Nuclear Medicine in Urology and Nephrology

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NUCLEAR MEDICINE IN UROLOGY AND NEPHROLOGY

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Foreword

The cooperation and integration of the scientist and clinician within a single hospital complex has significantly advanced non-invasive techniques in nephro-urological investigation. The consequent reduction in morbidity has allowed the surgeon to plan his operation more carefully and to achieve greater success from the selected surgical procedure employed. Nuclear medicine procedures provide information not obtainable by other methods. When used in combination with radiological techniques and ultrasound, an accurate diagnosis should be assured.

The greatest contribution of nuclear medicine to urology is the assessment of the dynamism and functional capacity of the urinary tract without submitting the patient to traumatic procedures and high radiation dose. It is readily available to the paediatrician, nephrologist, transplant surgeon and oncologist.

The amalgam of urologists and specialists in nuclear medicine has been essential to the concept of this book, which should be useful to all students and workers in the field of nephro-urology.

The views presented throughout the various chapters are those of a group of clinicians and scientists working mainly at the Manchester Royal Infirmary. I do not think that anything has been lost by this concerted approach; rather the work has benefited by the resultant clarity and consistency.

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Preface

During the last few years nuclear medicine has become a major medical specialty interacting with most otner clinical disciplines. The purpose of this work is to provide a concise but comprehensive volume, describing and evaluating the current applications of nuclear medicine to urology and nephrology.

The book is in three Parts. The first presents a description of the nuclear medicine techniques and their interpretation. The second discusses in depth their application to specific clinical problems. Part 3 deals with basic principles and expands on the relevant theoretical and technical aspects not covered in detail in Part 1.

While setting out the book in this way has necessitated the use of many cross-references, we believe this to be justified in the interests of the overall balance of the presentation. Thus the clinician interested in the application of the techniques in clinical practice will find the information in Parts 1 and 2 and may refer to the relevant technical details in Part 3 if he wishes. Conversely, nuclear medicine specialists and physicists may wish to read Part 3 in more detail.

Where appropriate, SI units have been used, but, at the time of writing, they have not gained wide acceptance in radiation dosage or dosimetry and the authors make no apology for retaining the use of the curie and the rad.

In Chapter 16 the reader will find a carefully selected choice of passages in small print covering the detailed mathematics involved in nuclear medicine techniques. These passages may be omitted without detracting from an understanding of the principles behind quantification techniques.

Although this book is primarily intended for urologists, it is hoped that it will also be of value to those working in the fields of nephrology, nuclear medicine, radiology and medical physics.

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Introduction

Nuclear medicine is a new clinical specialty whose distinctive feature is the use of radioactive materials. It has been defined by the World Health Organization as the branch of medicine 'taken to embrace all applications of radioactive materials in diagnosis, treatment or medical research with the exception of the use of sealed radiation sources in radiotherapy' (WHO, 1972). Its evolution as a scientific discipline has its origin in the development of the atomic theory, whose philosophical basis may be traced back to ancient Greece. In 500 B.C. Leucippus of Mileto put forward his 'dichotomy theory': if one were to divide anything into two parts, and repeat the process over and over again, there would come a point at which further subdivisions were impossible. At this point one would have obtained the individual *atom*. He also suggested that these atoms were separated by space, correctly recognizing the basis of the structure of matter. These theories were followed up by Democritus of Abdera, who postulated that atoms were distinct in shape and size and that it was this distinction that endowed different elements with their different properties. The atomic theory continued to find followers such as Epicurus in Greece and Lucretius in Rome, who expanded these principles in his didactic masterpiece *De Rerum Natura*. While little of the writings of Leucippus, Democritus or Epicurus survives, the work of Lucretius can be seen to this day, preserving the early atomists' views to modern times.

