PART XX

GUEST LECTURES ON NEPHROLOGY II

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NON-INVASIVE ASSESSMENT OF THE KIDNEY
What do nuclear medicine, ultrasonography, digital vascular imaging, computed tomography and magnetic resonance contribute to diagnosis in nephrology?

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Introduction

The history of renal disease started 150 years ago with the least invasive of all kidney tests: urinalysis. The assessment of renal function became more elaborate with the measurement of blood urea. The definition of the clearance concept and the subsequent equation between some functions of the kidney and the clearance of definite solutes such as inulin and PAH led to a more invasive approach which remains the reference for all methods of renal function determinations [1]. Inulin and PAH clearances are, however, cumbersome and entail a definite discomfort and morbidity for the patient.

The development of renal function tests was paralleled by an improvement in the methods evaluating renal morphology. Retrograde pyelography was followed by the less invasive intravenous pyelography and its refinements. Direct vascular visualisation through aortography provided new insights in renal disease. Renal biopsy eventually gave the microscopic counterpart of the renal imaging techniques.

As a result, the nephrologist who used to be a benign looking practitioner contemplating a vessel full of urine became a potentially aggressive scientist endowed with an increasingly effective investigative and therapeutic armamentarium and its frightful counterpart, the ability to inflict significant iatrogenic morbidity and mortality.

Several progresses in technology have made it possible during the last 10 years to substitute non- or less invasive methods for the evaluation of renal function and morphology. In this review I will not try to list them all: I will rather put some of them in perspective, looking critically at their underlying assumptions, at their relation with standard techniques and their usefulness in the daily practice of renal physicians.

The newer non- or less invasive methods of kidney evaluation can be categorised into a few chapters: I will concentrate mainly on nuclear medicine, its assets, its pitfalls and sometimes its illusions; I will subsequently outline what
may be expected today from ultrasonography, digital vascular imaging, computerized tomography and magnetic resonance.

**Nuclear medicine**

As soon as it became possible to attach a radionuclide to inulin or PAH, many laboratories substituted beta or gamma counting techniques for the more traditional but cumbersome chemical methods. Concern for the tightness of the radioactive label attachment to the molecule and for the degree of radiation exposure led promptly to the investigation of various radioactivity labels and to the development of new compounds to replace inulin and PAH. It must be recognised, however, that the fate of several of these substances differs markedly from the original ones or in some cases is even poorly defined at the present time.

The development of elaborate gamma cameras supplemented with a computer programmed handling of the data has led to the substitution of in vitro measurement of the radiolabelled compounds by in vivo determination of their accumulation rate in different organs. Images were thus obtained together with functional data. Here again new problems arose: differentiation of the compound accumulated in the organ from that diffusely present in the background, absorption of the emitted radiation by tissue layers of variable thickness interposed between the scanned organ and the camera.

The variety of substances with different radioactive labels, the diversity of counting and imaging methods and the complexity of computer data handling have resulted in an array of non-invasive tests whose significance and validity is not always critically established.

To illustrate this observation, let us look at the methodology of renal plasma flow measurements.

**Renal plasma flow measurements: two examples**

PAH is almost completely extracted from the blood during its first pass through the kidney and eliminated in the urine [1]. Measurement of its concentration per millilitre plasma and of its urinary excretion allows the computation of the volume of plasma cleared by the kidney per unit time, i.e. renal plasma flow. Accuracy requires also the determination of the percentage extraction of PAH from arterial blood: under normal circumstances the extraction averages 90 per cent so that the clearance of PAH equals 90 per cent of the actual renal plasma flow. In diseased kidneys, however, the extraction ratio falls with an attendant decrease in PAH clearance independent of renal plasma flow.

*The development of a single blood sample, single injection method of renal plasma flow measurement*

An initial effort to fix a $^{131}$I label on PAH in order to allow gamma counting proved unsuccessful. Tauxe et al proposed 20 years ago replacing PAH by a substance more easily labelled with $^{131}$I: orthiodohippurate, i.e. hippuran.
They demonstrated a good correlation between PAH and hippuran clearances but the latter was lower by an average of 28ml/min. This discrepancy increased for PAH clearance above 300ml/min reaching 15 per cent at 675ml/min. Still the authors concluded that “the deviation of PAH clearance is not of sufficiently great magnitude to alter clinical interpretation and appreciation of the data”.

A further change in methodology was proposed in 1964 by Tauxe in order to avoid cumbersome urine collections [2]. Sapirstein et al [3] had reasoned 10 years earlier that the blood decay of intravenously injected creatinine was determined first by its equilibration through its diffusion space and second by its renal elimination. They proposed a mathematical treatment of the plasma disappearance curve based on a two compartment model, thus allowing the calculation of the blood clearance of creatinine, i.e. the glomerular filtration rate. Tauxe’s group [4] applied these principles to hippuran in order to measure renal plasma flow. To be valid the method requires that the tested compound should have no protein binding and should not be metabolised or excreted by any non-renal route. These conditions are not completely met for hippuran which has weak protein binding and a small but significant extrarenal excretion [5]. To validate this approach, Wagoner et al [4] measured during 75 minutes the blood decay curve of $^{131}$I hippuran injected in a single shot. Renal plasma flow was then calculated from the two exponential components of the disappearance curve. Correlation with traditional PAH clearance was again satisfactory but blood hippuran clearance was lower than standard PAH clearance with a tendency to deviate more as the clearance increased. Blaufox and Merrill [6] further simplified the method by drawing only two blood samples at 20 and 30 minutes. The mathematical computation relied only on the late exponential of the decay curve. Again a good correlation was found with standard PAH clearance but this time hippuran clearance exceeded PAH clearance by 10 per cent, the difference ranging from -11.7 per cent to +29.5 per cent. Interestingly, four patients with no renal function had a blood hippuran clearance ranging from 42 to 100ml/min.

