutron bombardment of selected elements in reactors, preplanned artificial radioisotopes could be produced. Soon, a broad spectrum of radioactive tracer-elements and chemical compounds was made available[19]. The first nuclear reactor at the University of Chicago was operated successfully (E. Fermi: 2 December 1942). Around this very first pile the huge gamble of the World War 2-Manhattan Project (1942–1945) assembled.

The reactor was later removed and reassembled at the Argonne Laboratories near Chicago. On 14 June 1946 the peaceful use of the uranium chain-reacting pile was announced in 'Science'[1], and soon therafter the first compound labelled with carbon-14 was delivered for bio-scientific applications. Radioisotopes were made available now at low cost and in great quantities by commercial production.

Registration technique made progress in parallel. Since 1929 Geiger-Müller tubes, most often home-assembled, had been the standard. They are well suited for the detection of β-particles, but also usable with gammas. Portable radiation survey meters still today rely on their principle. Counting, which the Curies did by eye, observing visible scintillations in luminescent crystals of halogenides, could later be done by machines, i.e. by scalers and ratemeters; but until the 1960's the electronics still depended on slow valves. Modern scintillation detectors, consisting of two components, a scintillator and a photomultiplier, have assumed the dominant position in instrumentation for medical applications of radioisotopes. Imaging devices emerged, beginning with constructions based on a moving detector. Such a 'scanner' collected the data sequentially and reproduced the distribution as a two-dimensional picture[1,11,52]. The collimator was introduced, to restrict the field of view to radiation coming through one or more holes from a small volume of the radioactive object at any time. Alternatively, time-coincident detection was used for collimation of photons emitted from positron annihilation that possess inherent directional properties[8,81].

Hal Anger invented the stationary detector device, i.e. the gamma camera in the early 1950's[2,3], which was in use nearly 10 years later. An array of scintillation detectors was able to perceive both intensity and positional information simultaneously. A pin-hole aperture served as the collimator, the basic principle of which, probably unknown to Anger, was reported by W. K. Röntgen in 1895: he then used this 'collimator' to make images of the anode of his X-ray tube on film. Modern cameras gain sensitivity thanks to multihole collimators with straight-parallel holes (or variants): photons from a source can pass through more than one hole and produce satellite radiation images on the detector[3]. A true-to-scale display on film was and is the main procedure to get images of a tracer distribution. Computer processing of scanned data is the modern extension: data handling and any kind of sophisticated transformation of raw information are produced as clinically readable printouts. Additional mathematical processing produces 'parametric scans', which are able to present events registered over time in time-coded pictures, which may also mix information coming from more than one tracer distributed within the same organ. Thus, complex physiological processes are made visible; but this is a development which has just started (table 1).

The tracer principle

Artificial radioactivity was discovered by Irene Curie and her husband Frederic Joliot in 1933[36]. Tracer studies, however, had already been performed in 1913 by Georg von Hevesy[76]. He became an innovator in the life sciences when he started his studies on phosphorous metabolism in rats and humans, utilizing artificial radioactive phosphorus, P-32, made available by bombarding sulphur with neutrons[12]. Its decay under emission of a fairly penetrating beta radiation, and its half-life of about 14 days, were attractive properties; the electrons could easily be detected by means of a Geiger-Müller counter, and phosphorus plays an important part in the metabolism of living organisms. P-32 thus

Table 1. Evolution of nuclear medicine as a clinical discipline.

		Radiopharmaceutical	Instrumentation	Technique	Physiological modelling	Procedure	Reference
I	1896	**METALLIC RADIUM** commercial production	Piezoelectric measurement for dosimetry	in vitro	Radiation source direct contact to tumour	**Brachytherapy of cancer**	37 6, 36
	1913	RaD (Lead: >30 radioisotopes)	Film-blackening		Chemical identity of RaD and Pb	**Radioactive indicators** in analytic chemistry	75, 68 48
	1924	RaF (Bismuth: 28 radioisotopes)	Geiger-Müller tube	ex vivo	**in animals:** distribution, excretion	**Biological fate** of a medicament against syphilis	68 13
	1931		Cyclotron				44
	1934		Nuclear reactor				19, 20
II	1934	Heavy water			**TURNOVER, EXCHANGE RATES**	Biological fate of body water	68
	1935	P-32			**Metabolism**	Phosphorus metabolism in rats	12
	1938					Formation of phosphatides in the brain tissue of adult animals	74
		Na-22				Biological fate of sodium	26
	1939	I-128		in vivo	in men: uptake, excretion	Iodine metabolism of the thyroid	25, 28
	1937	P-32 (Phosphate)		in vivo	**Metabolic therapy**	Treatment of chronic lymphatic leukemia	45, 46
	1942	I-131				Treatment of hyperthyrodism	28, 24
III	1948	Nitrous oxide (gas)			**DYNAMIC CLINICAL STUDIES**	Quantitative determination of cerebral blood/brain barrier	56
	1950		Scintillation counter, pulse height analyser	External measurements Double isotope studies			
	1952	I-131 labelled X-contrast				Renal function: uptake, excretion	73
	1956					Radioisotope renogram	80, 62, 54
	1962	Kr-85 (Krypton gas)			Uptake and clearance (after breathing)	Regional cerebral (=cortical) blood flow	43
	1952		Rectolinear scanner, collimator	Distribution: whole body, organs	**Regional function, static**	**In vivo biochemistry**	
	1953		Gamma Camera				2
	1970					Lung circulation: regional distribution	4, 5

Table 1. (cont.)

		Radiopharmaceutical	Instrumentation	Technique	Physiological modelling	Procedure	Reference
IV	1955	I-125 serum albumine			**COMPREHENSIVE CLINICAL STUDIES**	Differential diagnostics of intercranial space occupying lesions	56
		Xe-133 (Xenon gas)				Ventilation and perfusion (lung)	60, 65; 17, 7
	1969					Sequential scintigraphy of the brain	64
	1956		Computer	Triggering, mapping of sequential events	**FAST DYNAMIC STUDIES**	Regional myocardial wall motion (equilibrium technique)	30
	1975					Radionuclide ventriculography (first pass technique)	66, 67
	1971	Tc-99m phosphonates				Bone scintigraphy as routine examination	72 81, 8
	1975		Positron emission tomography (PET)	Reconstructive Tomography	Regional function with 'biological radioisotopes'		
	1977	F-18 FDG (Fluorodesoxyglucose)				Regional glucose utilization	69
						Regional myocardial perfusion and energy production	
		TI-201 Thallium chloride			Redistribution protocol (after single injection)	Characterization myocardial perfusion defects	57
	1977		Rotating camera-detection system		Regional function with gamma emitting radioisotopes		
	1978	Tc-99m HMPAO				Tomography of cerebral blood flow	9, 10
	1980	Tc-99m hexamibi				Tomography of myocardial perfusion	9, 66
V		J-131, In-111, Tc-99m labelled antibodies		ANTIBODIES, binding to specific (tumour-) epitopes	HIGHEST SPECIFICITY; SECURING AND LOCALIZATION	Diagnostics of solid and generalized tumours	42, 51, 77, 22
						Internal Radionuclide therapy	41, 42, 70, 79
		In-111 somatostatin (as an example)		LIGANDS, ANTAGONISTS to (tissue specific) RECEPTORS		Tumour verification and therapy	40

was a welcome candidate to encounter von Hevesy's interest in the use of radiactive tracers in biology. The same year, 1935, he published on activation analysis, together with Hilde Levi[48]. They detected impurities in samples of rare earth compounds exposed to neutrons.