In the seventeenth century Robert Boyle investigated and defined the elements as substances which could not be broken down into simpler constituents – a modernization of Democritus' ideas – and a century later Lavoisier extended the principle by distinguishing between elements and compounds. In 1808 John Dalton published his *New System of Chemical Philosophy*, which included two fundamentals of our modern understanding of the nature of matter: (1) all matter is composed of atoms and (2) chemical combinations take place between atoms. In November 1895 Wilhelm Conrad Röntgen discovered X-rays, and four months later Henri Becqueral made a momentous discovery during his experiments on phosphorescence. He developed a photographic plate which had been left in its wrapping in a drawer together with some uranium salts. To his surprise, he found an intense silhouette of the uranium salts, and postulated that they were emitting some rays of unknown nature which had certain properties

in common with X-rays (Becquerel, 1896). Shortly afterwards Marie Curie confirmed this postulate and discovered that thorium emitted similar rays to those of uranium, which she called Becquerel rays. This new form of energy was later called radioactivity and uranium and thorium were termed radioelements. In 1898 Pierre and Marie Curie discovered radium, a radioelement more active than either thorium or uranium.

At this time Ernest Rutherford began to study radioactivity, first at McGill University, Montreal, and later in the Cavendish Laboratories at Cambridge. In 1911 he proposed his theory that all atoms consist of a small, positively charged nucleus in which practically all the mass is concentrated, surrounded by orbiting electrons. Bohr, working with him in Manchester, further clarified the orbital systems and distinguished between atomic weight and atomic number, so introducing the concept of isotopes as species of an element which are chemically identical but physically different. Out of this pursuit of the atomic theory grew an entirely new branch of physics – nuclear physics.

In 1927 Blumgart and Weiss injected aqueous solutions of radon intravenously and monitored the velocity of blood flow between one arm and the other with a cloud chamber (Blumgart and Weiss, 1927). This was almost certainly the first recorded nuclear medicine investigation, but the major developments in this field had to await the availability of artificially produced radioactivity. In 1932 Chadwick discovered the neutron, which led to the definition of a nuclide as a particular combination of nuclear particles – protons and neutrons. Two years later Frederick Joliot and Irène Curie bombarded aluminium with alpha particles and produced phosphorus-30, the first radioactive nuclide to be produced by nuclear transformation. In the same year Ernest Lawrence invented the cyclotron and in 1942 the world's first nuclear reactor, designed by Enrico Fermi, came into operation. The tremendous flux of neutrons within the reactor provided the possibility for production of large quantities of a wide range of radioactive nuclides which have become available since 1945. Probably the most important of these has been molybdenum-99 because it decays into a short-lived metastable daughter nuclide – technetium-99m – and has led to the introduction of the technetium generator.

In the early days of medical application of these new tracer materials the only effective radiation detector available was the Geiger–Müller tube. Its efficiency was unfortunately very low when detecting gamma rays – especially the energetic 364 keV gamma ray emitted by iodine-131, one of the earliest radionuclides produced. In 1947 Kallman, working in Germany, and Coltmann and Marshall, independently in the USA, showed that the radiation-induced scintillations from calcium tungstate crystals could be detected by optically coupled photomultiplier tubes. In 1949 Benedict Cassen explored the possibility of making a sensitive directional gamma ray detector, using a side-window photomultiplier and a calcium tungstate crystal, and was able to detect more than 25% of ^{131}I gamma rays (Cassen, Curtis and Reed, 1950). Later tests showed that rabbit thyroids could be rapidly and accurately located in this way after the administration of 10 mCi of ^{131}I. This having been demonstrated, a detector was set up on a stand and point-by-point counts were made over the thyroid on patients at the Veterans Administration Hospital in Los Angeles. From 100 to 200 μCi of ^{131}I was administered and the thyroid was completely mapped in 1–1½ h. Because of the length of time this took, the system was automated, and thus the first rectilinear scanner came into being. Calcium tungstate was replaced

in 1951 by thallium-activated sodium iodide crystals, already extensively studied by Hofstadter (1948). The scanner was further refined by employing focused multichannel collimators and developing data-presentation and -processing techniques. In 1957 Hal Anger introduced a further significant advance in nuclear medicine instrumentation: the position-sensitive scintillation detector system and its incorporation into the 'gamma camera' (Anger, 1957). This device is able to produce an image of distribution of radioactivity with greater efficiency and more operational simplicity than the scanner.