The last step away from reference methods was proposed by Tauxe et al in 1971 [7]: renal plasma flow was derived from a single plasma sample drawn 44 minutes after the injection of hippuran. The complexity of the reasoning underlying this approach is worth mentioning. The data basis consists of blood hippuran clearances calculated from decay curves obtained in 116 patients. First Tauxe et al [7] calculate the distribution volume of hippuran at various sampling times as the total injected dose divided by the plasma concentration. Subsequently they compute, the relationship existing in their population between blood hippuran clearance and distribution volume at one given time. Whatever the chosen sampling time the relationship assumes a quadratic form. However, the lowest standard deviation around the regression is obtained for the 44 minute sample. The authors then propose this empirically derived equation to calculate effective renal plasma flow from a single blood sample obtained at 44 minutes. The influence of oedema or severe renal insufficiency on the significance of a single blood sample value is not considered. The drawback of such an empirical approach is illustrated by the fact that 11 years later the same group redefined the quadratic equation on the basis of a larger number of
observations and found that the new equation modified significantly the calculated renal plasma flow above 400ml/min and below 150ml/min [8].

This story illustrates the limits of apparently sophisticated tests: the progressive erasure of significant differences between the new method and the more physiologically pertinent reference methodology, the empirical nature of nomograms from which physiologically relevant parameters are calculated, the lack of validation of the nomogram in other clinical conditions such as volume expanded states or severe renal failure. As may be expected the methodology is subsequently applied under different clinical conditions without reference to its possible limits.

For instance Holland et al [9] measured single blood sample renal plasma flow in 32 patients with acute renal failure in order to determine if this parameter predicts subsequent recovery. They claim that renal plasma flows above 125ml/min have a good prognostic value. Neither the possible influence of an expanded extracellular volume, characteristic of acute renal failure, on the 44 concentration of the tracer, nor the fact that anephric patients may have a 51ml/min renal plasma flow with this method, are taken into consideration.

These comments are not meant to deny the possible value of single blood sample renal plasma flow determinations. They just underline how indirectly the method relates to physiologic phenomena and hence how fragile it may be. The clinician eager to obtain numbers and happy to reason in physiologic terms should be aware of these pitfalls.

Intrarenal blood flow distribution assessment

More can be said about the assumptions hidden in techniques designed by Britton’s group to non-invasively assess cortical and medullary blood flows.

The basic assumption of this approach is that the transit time of hippuran is longer through juxtamedullary than through cortical nephrons. The amount of hippuran extracted from blood by each of these two nephron populations is determined by the volume of blood flowing to their proximal tubules. The distribution of blood within the renal cortex can thus be estimated by measuring the relative amount of hippuran with longer and shorter transit times [10,11]. Britton and Brown [10] indeed found that the spectrum of transit times was bimodal and suggested that the two modes represented transit times through cortical and juxtamedullary nephrons.

A computer assisted gamma camera records uptake and removal of hippuran by the kidneys. Background, measured in a non-renal area, is subtracted to provide real tissue accumulation. Subsequently a middle area (region of interest) representing middle regions and inner cortex overlapping the outer medulla is outlined by the observer on the image provided by the camera. Hippuran accumulation in this area is calculated by the computer. Transit times are then calculated for each area: the cortex provides mainly shorter transit times representative of cortical nephrons whereas the middle region contains both long and short transit times. Subtraction of cortical transit times from the middle region yields the residual spectrum of juxtamedullary transit times. The areas under each mode are determined and the results expressed as the contribution
of the cortical nephron component as a percentage of the total area.

A number of uncertainties are present in the basic assumptions of this method [12]. They concern the extent to which the area under each transit mode is proportional to the amount of plasma flowing through the corresponding nephron population, whether or not such a relationship holds in situations affecting renal blood flow and the hypothesis that short and long transit times are matched with cortical and juxtamedullary nephrons. Furthermore, the reliability of the delineation of small regions of interest within the kidneys remains in doubt.

The method was validated in man [10] by the demonstration that during sodium restriction the proportion of hippuran flowing through the nephron with shorter transit times was more than twofold larger than that flowing with longer transit times. During a high sodium intake the proportion of short transit time hippuran falls with a concomitant rise in longer transit time hippuran. These changes are interpreted as an increased juxtamedullary blood flow in response to a high salt intake, a pattern documented by other methods in animal experiments.

A similar agreement is unfortunately lacking in other conditions. Aortic constriction of haemorrhagic hypotension are also known to result in an increased fraction of renal blood flow directed to the inner cortical nephrons. Still, the transit time method fails to detect a parallel increase in hippuran appearance in deep nephrons [10]. This finding illustrates the lack of reliability of this method when renal blood flow falls below 60 per cent [13].