The approach of von Hevesy and his coworkers proved to be most successful and important to biology. 1) They described the technique of inducing radioactivity, and established then the radiation properties of these elements. 2) On the basis of his observations, von Hevesy could prove that the potassium isotope K-40 is responsible for the natural radioactivity of potassium. 3) The discovery and basic development of neutron activation analysis was of highest importance, although von Hevesy was engaged with it for a short period only. These pioneer experiments relied on neutron sources at least ten millions times weaker than the powerful units available today, and electronic analysers were much less sophisticated.

Von Hevesy interpreted, to give an example, the formation of bone as a dynamic process; 'the bones take up phosphorus atoms continuously which are partly or wholly lost again and replaced by other phosphorus atoms'[12]. This sweeping statement was not in agreement with the views held at that time. Even the editor of 'Nature', personally well known to von Hevesy, took some precautions in an editorial comment, probably wanting to place himself at some distance from such untraditional thinking. This very first report also documented an exemplary multidisciplinary cooperation. That paper was signed by the head surgeon of the Finsen hospital in Copenhagen, who placed the experimental animals, laboratory facilities and technicians at von Hevesy's disposal. Moreover, it was not only a description of what the authors had done. Once more, and in best tradition of W. K. Röntgen, the presented results were placed in a most untraditional context. This pioneer experiment was to become a signal to biologists: the location and the movement of 'labelled' atoms and molecules as a function of time, their exchange with stable ones and their incorporation into different compounds were made visible and the techniques used did not influence the processes observed.

More than 30 publications spun off the radiophosphorus story during the following 8 years, at first related to general metabolic aspects like its diffusion and excretion, later proceeding to more and more specific items, like in vivo formation of organic compounds, and their rate of renewal and turnover[47]. P-32 could also be nonspecifically used as an indicator in blood volume determinations. His coworker H. v. Euler introduced P-32 techniques into radiobiology; effects of *Röntgenstrahlen* on nucleic acid metabolism in normal and tumorous tissue were presented during the mid 1940s[74]. Within five years several hundred papers had been published, including works on artificial isotopes of bromine, chlorine, carbon, cobalt, iron and sodium. Von Hevesy received many honors, among them the Nobel Prize in Medicine 1943 and the U.S. Atomic Energy Commission Atoms for Peace Award in 1959. He remained active until shortly before his death at the age of 80 in 1966. The impact of von Hevesy's revolutionary concept of the dynamic state of body constituents was summarized by R. Schoenheimer in 1942, who together with his associates systematically extended the tracer principle to humans[68].

In 1937 Hamilton and Stone used radiactive sodium in animal experiments[26]. Another important step towards clinical use of radioisotope was done by J. H. Lawrence, K. G. Scott and L. W. Tuttle in 1939 who published on phosphorus metabolism in lymphomatous animals and studies of leukemia[46], followed by a 'preliminary report on a new method of treatment of leukaemia and polycythaemia' using P-32, one year later[45]. The late publications of J. H. Lawrence were already presented in clinical journals. In 1940 J. G. Hamilton and M. H. Soley described 'Studies in iodine metabolism by thyroid gland in situ by radioiodine in normal subjects and in patients with various types of goiter'[25]. T. S. Hertz, however, together with A. Roberts, was the first to apply radioactive iodine in the therapy of Graves' disease (1942)[28,29]. It was this year that a first survey of therapeutic methodology appeared in the *Journal of Clinical Investigation* on both the diagnostic and therapeutic use of radioisotopes, presented by Hamilton and Lawrence[24]. Radioactive strontium was introduced into medical use as a new radioactive element[14], and was followed by others in quick succession, of which the introduction of technetium (Tc-99m)-labelled phosphonates for improved skeleton imaging was one important milestone[72].

Radiopharmaceuticals

More than 900 radioisotopes are known, some 28 for example of iodine, eight each of carbon or phosphorus; most of them are, theoretically, available. For practical purposes, pure alpha-emitters have been considered as ideal for therapeutic applications. However, the elements in consideration cannot be internalized within the cell itself; quantification is out of range for clinical laboratories. Beta-emitters have gained high importance. Their in vitro detection (for laboratory tests and monitoring) is easy; their domains are metabolic and intracavitary therapy. Y-90, P-32, and I-131 whose gamma emission contributes 10% to absorption, are the most often used. The ideal gamma-emitter has no additional particle emission and shows a 100–200 keV energy range which fits into the absorption optimum of modern scintillation counters. Its half-life is short enough to keep absorption low, but is long enough to enter biological cycles bound to a radiopharmaceutical.

Technetium Tc-99m fits this profile, but presents two additional advantages, i.e. its production 'at home' from a generator, and its high chemical reactivity.

The 'biological' elements, i.e. carbon, nitrogen, oxygen are available as positron-emitters (fluorine F-18 must serve as substitute for H), and their half-lives are measured in seconds and minutes: their incorporation into radiopharmaceuticals requires specialized chemotechniques, their registration dedicated instrumentation.

Their major fields of application separate radiopharmaceuticals into two main categories:

1a) basic research in biochemistry and pharmacology,
b) basic research in physiology;
2a) diagnostic and therapeutic 'metabolic' use in nuclear medicine,
b) brachytherapy.

1) In the first category, labelled drugs are used as tracers that provide fundamental information about the pharmacology of the stable drug. Or a radiopharmaceutical may serve as a way of observing biochemical interrelationships on a more fundamental base. Representatives are radiolabelled neurotransmitter ligands or antagonists, which may help to understand better the various pathways of transneural information, or tracers which match the high specific epitopes of antigens, i.e. labelled antibodies. A minority of them are found in the second group; the use of such a selected 'drug' as a standard diagnostic instrument takes advantage of the mass of information collected previously, i.e. of their thorough preclinical evaluation.