The artificial production of radioactive tracers and the availability of equipment for their detection was quickly followed by attempts to put them to use in the clinical field, including the investigation of patients with diseases of the kidneys and urinary tract. In 1952 Oeser and Billion devised a method for measuring renal function by injecting ^{131}I-labelled Uroselectan B or Iopax intravenously and measuring their elimination by determining an activity–time curve from the excreted urine. However, they failed to recognise the potential value of actually measuring the radioactivity over the renal areas. This was attempted for the first time by Kimbel (1956), who generated an activity–time curve from the region of the kidneys after the injection of [^{131}I]-Perabrodil M and [^{131}I]-Urographin. It was left to Taplin to put renography on a firm clinical footing when he used two collimated scintillation detectors, two ratemeters and two chart recorders to measure the changes in renal activity following the injection of [^{131}I]-Urokon. Although this was unsuccessful, the procedure was repeated with [^{131}I]-Diodrast, which gave a pattern closely resembling the present-day renogram (Taplin *et al.*, 1956; Winter and Taplin, 1958). All these agents suffered from being handled slowly by the kidneys and accumulating in extrarenal tissues, but these disadvantages were overcome in 1960 with the introduction of ^{131}I-labelled ortho-iodohippurate (hippuran) by Tubis, Posnick and Nordyke (1960). Hippuran had already been used in urography (Swick, 1933), and its rapid uptake and elimination by the kidneys had been shown to be similar to that of para-aminohippuric acid (Smith, 1951). Its tagging with ^{131}I for renography represented a significant step forward and it is still the agent most widely used today.

The first attempt to produce renal images using radionuclides is said to have been by Goodwin, who tagged the radiographic contrast agent Diodrast with ^{131}I; Winter also tried this technique, but both attempts were unsuccessful (Winter, 1963). Haynie and colleagues (1960) demonstrated renal infarcts in dogs using a contrast infusion of [^{131}I]-hippuran with some success, but because of the large radiation dose involved with the infusion, the application of this technique in the clinical field was unacceptable. In 1956 the mercurial diuretic Chlormerodrin was labelled with ^{203}Hg and this was later used successfully in clinical renal imaging (McAfee and Wagner, 1960). In 1964 Sodee introduced ^{197}Hg, which has a shorter half-life than ^{203}Hg and was thus a more suitable agent. More recently the technetium-99m agents have been widely adopted. The most commonly used compounds to which this radionuclide is labelled are currently DTPA (diethylenetriaminepentaacetic acid) (Hauser *et al.*, 1970), gluconate (Boyd *et al.*, 1973) and DMSA (dimercaptosuccinic acid) (Englander, Weber and dos Remedios, 1974). Any technetium compound, or indeed pertechnetate as eluted from a generator, may be used for first-circulation studies of renal perfusion.

A further notable development of concern to the urologist was the introduction of suitable radiopharmaceuticals for skeletal imaging. A number of agents have

been used, such as ^{85}Sr-, ^{18}F- and ^{99m}Tc-labelled compounds. These latter agents have achieved widespread popularity both in the detection of metastatic disease and in metabolic and other benign skeletal disorders. The detection of bone metastases in carcinoma of the prostate is the main indication for the procedure in urological practice.

The techniques of renography, renal scanning, clearance studies and bone scanning described in this book have developed as a result of the multidisciplinary inspiration, dedication and research of physicists, chemists, pharmacists, biochemists, mathematicians and clinicians. They have reached a point where a wealth of information is available to the urologist conversant with their capabilities and limitations. The procedures are, in the main, simple, rapid and non-toxic, and allow the acquisition of information often unavailable from other sources. This book is an attempt to describe the techniques currently available, the direction in which nuclear medicine is developing in the urological field, and the value of the procedures to the clinical urologist in the management of his patients.

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Part 1: Techniques

2

Renography

Renography is a method of monitoring the arrival, uptake and elimination of a radiopharmaceutical by the kidneys to give an assessment of individual renal function. The radiopharmaceutical must contain a gamma-emitting nuclide in order that external detection can be accomplished. The most widely used agents for this purpose are ^{131}I-labelled ortho-iodohippurate (hippuran), the kinetics of which are well known and documented (Blaufox, 1972), and more recently [^{99m}Tc]-DTPA (Neilson, Lehd Møller and Trap-Jensen, 1977). The advantage of hippuran is that, after intravenous injection, about 80% of the compound passing through the kidney is actively secreted by the renal tubules, while a much smaller proportion is filtered at the glomeruli. This results in fast and efficient extraction of the tracer from the blood and passage through the kidneys to the bladder. Kenny, Ackery and Fleming (1975) have shown that the mean renal transit time in 19 normal patients injected with [^{123}I]-hippuran was 2.23±0.27 min.