This example illustrates how an uncritical use of computer generated numbers may lead to false interpretations, waste of resources and poor medicine. Still these non-invasive methodologies used as research tools have already led to interesting conclusions and some of them provide routinely critical information to the clinician. In the subsequent part of this presentation I will briefly review them.

Current methods

Renal function: tests without imaging

Glomerular filtration. Clinicians rely on creatinine clearance to assess glomerular filtration rate. They follow serum creatinine as an index of glomerular filtration knowing that daily creatinine excretion is more or less constant. Convenient and cheap, this method has important limitations [14,15]. To circumvent them it has been proposed to calculate glomerular filtration from the blood disappearance rate of an injected radiolabelled compound excreted solely or mainly by glomerular filtration.

Several compounds have been utilised, mainly $^{51}$Cr EDTA, $^{131}$I iodothalamate and $^{99m}$Tc DTPA. The renal handling of the first two compounds has been well studied [15,16]. EDTA clearance is approximately 10 per cent lower than inulin clearance. There is an extrarenal clearance of approximately 4ml/min. The coefficient of variation is 4.1 per cent in patients with clearance values above 30ml/min, compared with 12 per cent reported for creatinine clearance [17]. Below 30ml/min, however, the coefficient of variation rises to 11.5 per
cent [15]. Iodothalamate clearance is virtually equal to insulin clearance [18]. DTPA has a significant five per cent protein binding and its single injection clearance is eight per cent lower than iodothalamate [19]. The renal handling of DTPA under various degrees of renal impairment and its extrarenal pathways need further in depth evaluation [20]. These methods are valid only if glomerular filtration exceeds 50ml/min. Below this value results are less reliable and care should be taken to extend blood sampling beyond the usual four hours.

Although definitely more accurate than creatinine clearance, these methods are certainly more time consuming for the patient and more expensive without providing a wholly adequate measurement of glomerular filtration. In my opinion their usefulness is limited to research purposes as illustrated by two recent examples: Parving et al using blood EDTA clearance demonstrated elegantly in diabetic patients the benefit of blood pressure control on the decline of renal function [21]. Similarly Donadio et al [22] studying in a double blind randomised study the benefit of anti-aggregatory agents on the evolution of membranoproliferative glomerulonephritis concluded that the treatment had a favourable effect on the evolution of glomerular filtration measured by blood iodothalamate clearance. The evolution of the simultaneously determined serum creatinine and creatinine clearance confirmed this observation but, due to the scatter of the data, the difference between treated and control groups failed to reach significance.

**Renal plasma flow.** In the previous examples the methodology of renal plasma flow measurement has been extensively discussed. Suffice to say that the blood clearance of hippuran assessed by multiple or single blood samples relates to PAH clearance with several limitations, especially in severe renal failure and possibly in volume expanded states. Furthermore, extraction coefficient of hippuran may change in acute conditions and thus profoundly alter the physiology significance of its blood clearance [23].

External monitoring by a gamma camera of renal uptake one and two minutes after the injection of hippuran may allow the calculation of separate and global renal blood flow. Results depend on the method used to measure the background emission to be subtracted from kidney uptake [24].

The usefulness of these methods in current clinical practice is not evident. It has been claimed to have a prognostic value in patients with acute renal failure [19]. Even if confirmed the value of this information in patient management remains an open question.

By contrast, as a tool designed to provide a specific answer in a research programme this method provides valuable information. Textor et al [25] for instance have utilised hippuran blood clearance to assess the effect of a beta blocking agent on effective renal blood flow. Cardiac output was simultaneously measured. Repeated studies over a four months’ period demonstrated that contrary to other beta blocking agents, nadolol redistributed blood flow to the kidneys, the fraction of cardiac output reaching renal circulation rising from 17 to 22 per cent.
Static renal imaging

The avid uptake of a radiolabelled compound by the kidney may provide accurate images on the gamma camera. $^{99m}$Tc DMSA has replaced HgCl$_2$ for such studies, the Tc label providing a smaller radiation hazard than $^{97}$Hg, as a result of its short half-life and radiation characteristics (in renal radiopharmaceuticals – an update) [20]. DMSA is 90 per cent protein bound. It is readily taken up by the kidney mainly in the cortex, within proximal and distal tubular cells. Its urinary excretion is slight. DMSA clearance does not correspond to any single renal function parameter. Its fate may be significantly altered by changes in hydration and acid base balance [26].

Scintigraphy of the kidneys has been advocated in children below the age of five with urinary tract infection and/or vesico ureteral reflux [27]. Merrick et al have indeed demonstrated [28] that the detection of scars was marginally more frequent with DMSA scanning than with an intravenous pyelography. Taking into account the fact that an intravenous pyelography is mandatory in the evaluation of recurrent urinary tract infection in children, the value of a slightly better scar identification in the management of children remains to be determined. The subsequent development of scars is more easily followed with nuclear imaging, but the value of this information is determined first by the likelihood of the development of scars in the subsequent years and second by the decisions that hinge upon their demonstration. At present it is thought that the development of scars in normal kidneys is very unusual [29–31] over the age of four. Furthermore, the therapeutic consequences of scar identification are limited, now that the value of surgical correction of vesicoureteral reflux is disputed [32]. Only long-term studies will demonstrate the possible benefit of an accurate delineation of renal scars in children. Until that moment this technique should probably not be incorporated systematically in the work up of urinary infection.