2) The radionuclide remains the essential part of a drug which is applied either to get diagnostic information – the substance is sent along a physiological pathway –, or given to suppress or even destroy a biological function. For example, this may be the exaggerated activity of the thyroid gland in hyperthyroidism or the growth of a tumour or a tumour-like disorder. There remains a subgroup of radiolabelled substances which are prepared in order to carry ionizing energy directly to a target, i.e. intentionally under surgery or radiological intervention. They are designed to adhere to the surface of cavities; or, if contained in particles of well defined dimensions, they may carry ionizing energy into the vascular bed of a tumour. Here there are parallels with brachytherapy, applying sealed radiation sources, as it is still used.

Diagnostic nuclear medicine

A radiopharmaceutical programmed for diagnostic application may be chosen

1) for in vitro applications only,
2) because of its particular chemical properties that result in its tendency to accumulate in particular organs or regions of the body, where
3) uptake, storage and release can be measured from outside, non-invasively, or,
4) its distribution can be registered as a scintigraphic map of regional function.

Three steps in design and selection have to be considered: a) Does the diagnostic problem really need a physiologically-based examination, i.e. can a purely laboratory or another, more anatomically oriented method be used? b) Is a minimum radiation dose applied to obtain the desired information? Many of the physiological processes under study in medicine occur at sufficiently rapid rates that measurements can be made shortly after administration of the radiopharmaceutical, thus saving a proband from unacceptable radiation doses (fig. 1). c) Does the time course of

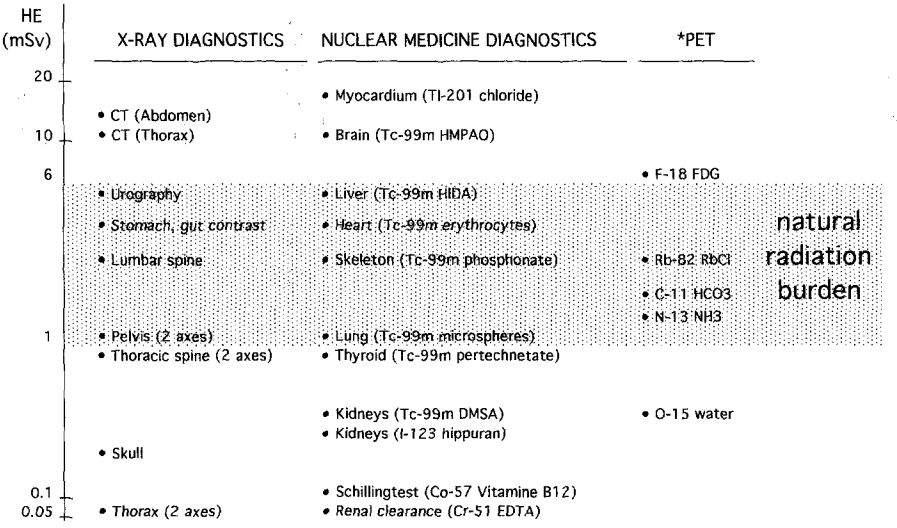

Figure 1. Mean effective doses absorbed after X-ray and nuclear medicine diagnostic procedures, compared with the natural radiation burden of the mid-European population. The graph shows a selection of the most often performed examinations[53]; some representative PET studies have been added[35].

Table 2. Normal regional distribution of mean indices of perfusion (Q), ventilation (V), exhalation (ME), and ventilation/perfusion ratios (V/Q), comparing upright (left column) and supine position (center); right column: data from a patient with respiratory insufficience (examination in supine position).

Supine (mean)		Sitting (mean)		Emphysema: sitting (patient: S.R. 63y)		
right	left	right	left	right	left	
		Q (regional)				
101.3***	104.3***	48.1	44.1	104**	80***	top
103.3***	107.1***	89.5	88.8	117***	88***	
91.7***	94.3***	143.6	143.3	114***	90*	bottom
		V (regional)				
32.5***	32.4***	30	29	74***	72***	top
32.7**	32.8***	31.9	31.8	93***	80***	
32.7	32.8**	32.3	32.2	145***	109***	bottom
		ME (regional)				
96.1**	95.6**	87.4	84.9	31***	32***	top
97	102.3*	97.2	98.5	32***	32***	
100.2**	105.2*	108.4	113.6	32***	32***	bottom
		V/Q (regional)				
0.95***	0.93***	1.9	1.96	0.71***	0.91***	top
0.94***	0.95***	1.09	1.12	0.79***	0.91***	
1.1***	1.12***	0.76	0.08	1.28***	1.21***	bottom

Statistics: *p = 0.05–0.1; **p = 0.01–0.05; ***p = <0.01. (For more information see ref. 60).

measurements and procedures fit into a typical diagnostic plan? Each situation must be decided on its own merits, i.e. the choice of the appropriate radiopharmaceutical depends on a particular question arising with a predefined disease or disorder. The procedures must fit into a schema which allows for repeated practical use, i.e. the procedure should be standardizable. This allows the collection of normal results, to define a baseline and to arrive at as strict a delimitation of pathology as possible.

Out of a large number of possible techniques, only a few practicable methods have survived to become diagnostic routine. The radiopharmaceuticals in use are provided by the industry which is responsible for chemical and radionuclide purity. In vivo use especially necessitates chains of quality controls; sterilility and pyrogen testing must be provided.

Historically, the nuclear medicine department has been a supermarket that offers a variety of tests. However, most of the in vitro tests are delegated today to centralized units of physiological chemistry, after the radioisotope specialists have perfected them. Imaging is left to the diagnostic radiologists if a clinical problem can be solved by an analysis of structural abnormalities; as a result, no indication has been left for static liver or brain scintigraphy.

The patients' problems can be viewed as molecular dysfunctions. Nuclear medicine provides molecular 'slices of life' joining histopathology as a way to characterize disease[77]. Without doubt, structure and function converge at the molecular level. Methods of modern nuclear medicine diagnostics typically combine (1) quantitative measurements of parameters describing the global function of an organ with (2) a topographic display of its regional distribution. Global function may be described by in vitro or even non-isotopically-derived tests, and anatomical precision improved by 'fusing' a scintigram (or tomoscintigram) with X-ray or MR images (see Elke in this issue). Importantly, function attributable to parts of an organ is to be defined by its share in the global function. Regarding the lung, blood perfusion and gas washin and washout were systematically examined by Ball and Gates applying non-isotopic tracer methodology[4,5]. Today, both ventilation and perfusion are scintigraphically separated and specified in percents of the global lung function (an examination that has gained importance in pre-surgery studies); even the contribution of lobes and segments can be evaluated. The normal gradient of regional blood and gas flow values, as determined from an average of multiple healthy persons, gives the basis for a comparison in rest and under a specified stress (table 2)[60,65].