2.1 METHOD

Detecting and recording the renal handling of the radiopharmaceutical can be done using either probe scintillation detectors or a gamma camera. A simple probe system may be used in conjunction with a dental-type chair (*Figure 2.1*), one detector being placed over each renal area. Additional information may be obtained from further detectors over the bladder, and the right infraclavicular area (for measuring blood background activity). Each scintillation detector channel (see Chapter 14) is connected to a chart recorder which produces a graph of activity in the kidneys, bladder and blood with respect to time. If an intravascular tracer such as ^{131}I-labelled human serum albumen (HSA) is given prior to the hippuran, a simultaneous analogue subtracted renogram on a second chart recorder may be obtained to demonstrate renal activity with the blood background contribution subtracted.

Accurate positioning using the patient's anatomical landmarks to locate the renal areas is more important if the probe system is used than if gamma camera

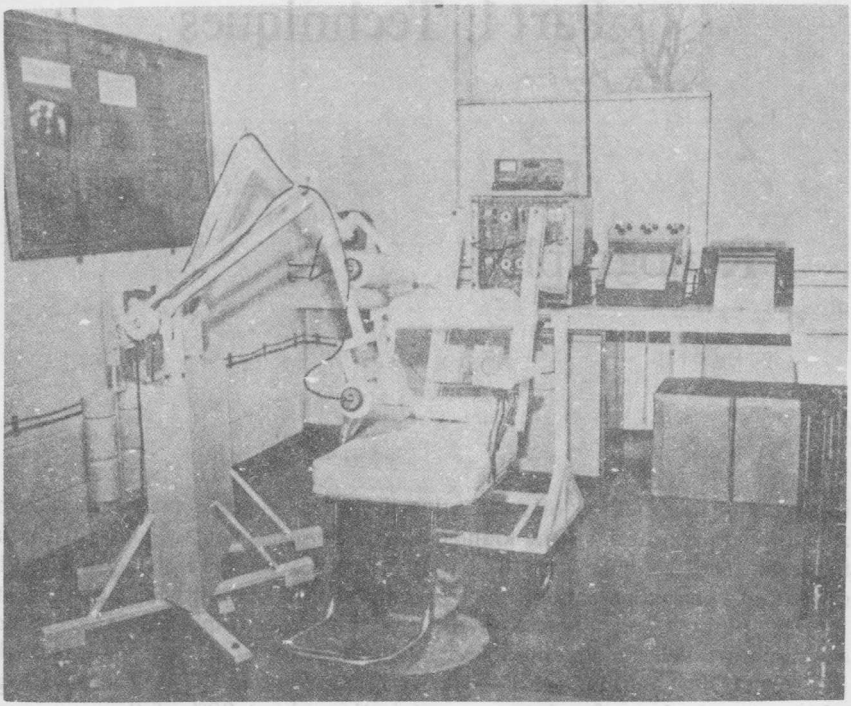

Figure 2.1 Detectors used for probe renography incorporated into dental-type chair and linked to scintillation detector channels and chart recorder

renography is performed. In the latter situation the large field of view and method of data recording and area selection make positioning easier and more accurate.

The detectors used for the probe system are fitted with collimators giving a field of view of 17 cm (vertical) by 9 cm (horizontal) at 5 cm depth (see Chapter 14). Their relationship to the anatomical landmarks is illustrated in *Figure 2.2*.

The lines of the vertebral spinous processes and the 12th rib are palpated and marked. The collimators are then placed with their lower edges 2–5 cm above the level of the iliac crests and their medial edges 2–5 cm from the line of the spinous processes, depending on the build of the patient. In this position the 12th rib, to which the kidney is often tethered by loose connective tissue, lies across the upper and lateral edges of the collimator. The right kidney detector is usually placed about 1 cm lower than the left.

By this method the kidneys will be accurately located in the vast majority of cases. With adequate supervision any inaccuracies can be quickly noted and corrected. If the urogram is used to site the kidneys, it must be remembered that the kidneys may drop 2–4 cm or more when the patient sits up.