Occasionally DMSA imaging has been proposed to elucidate the nature of an intrarenal mass or to demonstrate the presence of functioning tissue in the isthmus of a horseshoe kidney. Intravenous pyelography and computed tomography usually provide better information under these circumstances [33].

Renal and urinary tract imaging can be obtained with a great variety of radiolabelled compounds with different renal fates. Interestingly radioisotope skeletal surveys with $^{99m}$Tc diphosphonate or polyphosphate may disclose abnormalities of the kidneys. In 52 out of 1,711 scintiscans, Maher [34] reported major, unexpected renal or urinary abnormalities consisting of filling defects (carcinoma, polycystic kidneys, cysts) and urinary tract obstruction.

Dynamic renal imaging

The possibility to quantitate over time the renal accumulation of labelled compounds provides both anatomic and functional information. This approach has been utilised to measure separate kidney function and to assess renal allograft status.
Separate function studies. Split renal function studies relying on bilateral ureteric catheterisation are so invasive and time-consuming that they have never gained widespread acceptance. The advent of radionuclide methodologies has led to alternative methods. Various protocols have been utilised. With DTPA or hippuran an early (1–2 minutes) renal scan is obtained [33]. After background activity subtraction, the uptake of each kidney is expressed as a fraction of total uptake. Single kidney function is then derived from the global renal function measured simultaneously by a single injection blood clearance. With DMSA, a compound remaining within tubular cells for a long period, uptake is measured at 24 hours [35].

Several difficulties limit this approach: the organ of interest is not the sole organ within the field of the radiation detector, the radionuclide uptake is time dependent and, finally, the variable distance of each kidney from the detector results in differences of tissue absorption [36].

In practice, results appear unreliable when creatinine clearance falls below 30ml/min [37]. In patients with urinary obstruction or hydronephrosis, results may be contaminated by the pelvic accumulation of the isotope, a difficulty that can be circumvented by very early counting of hippuran or DTPA or by very late counting of DMSA. Despite these limitations, several reports have documented a good correlation between radionuclide and classical clearance split function studies [38,39]. However, a closer look at published results discloses a great variability for individual observations. For instance, MacKay et al [39] document a good correlation between hippuran renography and PAH clearance in individual kidneys. Still renal plasma flow is lower in the whole group with hippuran renography than with PAH clearance and in individual cases radionuclide clearance ranges from 40 to 160 per cent of the corresponding PAH clearance (Figure 1).

![Figure 1. Comparison of individual kidney conventional PAH and blood hippuran clearances. Affected kidneys suffer from renovascular lesions (9 cases) or parenchymal disease (5 cases). Blood hippuran clearance is expressed as a percentage of the conventional PAH clearance (calculated from data in MacKay et al 1981 [39]).](image-url)
The technique has been used mainly by urologists to evaluate single kidney function either prior to a surgical decision or in the follow-up. Despite claims that pre-operative assessment correctly predicted the subsequent functional recovery, several recent studies have provided evidence to the contrary [40–43]. The reproducibility of the method and its validation under the pathological conditions of the scrutinised disease are often lacking. Furthermore, the impact of the collected information on the decision making process has not yet been critically evaluated.

Separate renal function studies have also been advocated in the diagnosis and evaluation of renal artery stenosis. The radioisotopic renogram developed over 20 years ago was a first application of this principle [44]. Despite methodological improvement brought by gamma cameras and computers the low specificity of the method [45–47] has cast some doubts on its value in the screening for renovascular hypertension, and indication that digital vascular imaging might take over [48,49]. The relevance of separate renal plasma flow measurement to the prediction of the surgical curability of hypertension is not yet established and will be undoubtedly limited by the variability of results in individual cases (Figure 1).

As a research tool, however, separate renal function studies are of great interest to solve specific problems. Wentoing et al [23] have used DTPA renogram to document the effect of captopril on the function of a kidney with renal artery stenosis. They demonstrated a dramatic fall in DTPA uptake by the stenosed kidney while heterolateral function remained normal. This study combined with the documentation of a fall in the extraction ratio of hippuran and iothalamate allowed them to conclude that captopril probably reduced renal function in stenosed kidneys through a vasodilatation of the efferent arteries.

The renal transplant

During the post-operative period when the graft is not yet functioning, the clinician is often confronted with a diagnostic dilemma: what should be attributed to acute tubular necrosis, to graft rejection or to ureteral obstruction?

Radionuclide investigation of the graft has proved unique to guide the clinician. The patency of the large vessels can be ascertained with intravascular compounds such as $^{99m}$Tc pertechnetate [50] whereas the accumulation of DTPA or hippuran reflects intrarenal blood flow.

Several combinations of various compounds have been recommended. All have in common an initial assessment of the graft within 24 hours after the operation, the study is subsequently repeated at two to three day intervals and compared with the initial results [51] until recovery of renal function. One method [51] combines a series of hippuran scans obtained during 20 minutes with pertechnetate scans obtained at five second intervals during 40 seconds after injection [51]. In acute tubular necrosis, the scintigram reveals a continuous renal uptake of hippuran without evidence of radionuclide excretion into the bladder. Progressive recovery is heralded by the appearance of radioactivity in the bladder and subsequently by a fall in parenchymatous activity after the initial rise. The pertechnetate flow study shows only minor abnormalities.
Acute rejection superimposed on acute tubular necrosis is evidenced by a decline in the curve amplitude of pertechnetate. Hippuran uptake decreases when compared with the previous examination. Return to control values of these two abnormalities after steroid treatment confirms the diagnosis of rejection.