Such an unspectacular diagram makes lung 'images' like those of figure 2 easier to understand: various contrasts are displayed in black and white, and the grades of black mirror the regional tracer concentrations along a linear scale. The pattern of the distribution of gases (left side, figure 2) and blood flow (right side) reveal multilocular mismatch in the given case (figure 2, upper row). These three 'images' together illustrate pulmonary embolism: blood clots have occluded segmental and lobar pulmonary arteries which cause irregularities in perfusion distribution, but do not alter bronchial gas exchange. Chronic obstructive bronchial disease (COPD) follows another, strongly different functional pattern: impeded regional washin and late retention of the

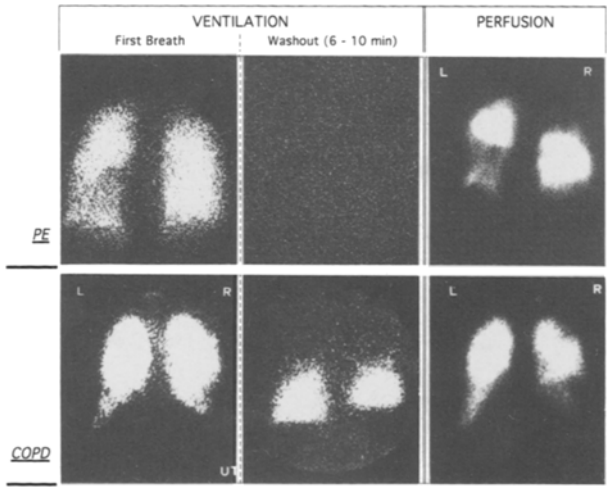

Figure 2. Ventilation and perfusion lung scintigraphy, analogous display (selections are given of representative images).
Top row: PE: Pulmonary embolism: normal distribution of first breath ventilation, no late retention of Xe-133 xenon gas; but multisegmental defects of perfusion distribution, as seen after i.v. injection of Tc-99m MAP (macroaggregated human serum albumen particles) due to thrombo-embolic obstruction of multiple lobar (right upper lobe, left lower lobe) and segmental pulmonary arteries. Bottom: COPD (chronic obstructive pulmonary disease): perfusion defects (predominantly located at the lung bases) caused by impeded ventilation: Xe washin (1. breath) decreased and retention prolonged (washout).

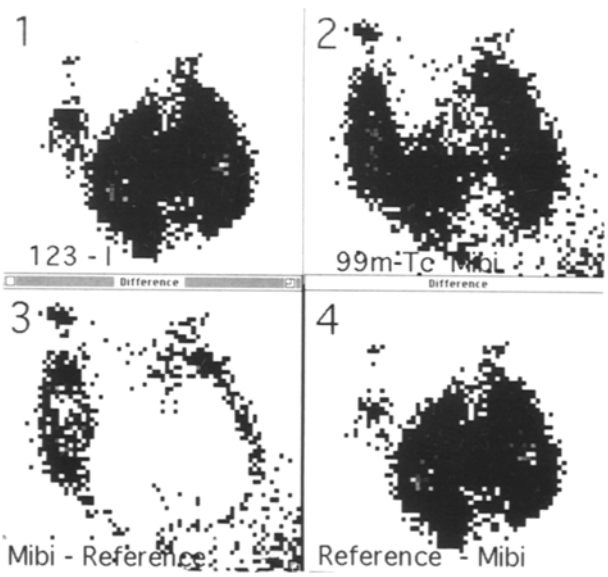

Figure 3. Thyroid scintigraphy: goiter with multifocal functional autonomy. (*1*) Functional scan showing the spontaneous distribution of retained I-123; (*2*) 'cellular' scan presenting regional distribution of viable thyroid cells, done after i.v. injection of Tc-99m MIBI, a tracer which is accumulated by the mitochondrias; (*3*) parametric isolation of spontaneously afunctional (i.e., in (*1*) suppressed) thyroid parenchyma: see for the slightly enlarged right lobe and residues of a left lobe which is impressed and elongated, edging the lateral portion of the autonomous nodules; (*4*) parametric isolation of the centrally located autonomous tissue.

radioactive gas (in place of air) at the bottom on both sides signal the obstruction of air ways which causes localized hypoperfusion (figure 2, bottom line). The scintigrams present uptake of the inhaled gas (first image of the Xe-133 study) and of the intravenously injected embolizing Tc-99m labelled macroaggregate (the perfusion study) in quantitative terms[60]; in practice, however, a glance at analogous images will satisfy the diagnostician.

Today, patients (and a majority of physicians) anticipate radioiodine to be distributed solely over the thyroid gland (fig. 3.1). Since this 'specific' presentation of an organ agrees with ultrasonography, thyroid scanning has returned to its true use. In the given example a double isotope preload reveals both function (1) and cell density (2) (the images are acquired almost simultaneously by the same camera); additional maps of afunctional thyroid tissue (3) and of regional functional excess (4) were obtained with the help of a computer program and are also presented in the final document. Additional protocols (a list of numbers, not printed here) contain quantitative data on the magnitude of the possible contrasts (in this case: =16). With a 'multinodular autonomous goiter' these data (and the size of the 'hot' areas, also readable from the scans) are the basis for dose calculations before treatment with radioiodine may be initiated. The same double isotope technique is in use to differentiate malignant from benign growth of thyroid nodules (fig. 4).

Brain studies utilize both diffusable flow tracers and non-diffusable radiopharmaceuticals, which represent blood volume distribution. Certain stages of localized brain damage due to ischemia are made distinguishable. Combined with patterns of glucose uptake distribution, and using standardized algorhythms, the computer will calculate a sequence of physiological data, again spread over the whole organ.

Similar techniques are used for myocardial studies: among various ischemic lesions of the heart wall, patterns of irreversible damage can be separated from reversible injury which, if necessary, may respond to surgical intervention (figs 5, 6)[57,66].

Myocardial scintigraphy includes perfusion studies, traditionally using Tl-201. Applications of thallium are still at a stage of continuous improvement; after two decades of use, the latest protocols provide additional information on residual viability in cold, i.e. possibly scarred, myocardial regions. Re-injection techniques are discussed, but the addition of an 18F-FDG emission-tomoscintigram seems to be, at the moment, the more reliable technique (fig. 5). 'Quantitative coronary angiography delineates intraluminal dimensions of macroscopic coronary arteries effectively. However, nutritive myocardial perfusion is dependent not only on the magnitude of luminal encroachment by atheroma, thrombi and complex plaques, but also on the segmental length and distribution of lesions, the presence and extent of collateral flow, intramyocardial tissue pres-