Some centres give a preliminary tracer dose of radiopharmaceutical before the test for renal localization; this should not be necessary if the above protocol is followed.

The test is usually performed with the patient sitting, since this is a more physiological reflection of his day-to-day posture. It is extremely rare to obtain

a pattern of obstruction where this does not exist because of postural 'kinking' of the ureters. Provided that they are comfortable, patients do not appear to have any difficulty in maintaining this position for the duration of the test. This also applies to children, who are often more at their ease sitting with a parent close by, or reading, than lying down. Naturally, this does not apply to infants. The patient requires no preparation other than that he be in normal state of physiological hydration. In practice, this means no extra fluid or fluid deprivation

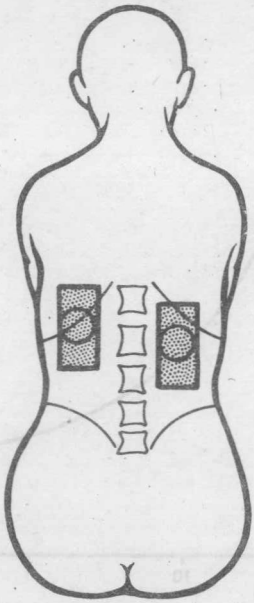

Figure 2.2 Schematic representation of probe placement for renography using patients' anatomical landmarks

before the test. It is important to avoid an oliguric state, since the resultant graph can mimic an obstructive pattern to a misleading degree owing to sluggish urine flow in the region of the detectors. The patient should empty his bladder before the test and again afterwards to check that an adequate flow rate of at least 1–3 ml/min is maintained during the test. It is unwise to perform renography on the same day as excretion urography, since many centres still insist on a period of dehydration before this investigation. In addition, the hyperosmolar contrast media used in this and other radiographic procedures can themselves compound anatomical obstruction to give misleading renogram appearances (Kaude and Nordenport, 1973).

Once the patient is positioned, 10–30 μCi of the [^{131}I]-hippuran is given into a suitable superficial vein. The injection must be accurate, since any extravasation will produce a flat curve due to continuing absorption of the tracer from the subcutaneous tissues. When analogue blood background subtracted renography is required, 3–10 μCi of HSA labelled with ^{131}I is given intravenously before the hippuran. However, this is not always necessary, for reasons which are described elsewhere (Chapter 16).

2.2 INTERPRETATION

The normal renogram performed in this way shows three classical phases (*Figure 2.3*), originally termed vascular, secretory and excretory, but better termed simply the first, second and third phases.

The first phase of the curve is a rapid rise corresponding to the increase in radioactivity beneath the detectors produced by the intravenous injection of radiopharmaceutical. To some extent it reflects the rapidity of injection and