Acute rejection in a normally functioning graft can usually be diagnosed without radionuclide studies. If they are performed, rejection is characterised by a delay and a decrease in parenchymal hippuran uptake.

Various methods have been proposed to quantify radionuclide uptake in the graft to facilitate diagnosis and comparisons [52,53] with a reported sensitivity of 90 per cent in the diagnosis of rejection.

All radionuclide methods utilised in the post-operative period rely on an initial 24 hour determination assumed to represent solely acute tubular necrosis, subsequent degradation being attributed to an added rejection. This assumption should probably be reassessed in patients treated with cyclosporine a drug whose nephrotoxicity is associated with an altered arterial blood flow in the graft. As a result, initial renal blood flow is low and the onset of acute rejection is no longer heralded by a sharp fall in perfusion [54].

*Radiolabelled cells kidney uptake*

Renal rejection as well as various renal diseases result in the interstitial or intravascular accumulation of leucocytes and platelets. Detection of these cells by radionuclide uptake has been proposed.

The first studies relied on $^{67}$gallium citrate which accumulates in inflammatory regions where it binds to leucocytes and/or acute phase proteins. The procedure developed for the detection of infections [55] has been utilised in the evaluation of acute interstitial nephritis [56,57], acute pyelonephritis [58,59] or renal amyloidosis [60]. Its diagnostic value in nephrology suffers, however, from a high rate of false positive results [61].

The injection of $^{111}$Indium labelled leucocytes or platelets, requires a smaller radiation dose, usually around 1mCi [55]. Labelled leucocytes [62] and platelets [63–65] accumulate in rejecting grafts. Despite earlier claims, recent studies have proved disappointing due to a high incidence of false positive and negative results [66]. In our own experience this technique does not provide a significant gain over more traditional methods for the diagnosis of rejection.

*The radiation hazard*

Whenever systematic radionuclide studies are contemplated the benefits must be weighed against the cost. The latter include not only the financial cost but also the loss of time for the patient and the radiation hazard.

The amount of radiation exposure per examination is generally within acceptable limits. However, when repeated tests are required, careful consideration should be given to the physical characteristics of the radionuclide. $^{131}$I hippuran has a physical half-life of 8.04 days. Although its biologic half-life lasts only 30 minutes in patients with normal renal function, it increases and eventually approaches the physical half-life in progressing renal failure. Furthermore, $^{131}$I
has a beta radiation absorbed by peripheral tissues. The majority of large nuclear medicine units are thus converting to $^{123}$I which emits only gamma radiation and has a 13.3 hours half-life. The radiation absorption by critical organs after the injection of 200$\mu$Cl of hippuran illustrates the hazard of $^{131}$I compared to that of $^{123}$I. Normally functioning kidneys absorb 20m rad with $^{131}$I versus only 4m rad $^{123}$I. Renal failure may increase these figures up to 60-fold [20]. Non-voiding results in an absorbed bladder dose of 2400m rad for $^{131}$I versus 600m rad for $^{123}$I hippuran. Thyroid exposure reaches 9600m rad with $^{131}$I and only 120m rad with $^{123}$I if thyroid uptake is not blocked before the test [20,51].

Technetium whose physical half-life is only 6.09 hours results in an even lower radiation exposure when coupled to DTPA or DMSA [20].

Conclusions

Confronted with an array of radionuclide tests the nephrologist remains very often in doubt as to their contribution to diagnosis and management.

Non-imaging techniques for measurement of renal function have little place except in a research situation. They are not equivalent to the standard reference methods and, although more accurate than currently available clinical techniques, they do not provide a gain in information offsetting their cost.

Static imaging techniques are to be compared with traditional urography. The anatomic information does not appear superior except, perhaps, in the detection of scars in pyelonephritic kidneys. This gain is, however, too marginal to justify inclusion of these tests in current clinical practice.

Dynamic imaging contributes both anatomic and functional data. It provides the clinician with critical information during the early evolution of renal graft, especially when acute renal failure develops. This technique also allows the separate assessment of individual kidney function. How useful this information is in diagnosis and treatment remains an open question. Urologists feel that on this basis they can predict preoperatively the chances of recovery of a kidney and plan accordingly, a conclusion contradicted by others.

Finally, the renal fate of gallium citrate and of labelled white cells or platelets can be easily followed. The sensitivity and specificity of these methods appear disappointingly low.

Ultrasonography

Ultrasonography has become, over the last 10 years, one of the most reliable non-invasive methods to assess renal morphology.

It has proved to be an invaluable help in the evaluation of renal tumours: it is now a critical step in all algorithms proposed to diagnose the nature of renal masses.

The ability of ultrasonography to identify cysts is utilised in the diagnosis of polycystic kidneys. It enables the further identification of hepatic or pancreatic cysts, a finding sometimes helpful in the differential diagnosis between multiple cysts and polycystic kidney disease [67,68]. Although ultrasounds are slightly
less sensitive than intravenous pyelography with nephrotomograms, their non-invasiveness qualifies them as the best method in the screening of relatives of patients with polycystic kidneys [69–71].