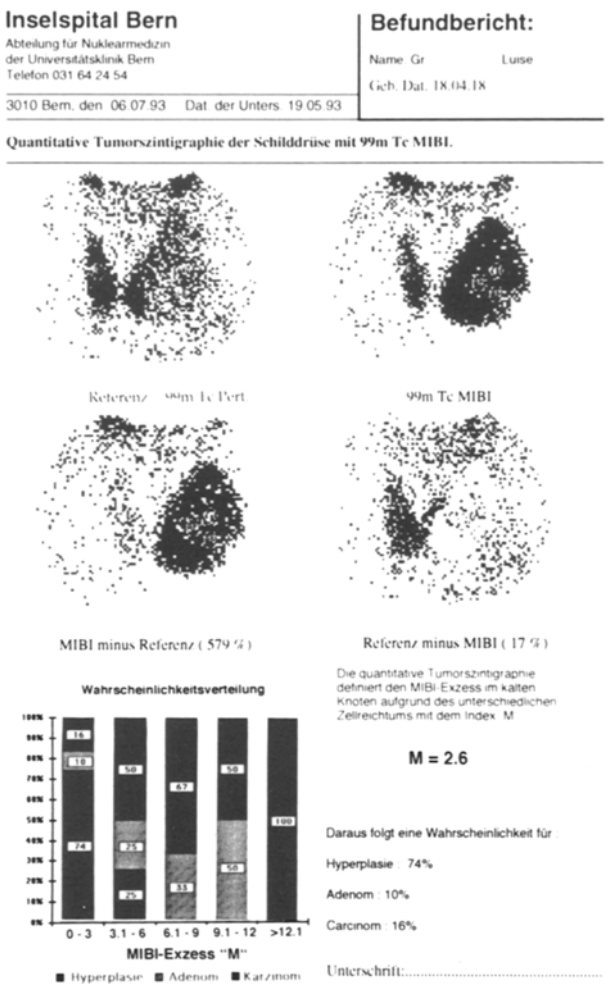

Figure 4. Protocol of a thyroid examination, showing 4 scintigrams of a uninodular goitre. Tc-99m pertechnetate (used as a radioiodine substitute) presents a cold i.e. afunctional) nodule in the left lobe (top, left); this nodule shows a hyperdense uptake after injection of Tc-99m MIBI, indicating the presence of viable cells (right). By subtracting the MIBI image from the reference, one results in an image of the isolated, now hot nodule (bottom, left), strictly separated from the functioning thyroid tissue (right). The MIBI excess was calculated as M = 2.6, which value gives a 16% probability of malignant growth. The registry (bottom, left) is continously adapted to increasing experience, thus improving the statistics: each patient with a final histologic diagnosis (after surgery) is going to be implemented.

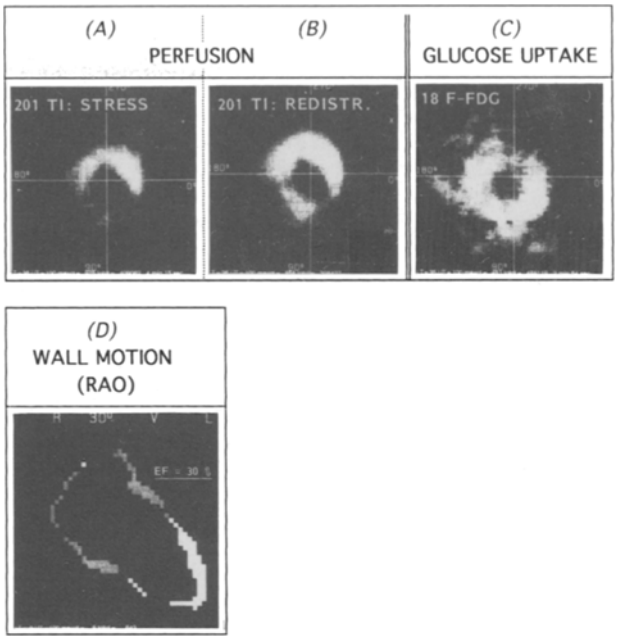

Figure 5. Myocardial regional perfusion and metabolism tomoscintigrams (top row): a composite presentation of midheart, short axis tomographic slices. *A* Tl-201 uptake acquired after stress, and, *B* three hours later in redistribution. *C* Regional glucose utilization in rest.
The patient suffers from a three vessel coronary heart disease and has survied 3 myocardial infarctions. He presents akinesia and hypokinesia of the inferior and posterior myocardial segments of his left ventricle [*D* Wall motion parametric picture, acquired (in right-anterior-oblique projection, using 'first pass technique' immediately after i.v. injection of 99m-T labelled serum albumen, showing the left heart ejection fraction (EF, in healthy persons > 50%) and regional wall excursions from diastole (outer contours) to systole (inner contours of the left ventricle)]. *A* Half of the myocardial circumference is absent due to insufficient blood supply under stress. *B* This defect has been partially restored with rest. *C* Glucose uptake is increased within all jeopardized segments (there is left some normal and non-glucose-dependent myocardium at the top), promising good recovery of this 'hibernating' myocardium after invasive treatment. (Missing glucose uptake of non-perfused tissue would have indicated irreparable scar.) In deed, after dilatation of the coronary arteries EF increased to values > 60%.

sure, the magnitude of vasoconstrictor tone, regional neurohumoral stimulation and vasoconstrictor and vasodilatator metabolites intrinsic and extrinsic to coronary vessels'[69]. Parametric display visualizes various grades of perfusion in a three-dimensional display; concomitant wall motion abnormalities are projected onto these images, which are completed with numerical data on global myocardial performance (figs 5, 6).

Nuclear medicine's greatest merit is its ability to quantify physiological processes non-invasively. And 'nuclear medicine has time.' Time is probably the single most important variable in nuclear medicine, the other two being volume and mass (K. Britton, 1983, after ref. 55). Activity-time curves were introduced in the 1950s[73,80] and found especially useful for renal functional studies, but would no longer be practicable if not done in combination with a simultaneous renal clearance determination; right and left kidney parameters are interpreted with knowledge of the global renal function value[54,62]. One of the most important steps towards a holistic understanding of tracers and their clinical utility came from Therese Planiol in the mid-fifties. She not only diagnosed and localized a cerebral lesion causing neurological deficits, using I-125 human serum albumine and the most simple instrumentation, i.e. a probe which sequentially gathered counts around the skull surface; she also observed the contrast rising or falling over 24 hours and found behavior patterns attributable to particular tumours and vascular lesions[56]. These results could be fully confirmed with the introduction of a

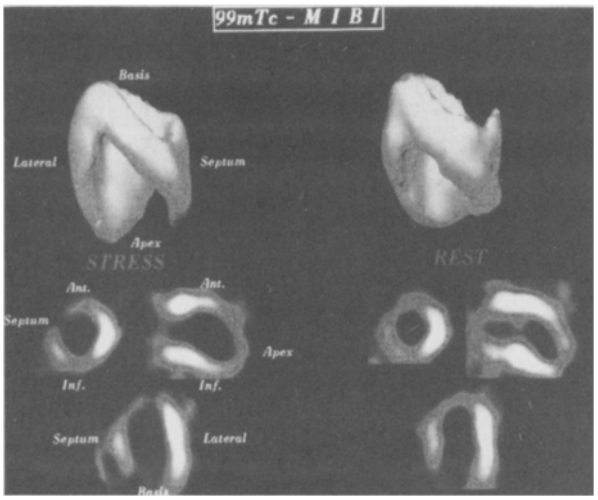

Figure 6. Myocardial scintigraphy: pseudo-3D reconstruction of the well perfused myocardium (under stress) and in rest (upper row, seen from posterior): The large defect includes the apex of the left ventricle and represents afunctional (not absent!) myocardium; this defect decreases with rest, indicating a rim of stress-induced myocardial ischaemia. The slices, displayed along short left ventricle axis, sagittal and long axis (bottom), represent cutouts from the standard presentation of a multitude of slices.

camera-dependent method[64]. Mme Planiol gave the signal for a new technique, applicable to other organs, summarized in table 1.