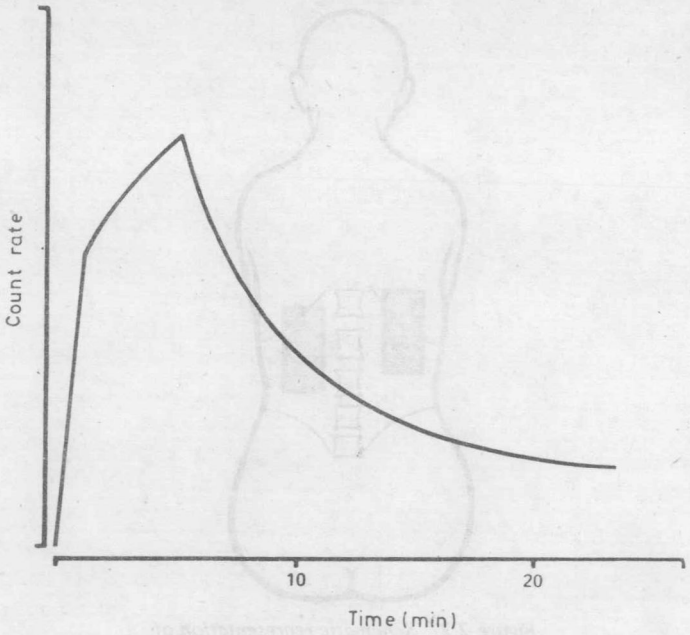

Figure 2.3 The normal renogram pattern, showing the classical three phases

vascular supply to the kidney. The radioactivity detected is that in blood, kidney and extrarenal tissues beneath the probe. After a few seconds this gives way to a more gradual slope – the second phase – which corresponds to the renal handling of the hippuran as it is taken up by the kidney and passed through the tubular cells to the lumen of the nephrons. The shape and duration of this part of the curve are dependent on several factors – supply rate, uptake efficiency, intraluminal transit and excretion, all play their part. The rising curve is due to the fact that more hippuran is arriving at the kidney through recirculation while none has yet left the renal pelvis. If no activity were to leave the pelvis because of an obstructive process, this second phase would continue to rise (*Figure 2.4*) and this pattern is usually found in obstructive uropathy. In the normal kidney, however, after between 2½ and 4½ min, activity starts to leave the renal pelvis, and at that point there is a sudden fall in the curve – the beginning of phase 3. This point corresponds to the time at which activity first appears in the bladder. The peak of phase 2 can be delayed by a variety of conditions, such as an obstructive process preventing excretion of tracer, renal artery stenosis causing a more prolonged gradual supply of tracer to the kidney (*Figure 2.5*),

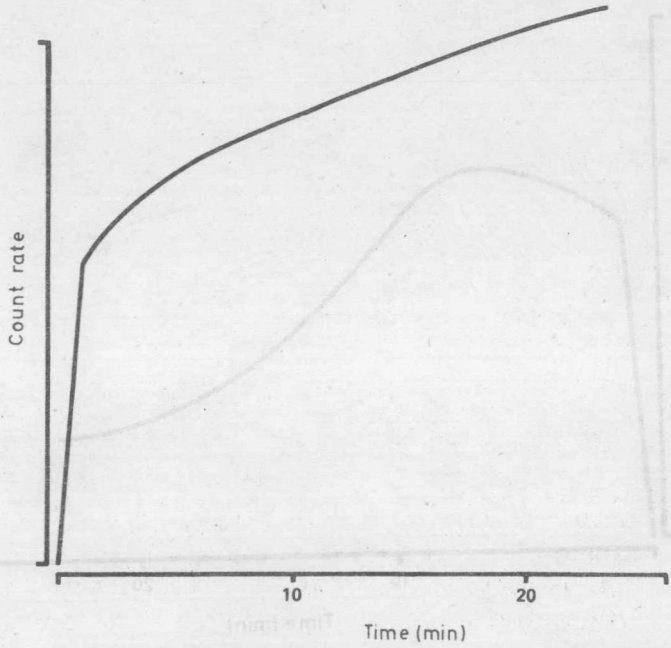

Figure 2.4 The renogram pattern in obstruction, showing an absent phase 3

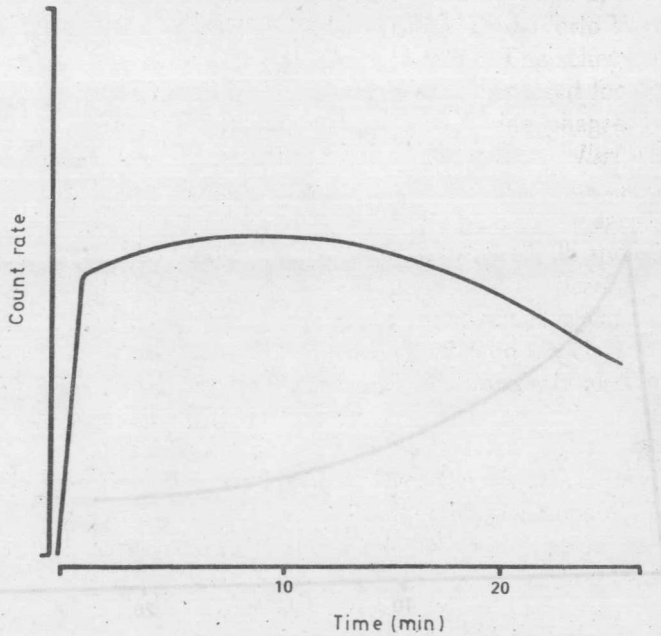

Figure 2.5 The renogram pattern in renal artery stenosis, showing flat prolonged uptake of tracer, delay in peak and prolonged excretion