Ultrasonography readily identifies hydrenephrosis [72,73]. It detects obstructive uropathy with a sensitivity of 90 per cent and a specificity of 98 per cent, a better performance than radionuclide studies with DTPA or hippuran, 26 per cent of which are inconclusive. This superiority results from the fact that ultrasonography, contrary to radionuclide studies, is independent of renal function [74].

Ultrasonography has thus become the initial screening modality in the evaluation of suspected urinary tract obstruction. Like any other method, however, it has its pitfalls: dilatation of the pelvis in incomplete obstruction may vary with diuresis; prominent collecting system and an extrarenal pelvis, as well as high flow states in some non-oliguric azotaemic patients [75], may give false positive results. These errors will be readily corrected by a subsequent intravenous pyelography [76]. The main hazard of ultrasonic diagnosis is the minimal dilatation obstructive uropathy. It may occur in patients with either retroperitoneal fibrosis or neoplastic encasement of the ureters [77,78]. If oliguria is present the mere visualisation of a clearly defined pelvis and ureter is sufficient evidence to diagnose obstruction; indeed, in the absence of urine secretion the urinary tract collapses.

The role of ultrasound scanning in the work-up of renal colic is also very promising. In a series of 21 patients with renal colic, 18 of whom had a stone, a sensitivity of 100 per cent in the detection of ureteral obstruction and/or stones has been reported [79]. In current practice, if inconclusive examinations are included, sensitivity is probably lower.

Sonography of the fetus has allowed the prenatal detection of urinary tract obstruction [80,81], a condition accessible now to therapeutic intervention [82]. Fetal renal dysplasia may be diagnosed in utero [83].

Ultrasound have also been successfully used in order to localise the kidney for renal biopsy [84] or for the percutaneous insertion of small catheters to drain renal or peri-renal abscesses or to place a nephrostomy [85–87]. The technique identifies the peri-renal haematomas resulting from these procedures [88,89].

In addition to its ability to outline the kidneys, to visualise a dilated urinary tract ultrasound scanning can identify, in the kidney, regions with differences in echogenicity. The corticomedullary junction may be recognised. This approach has led to the use of ultrasound in the diagnosis of renal parenchymal disease [90]. There is a good correlation between ultrasound evaluated kidney size and the histological evidence of sclerosis and atrophy. Echogenicity of the kidney measured in reference to liver echogenicity, also correlates with sclerosis in the biopsy specimen [91,92] and with creatinine clearance [92]. However, the scatter of the data around the latter relation precludes any meaningful interpretation of ultrasound results in the diagnosis of histologic type of renal disease.

The renal allograft has also been investigated with ultrasound in order to detect rejection. Findings suggesting rejection include a blurring of the corticomedullary junction, increased cortical echogenicity and hypoechoic areas in the
pyramids [93-97]. The most reliable signs are increased size and decreased echogenicity of renal pyramids [98] whereas blurred corticomedullary junction was found to be unreliable [98,99]. Although it has been reported that in acute tubular necrosis, the kidney is not modified [97,100], a decreased echogenicity of the central sinus complex has been noted [101] and increased renal size, together with hypoechoic pyramids has been occasionally reported [98]. Overall ultrasound scanning does not seem to add to radionuclide studies in the diagnosis of acute rejection, especially in early post-transplant renal failure.

An interesting development of ultrasonographic technique is the ultrasonic echo-Doppler flowmeter. Greene et al [102] have utilised a dual frequency real time two dimensional echo Doppler calibrated in vitro. Blood velocity and volume flow rates were measured in renal arteries of normal subjects. Results fell well within the physiologically accepted range. In a subsequent study [47] Avashhi et al utilised the same method in 68 patients with suspected renovascular hypertension. Eleven were technically inadequate. In 26 of the 57 other patients a comparison with angiography was available: sensitivity and specificity for the detection of renal artery stenosis were 89 and 73 per cent respectively. The same group has recently proposed an identical approach to diagnose renal vein thrombosis [103]. Compared with phlebography, the method has an 85 per cent sensitivity and a 56 per cent specificity. More experience will be needed to assess the usefulness of the new technology. At any rate it must be emphasised that, as in all ultrasonic methods, accuracy and reproducibility of results hinge upon the experience and skill of the operator.

In conclusion, at the present time, renal ultrasounds are of paramount importance in the detection of obstruction. They precede intravenous pyelography both in the approach of azotaemic patients [75] and of the patients with renal colic [79]. The detection of cysts, especially in polycystic kidneys, and of perirenal collections, as well as the work-up of intrarenal tumoral masses, are more cost effective with ultrasound than with other non-invasive techniques. The usefulness of ultrasonography in the diagnosis of renal parenchymal disease and of allograft rejection is not yet established and should be considered a field of clinical investigation. Finally, technical developments might allow in the future clinically useful ultrasonic determinations of blood flow in renal arteries and veins.