Brain scintigraphy gained importance in neurology and neurosurgery, but was increasingly rivalled by the upcoming new computer-aided tomography (see Elke in this issue). Regional cerebral blood flow determinations are still based on the rare gas desaturation PET technique[43], but have been adapted since then to single photon registration after the introduction of Tc-99m labelled tracers which are retained in brain tissue dependent on blood flow. Today, neuroimaging studies of various receptors, using analogues or antagonists of transmitter substances, have furthered the understanding of normal brain function and of the pathophysiology in several neuropsychiatric disorders, as the distribution of these receptors plays an important role in cognitive function. These neuro-physiological imaging studies are the domain of positron tomography (PET). Single-photon emission computed tomography (SPECT) utilizing brain perfusion agents has been increasingly used in the localization of epileptic foci. Early or late accumulation of fluoro-deoxy-glucose, methionine, thymidine, and of iododeoxyuridine by tumours are another field of recent interest.

The non-invasiveness and low radiation burden (see Roth and Fritz-Niggli in this issue) of typical examinations with radionuclides[35,53,61] paved the way for functional tests in which, performing the examination two times, a basic condition is compared with a second one under the influence of a pharmacological agent, or after physical intervention or even under emotional stress[9].

An example known since the fifties is the awakening of a spontaneously afunctional thyroid gland after stimulating pituitary hormone (TSH) has been injected. In Plummer's disease, tissue spontaneously suppressed via negative feedback due to excess hormonal production in autonomously functioning nodes takes up radioiodine again; a repeated scintigram strongly contrasts with the previous condition. Kidney studies done under water restriction are repeated after an acute water load and facilitate the differentiation between various patterns of urine flow obstruction. Myocardium suspected to suffer from borderline blood flow in coronary heart disease is stressed by labour or medicaments; myocardial scintigrams before and thereafter reveal permanent defects (i.e. infarction), reversible ischemia, or normality[9,10,39,57,67]. The distribution of regional brain blood flow reflects active brain regions under specified tasks[6,10,21,56]. Functional double isotope studies of clinical relevance can dispense with costly electronics when used for the evaluation of global organ conditions, as with the determination of extravascular lung water (with impending pulmonary oedema)[7,17], or for the scintigraphic differentiation of parathyroid tumours using standardized subtraction techniques[18]. This type of examination has gained importance since tomography and dedicated computers have been made available (fig. 7)[30,67]. Modern instrumentation utilizes more than one gamma camera head, thus gaining sensitivity. This makes tomographic presentation of normal and abnormal 'functional anatomy' possible. In three-dimensional mode, the neighbourhood of and the potential interrelationships between different pathologies is displayed. This procedure greatly improves the interpretation of diseases with a multitude of analogous or divergent lesions (fig. 7).

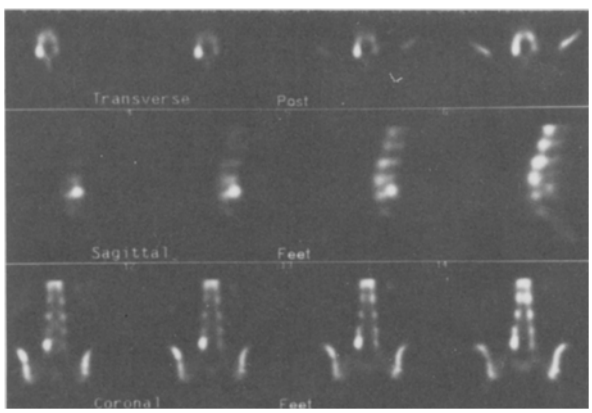

Figure 7. Osseous tomoscintigraphy (=SPET, using Tc-99m DPD) of the lumbar spine in a patient with low back pain. Selected are transverse (top), sagittal (center) and coronary slices (bottom). Maximum uptake is seen in a lesion that includes the right intervertebral (=facet-) joint, but extends to the adjoining articular and lateral processus: reactive spondylarthosis, or 'activated facet syndrome'.

Therapeutic nuclear medicine

Metabolic treatment is initiated by oral or intravenous application of radiopharmaceuticals which are transported to an organ on predefined physiological pathways and accumulated thanks to specific storage mechanisms. The radioiodine therapy of hyperthyroidism, characterized by thyroid hyperplasia and accelerated function works because of the high thyroid concentration of iodine; the radiation-induced damage inhibits thyroid follicle cell function. Three dosage principles may be quoted as examples of the procedure. 1) A fixed 'dose' of 3–5 mCi of 131-I (dose is used in the meaning of amounts, but is measured here in units of Ci [old] or Bq [new SI-units = 'Système International d'Unités'] – [see Elke in this issue]) is orally administered. A minority of the patients fails to respond; repeated 'doses' must be given to result finally in normal thyroid function or hypothyroidism. Such a procedure requires an (atypically) homogeneous distribution of goiter size, of radioiodine uptake and retention values. 2) This method considers gland size and uptake and is calculated as a fixed dose per gram of thyroid. Clinical experience may modify the applied 'dose', but there remains a system of arbitrary units adapted to one dedicated field of application only. 3) An amount of 131-I is calculated to deliver a predetermined radiation dose to the thyroid. Only this method is based on the radiation dose absorbed (in old units of rad = radiation absorbed dose, or new SI-units Gy = Gray = 100 erg/g tissue). No other method provides a consistent framework that uses universally accepted units and measurements and which is flexible enough to be applied to various types of hyperthyroidism in a landscape dominated by non-uniform goitres. This modality clearly prevails in Continental Europe; the principle can easily be transferred to methods applying various radioisotopes internally to other organs or biological systems. Its rules and calculations are valid in general, allowing an interindividual comparison of success and side-effects.