**Digital vascular imaging**

Renovascular disease is the single, most common curable form of hypertension. Until recently specific treatment entailed either reconstructive vascular surgery or nephrectomy. Taken together with the high cost and the morbidity of the angiographic diagnostic procedure [104], these facts have oriented current practice towards medical therapy for all hypertensions, reserving a more elaborate diagnostic work-up for patients whose hypertension proved resistant to treatment and who might eventually tolerate surgery.

This attitude has been transformed by two recent developments. Percutaneous transluminal angioplasty [105] has significantly reduced the morbidity of vascular
repair [106]. Simultaneously digitalised vascular imaging has provided a low risk, relatively pain-free procedure for the detection of renal artery stenosis [48,107]. Although digital vascular imaging does not qualify as a non-invasive imaging technique, it may be worth mentioning because it is so less invasive than arteriography.

Hillman et al [48] have claimed that digital vascular imaging is cost-effective in the screening for renovascular hypertension. They compute a total cost of 1240 US dollars for conventional diagnostic procedures including excretory urography, radionuclide study and arteriography versus only 300 US dollars for digitalised vascular imaging. They subsequently calculate that it is cheaper to screen 100 hypertensive patients and to treat eventually five to 10 of them by transluminal angioplasty than to maintain all 100 patients on sustained medical treatment. The validity of this approach hinges upon the reliability of digitalised vascular imaging and the long-term benefit of percutaneous transluminal angioplasty. The latter appears promising [49,108] although caution has been advised by Flechner et al [109]. The sensitivity and specificity of digitalised vascular imaging in renovascular hypertension is encouraging. Smith et al [110] compare the digitalised vascular imaging with angiography in 32 hypertensive patients. A total of 76 arteries were examined by two observers. Sensitivity ranged from 83 to 87 per cent and specificity from 79 to 87 per cent. The main difficulty accrued from subtraction artefacts and a relatively low spatial resolution resulting in false positive stenoses. Furthermore, a poor circulatory condition may result in an excessive dilution of the contrast media and thus in inadequate images. As a result of improved technology Schwarten [49] observed in 30 patients an almost perfect agreement between arteriography and digitalised vascular imaging: in 26 there was agreement both as to the diagnosis and the grade of the disease. In four, renal artery stenosis was present, but there was a discrepancy on its severity as a result of heavy calcification in the peri-renal aorta, a diminished cardiac output and an artefact. Furthermore, digitalised vascular imaging allowed an adequate follow-up after percutaneous transluminal angioplasty.

Digitalised vascular imaging has also been successfully applied in hypertensive transplanted patients and allowed the detection of graft artery stenosis [111] amenable to transluminal angioplasty [112].

**Computerised tomography**

Computerised tomography provides an excellent delineation of renal structures. Without the use of intravenous contrast material it may readily inform on the presence of tumours, stones, hydrenephrosis. After contrast media injection the nephrogram allows a precise evaluation of parenchymal thickness. Cysts may be accurately delineated and the uptake of the iodinated material by a tumour evaluated [113]. In these indications computerised tomography complements intravenous pyelography and is thus not a first line procedure.

Computerised tomography allows the direct investigation of the retroperitoneal space. It is especially useful in the delineation of renal tumours [113] and in the exploration of ureteral obstruction. Its sensitivity in the staging of renal
neoplasms is considerably higher than that of sonography [114]. Retroperitoneal fibrosis, compression by lymph nodes [115], tumour thrombi within the vena cava [113] are well visualised.

More recently it has been proposed to evaluate renal function by measuring the changes in density of different areas of the kidney during the injection of contrast material. The method has been used for the evaluation of renal graft on the basis of repeated scanning of the same renal slice [116]. The duration of each scan, between one and five seconds, causes some difficulties due to variations in kidney position. New high-speed, volume imaging tomography scanners are developed [12]. They are able to scan simultaneously 120 1.8mm thick transverse kidney slices in 0.011 seconds. Repetition of the whole kidney scan 60 times per second allows an assessment of intrarenal blood flow distribution. It remains to be seen whether this approach provides a more accurate and cost effective assessment of renal function than radionuclide studies.

Magnetic resonance

Magnetic resonance produces remarkable images of internal structure of the human body without contrast media and ionising radiation. The potential hazards are exposure to static and rapidly changing magnetic fields and the heating from radiofrequency pulses [117]. Up to now none of them seem to have materialised.

An acquisition time longer than one minute has limited the use of magnetic resonance mainly to structures that can be reasonably immobilised such as the brain. Applications to the kidney are still limited by movement artefacts which might be reduced in the future by appropriate gating. Cortex and medulla are clearly delineated. Hydronephrosis, cortical oedema during rejection are visualised [118,119]. Tumours are readily differentiated from cysts and tumour invasion into renal veins may be visible [120]. The significance of the wealth of new data provided by magnetic resonance is just beginning to be investigated; it is too early to assess its place and its exact contribution in the evaluation of renal function and morphology.

Conclusions

Concepts of decision analysis concepts in medical diagnosis allow a proper evaluation of tests [121]. The value of a test depends upon its ability to significantly modify pre-test diagnostic probabilities. Very few of the more recent sophisticated tests have been evaluated in this way. Although many bear a more or less close relationship with disease processes, the actual help provided to the nephrologist confronted with a specific diagnostic or therapeutic decision remains to be ascertained. Such an evaluation is difficult: first of all each patient is unique in so far as the a priori probabilities obtained by clinical history and physical examination vary from one patient to another. Further the quality of the information provided by the different tests varies among institutions. Hospitals benefiting from outstanding radiology services, for instance, have tended to develop less elaborate nuclear medicine facilities; the experience of the operator
remains a critical element of the accuracy of sonography. Still the contribution of each test should be critically scrutinised before accepting its incorporation in routine practice if waste in time and resources are to be avoided.