In the case of hyperthyroidism due to Graves' disease (immunologically-induced hypertrophic disease in which the whole body of the gland is externally overstimulated), smaller doses (<150 Gy) are used to reduce the mass of active cells. With Plummer's disease (due to thyroid tissue autonomously growing and functioning), ablative doses of ≥ 300 Gy are required; it is this hyperthyroidsm alone which can really be cured by eradicating its cause[30].

Now, after more than 50 years of experience, 131-I treatment is recognized as the simplest, safest, least expensive and most effective form of therapy for most patients. Hypothyroidism is a potential complication, especially in Graves' disease, but radioiodine shares this with surgery. Its rate is minimal ($<3\%$/after 1 years) in Plummer's disease; this is in strong contrast to surgery, which is in addition burdened with recurrences or local complications[30,38].

Radioiodine therapy of differentiated thyroid carcinoma is the most important additional treatment after surgery. Doses of >300 Gy are applied to eradicate residual thyroid tissues; higher doses, often sequentially applied, are needed for tumour reduction or elimination[15]. Papillary carcinoma still kills 20% of cases over more than 10 years, but these are mainly the older patients. With malignant goitre of the young, however, survival rates of better than 90% are achieved now, in contrast to less than 30% before the introduction of radioiodine[57].

Radiophosphorus 32-P therapy in myeloproliferative diseases is still important in polycythaemia vera. Intravenous application is easily done and can be repeated (after years of disease-free intervals).

Meta-[131-I]-iodobenzylguanidine therapy of malignant pheochromocytomas and neuroblastomas will be a highly successful adjunct in treating these neuroendrocrine tumourous lesions. Most experience stems from treatments of late stages of these diseases; its introduction as a primary adjuvant after (and before) surgery promises earlier tumour reduction, faster recuperation of well-being and improved survival[70].

Still in development is the therapeutic application of antibodies docking at tumour-associated antigens, and of receptor-specific radiopharmaceuticals in malignant and non-malignant diseases[99–102].

The use of radiolabelled antibodies for cancer therapy requires specification of two basic parameters: the amount of antibody that should be administered and the amount of radioactivity that should accompany the antibody. A systematic approach to the selection of these two parameters must include consideration of each patient's tumour burden, antibody clearance kinetics, and the antibody-antigen interaction. A large body of experience will be necessary to find the best compromise between destructive doses to the target and tolerated co-irradiation of normal tissue. One problem is the rather slow transport of the energy-carrying vehicles. Uptake and retention are sufficient to deposit doses higher than 80 Gy to the target.

Various beta-emitting radiopharmaceuticals have been introduced for the treatment of recurrent malignant pleural and abdominal effusions; they have declined in importance since the introduction of improved chemotherapy. In joint diseases they have an increasing application: with shorter halftimes and beta energies appropriate for various ranges in tissues side-effects are minimized and higher doses made applicable with improved long-term outcome in potentially crippling diseases[27].

Following a similar principle of mechanical deposition, the use of intra-arterially injected radioactive particles of a size large enough to lodge in end arterioles and

capillaries is a particularly attractive mode of therapy. The application of a highly selected end-arterial distribution of doses 20 to 30 times greater than achievable by external beam therapy seems to be ideally suited to the treatment of solid tumours[27]. Progress in interventional radiology now allows access to more peripheral tumor-feeding arteries. Thus doses can be augmented to levels that really eradicate tumours, whereas the irradiation of adjacent tissue is reduced to innocuous doses[63].

Radiation measurement and protection

The measurement of radiological units considered both X-rays and radioactivity in parallel. At the International Congress on Radiology and Electricity in Brussels in 1910, Ernest Rutherford chairing the radium standardization committee, presented the CURIE unit in honor of Madame Curie. The first international standard contained 21 mg of pure RaCl2 sealed in a glass ampule, but this was abandoned in 1930, when Ci was defined in terms of absolute disintegrations per second, facilitating its more general application to natural and artificial radioactivity[37].

Later revisions of international units definitely based on fundamental physical terms (see Roth and Fritz-Niggli in this issue), restricted the terms to activity, energy dose and equivalent dose, and introduced 'new' names of pioneers in the field, i.e., Gray (1 Gy = 100 rad) for energy dose, Sievert (1 Sv = 100 rem)) for biologically absorbed dose or 'equivalent dose', Becquerel (1 Bq = 1 desintegration/second, 3.7 × 1010 Bq = 1 Ci) for the quantity of a radionuclide (ICRP Nr.26, 1977[31]). Activity to dose relationships were formulated by Marinelli and Hill[21a, 50, 59] and finally revised by a Committee on Medical Internal Radiation Dose 'MIRD'[49, 71]:

$$D = A \times F \times Teff \times k / M$$

D (Gy), A (MBq),
F (% distribution factor)
Teff (effective half-life),
M (g absorbing tissue)
k (Gy × g/MBq × d,
available in tables).

Today 4 classes of tissue are weighted (WT from 0.01 for skin and bone surface rising to 0.2 for gonads); the 'effective equivalent dose' (HE = equivalent dose × WT) takes into account risks due to stochastic radiation damages, i.e. cancerogenic and genetic effects[32, 35, 58]. This allows a direct comparison of doses absorbed from X-ray and nuclear medicine examinations (table 2)[53].

The establishment of radiation protection standards has grown out of discussions among the major radiological societies and moved from 'tolerance' to 'maximum permissible doses'. Once again, the evolution mirrors progress in techniques. It began with 'erythema doses', which were biological measurements: the effects were visible by eye, indicating too great an exposure, and has advanced to the registration of decay events and direct absorption measurements[33, 34].

Nuclear medicine as a speciality in its own right

What types of information do radioactive tracers provide, how can they be used in general to solve problems in medical diagnosis? Changes in physiological processes are made visible, and even more importantly, are made quantifiable. The 'ontological' doctrine of strong causal specificity is complemented by a more complex view, by which internal mechanisms of inherited or acquired 'errors of metabolism' are disclosed[78]. Tracer methodology also elucidates the body's responses to various injuries: bone seeking radioisotopes report on the non-specific reaction of normal bone during tumourous growth, or on trauma or metabolic disorder; they are not accumulated by the primary cause itself. The approach to a diagnosis is an indirect one, then, and findings are interpreted as the response of the organism to a harmful factor in the internal or external environment. Such a lesion is specific in proving the bone's ability to react, but not in giving a clear indication of the cause. Or, to give another, more speculative example: radio-labelled 'tumour-associated' antibodies promise direct visualization of cancer, a diagnostic method of the highest specificity thinkable. Thus, it is this mixture of highest and lowest diagnostic specificity within the field of modern nuclear medicine which makes a full comprehension of its statements difficult. No doubt, to understand these biological reactions requires sound knowledge of the nature of the process and of the multiplicity of factors which might have altered a 'typical' response. Broad clinical understanding and some awareness of the complexity of a given situation are prerequisites to interpret the information presented by an individual set of diagnostic results, and interdisciplinary team work is mandatory. On the other hand, with thyroid diseases, nuclear medicine physicians have taken the opportunity to accumulate that level of competence that enables them to provide complete diagnostic information on specific clinical pathology, especially as treatment with radioiodine has become more popular than surgery or conventional treatment.