In this respect the best tool to assess kidney morphology remains the plain film of the abdomen with tomographies and intravenous pyelography. Ultrasound will be preferred as the first step when ureteral obstruction is to be ruled out, for instance in acute renal failure or exacerbation of chronic renal failure. It will also take precedence over intravenous pyelography in the screening for polycystic kidney disease. Ultrasound on the other hand will complement intravenous pyelography in the evaluation of renal tumours, in the elucidation of peri- or para-renal collections such as haematomas, lymphoceles or urinomas.

Computed tomography will be requested when accurate delineation of renal or retroperitoneal structures is necessary: for instance in the staging of renal neoplasms or in the evaluation of the retroperitoneal space of patients with ureteral obstruction.

Digitalised intravenous angiography provides a relatively non-invasive way to delineate renovascular morphology. Its place as the best screening method for renovascular disease remains to be confirmed.

Finally, radionuclide scans with DMSA appear to provide a slightly better delineation of pyelonephritis scars than intravenous pyelogram. Although some urologists feel that this information is critical in reaching therapeutic decisions, evidence supporting this view is still wanting.

Renal function tests have proliferated during the last 20 years. Creatinine clearance and serum creatinine remain the cornerstone of renal function evaluation. These tests are cheap, easy to perform everywhere and their many limitations and pitfalls are well known to the nephrologists. More sophisticated radionuclide tests provide probably a more accurate estimate of renal parameters. However, their routine use outside clinical research does not yet seem to provide operational benefits outweighing their cost. Furthermore, the many assumptions underlying several of these tests are not apparent to the nephrologist who might overestimate the significance of the results. This conclusion should be amended in two areas. Radionuclide tests provide a unique service in the evaluation of post-transplant failure when differentiation between acute tubular necrosis and rejection is of critical importance for patient management. Radionuclide tests are also the only available method to assess separate renal function. Many factors limit the accuracy of these determinations. Still, many urologists feel that the information obtained is of paramount importance in the decision to operate on kidneys with either stones or severe hydronephrosis, a statement firmly disputed by others. Here again an evaluation of the real benefits accruing from the obtained information above that already available from conventional tests and the intravenous pyelography remains to be done.

Improvement in technology, better knowledge of the physiological aspects of the different test compounds and above all a critical look at the results will probably profoundly modify in the coming years our present diagnostic procedures.
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Open Discussion

VANHERWEGHEM (Brussels) You concluded that intravenous pyelogram remains the first line procedure for renal assessment? Could you comment on possible nephrotoxicity of contrast agents, especially in patients with renal insufficiency.

VAN YPERSELE You quite rightly point out that contrast agents may have a deleterious effect on renal function. Predisposing factors have been identified, thus minimising the incidence of this complication. Still intravenous pyelography should be performed only when specific questions are asked and when the value of the answer outweighs potential risks. For most morphological problems facing nephrologists the intravenous pyelogram remains the best deal.

KERR (London) Please comment further on the best method of assessing renal scars? You quote the IVP as the best test but the observed error is too high to make it useful in following the progression of renal scarring. Do DMSA scanning, or CT scanning or any other techniques offer any advantages?

VAN YPERSELE Yes, DMSA scanning appears slightly superior to IVP. Taking into account that the first morphologic assessment of the kidneys in chronic pyelonephritis is at any rate an IVP, the question remains whether the added information provided by DMSA is useful from an operational point of view. It is true that subsequent follow-up of scars can be obtained with DMSA. But again, where does this information lead? As you know, surgery on vesicoureteral reflux is less popular these days and I know of no study demonstrating that scar progression results in an indication for surgery. Thus for the practising nephrologist I believe it has no benefit. For those physicians who are interested in scar formation as a topic of clinical research the attitude is different: DMSA provides interesting data.

WILL (Leeds) You have mentioned the use of IV urography as screening for abnormality and triggering further non-invasive investigation. Would you comment on reciprocal serum creatinine plotting as the commonest non-invasive procedure which triggers further testing?
VAN YPERSELE I have necessarily limited my presentation to a few non-invasive approaches — thus urinary enzymes, changes in the blood concentration of various compounds such as beta-2 microglobulin etc have not been considered. I wholeheartedly agree with you: the changes of the reciprocal of creatinine over time are linear in several diseases. Any departure from this evolution raises questions about the occurrence of aggravating potentially reversible factors. This is another way to non-invasively follow renal function.

RIZZONI (Padova) Is renography with injection of frusemide more useful than IVP in the diagnosis of obstruction of higher urinary tract?

VAN YPERSELE Renograms have had their time. Some improvements such as the superimposition of an acute frusemide-induced diuresis have added information. However, this method remains limited by several physiological factors such as the state of diuresis, the intensity of the diuretic response etc, so that a high rate of false negative and positive results is reported. By contrast, frusemide injected during an IVP provides dynamic images of the pyelic region and helps assess a possible obstruction of the urinary tract.