Nuclear medicine covers basic research and clinical medicine from both diagnostic and therapeutic points of view. As a medical speciality, however, its evolution followed two divergent paths. In Europe the clinical approach to practice clearly predominates; the phase of 'comprehensive clinical studies' clearly dominated over technologically driven apprenticeship of medicine. The reasons for the self-confidence probably lay in the extent of iodine deficiency in Continental European countries. The large population of persons suffering from

various goitres elicited an impressive degree of success in diagnosis and categorization of thyroidal diseases and, not least, in treating goitres. This rich clinical activity, boosted by legislation and governments (which were mainly obsessed with radiation safety considerations), gave European nuclear physicians the chance to invest the wealth of experience in both clinical fields. Their basic research consistently remained close to the demands of medical practice. In consequence, with less fragmented expertise, costs remain low, the handling of (potentially dangerous) radioactive substances is kept reliable, the ability to exploit changing technologies is maintained.

Indicative of the 'goitrogeneous' hypothesis of a dichotomic development was the slow growth of nuclear medicine in the United Kingdom, northern America and Scandinavia, where goitres are (nearly) unknown. Nuclear medicine has remained in a state of dependence on diagnostic radiology or clinical pathology, respectively. The stage IV of evolution (table 4), dominated by comprehensive studies, has not been reached, or has been cautiously introduced in some isolated parts, most often by immigrants. In the USA, especially, where the future of nuclear medicine is planned together with anatomically orientated techniques, further fragmentation is expected under a strategy of organ-related imaging programs in large radiology departments[51]. Diversification in staff education and recruitment clearly favours anatomical imaging; modern nuclear instrumentation, represented today by highly sensitive camera systems, are still compared by criteria of resolution and detail recognition. Nevertheless, the vision of a 'sliced physiology' is still held[77].

Nuclear medicine has grown into a medical discipline in its own right[16]. It is recognized as a clinical speciality in all European countries. In the English speaking countries, less so in Continental Europe, the rather young discipline has to endure multifold irritations, mainly caused by competing diagnostic modalities like ultrasonography and magnetic resonance imaging. Nevertheless, complexity in the diagnostic and therapeutic fields alone established an order of management that supports its further autonomy. It is the full time specialist, who is responsible for applying radionuclides to living humans, for radiation protection of diseased people as well as of his coworkers and the population as a whole, who is finally responsible for this discipline. He needs thorough training which can be exacted only from senior specialists experienced in all three branches of the discipline.

Future of nuclear medicine

Radionuclide procedures will show a continuous increase in demand and utilization. New classes of radiopharmaceuticals are going to be introduced, ringing in a next stage in the evolution (table 1). Expertise in biochemistry and immunology is required in nuclear medicine; and 'imaging' will finally find its place as the technical servant for improved comprehensive presentations of functional data. Although the need will increase for individuals who devote most of their practice to nuclear medicine, responsible for advancing the technical aspects, staffing the PET facilities, testing new radiopharmaceuticals and new software and developing new instruments, the future of nuclear medicine physicians is less clear. In the English speaking countries, where the efforts to fit the use of radioisotopes into the broader imaging world will promote scintigraphic techniques and their applications, their future is bound to radiology groups; nuclear medicine programs are offered as part of the overall delivery of imaging services. The expansion of the scope of radiology, however, and its trend towards subspecialization into areas of neuroradiology, cardiovascular radiology, cross-sectional imaging, pediatric radiology, abdominal imaging, will leave little space for an independent nuclear medicine[51]. This list is open to expansion; no doubt, radiology and the more minor discipline nuclear medicine, will be allocated to organ-oriented clinical disciplines. 'Imaging consultants' will be engaged in the interpretation of the studies issued by their organ division[51]. These specialists will distinguish themselves by their extensive knowledge of organ anatomy and physiology, as well of its irregularities. Radiology departments will change their organizational structure. Students and residents will probably favour the integration of all imaging modalities for the establishment of a diagnosis. As seen from Europe, which still concentrates on technical skills and instruments, this solution is to pinpoint one important aspect only, the most expensive one: with more fragmentation, the expenses in practice will rise. How will the organ-dependent specialist follow the dynamics of changing technologies?

Will nuclear medicine be the very first subdiscipline to dismantle this inappropriate form of internal organization? Because the laws of molecular medicine work ubiquitously, i.e., in more than one organ and not limited to regions of the body, their clinical applications do not fit into the needs of an anatomically orientated approach. Moreover, the balance between useful and destructive, diagnostic and therapeutic use of radioactivity has its own burden of responsibility. The nuclear medicine in situ diagnostics of molecular abnormalities will continue to promote better understanding of intra- and intercellular communication: 'diagnosis will be molecular, treatment will be molecular, and monitoring the response to treatment will be molecular'[77].

Finally, coming back to practical aspects, the majority of specialists work outside the larger hospitals or university-linked institutions, unable to offer full imaging and nuclear medicine service at normal costs.

Therapeutic nuclear medicine might find its place under the shelter of radio-oncology departments, and participate in well established health physics, making use of their access to natural sciences; but will it really find there that independence of research, guided by competent scientists and practitioners in the field of unsealed radionuclides? Nuclear medicine needs direct contact with biological chemistry, immunology, i.e., with laboratories in which the future of 'metabolic' research in its broadest sense is safe. Where will the inspiration of a continuous intensive use of those products that the biological sciences will provide, like, to speak of recent developments, immunogenic agents for therapeutic[41,79] and diagnostic purposes[22,42], for receptor ligands and the new class of peptides[40] come from, if not from a prosperous discipline which, since its birth and throughout its history, has been dedicated to medical use of unsealed radioisotopes and comprises basic (clinical) science, diagnostics and therapy?

Nuclear medicine seems to be better prepared to answer future challenges in Europe, where it has been recognized officially as an independent speciality. In some countries government regulations even limit the practice of a physician to one speciality. Strategies of organ-related imaging programs are conceived as a result of a defensive understanding of the radiologist's role, and not of a reflection of what is best for the patient[16]. Nuclear medicine institutions have their own medical service, and they are well prepared to deliver their own contributions to health care. Therapies will immensely add to their clinical responsibility. Cooperation with Röntgen departments will continue, attention will be directed to inspirations dervied from results in basic life sciences and to the demands of the clinics: the nuclear medicine physician was, is and will be judged by his or her ability to work jointly within an interdisciplinary team.

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