

Old and new tests of renal function

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In 1827 a lecturer in clinical chemistry at Guy's Hospital, one John Bostock, demonstrated impaired urinary concentrating ability in a group of Richard Bright's patients with advanced renal disease, thus performing the first modern renal function test.¹ My purpose in this presentation is to review the subsequent development of the study of renal function in health and disease, with emphasis on those methods which have proved to be of enduring clinical value. The techniques of the experimental renal physiologist will not be discussed, although they have contributed greatly to present-day understanding both of how the kidney works and how it fails. It is both logical and clinically appropriate to begin with the measurement of glomerular filtration rate (GFR); logical, because filtration is the first step in the elaboration of urine and appropriate, because in clinical practice GFR is by far the most important single index of renal function. Many complex tests of segmental tubular function have been devised, but these are rarely indicated in clinical practice and I shall confine my discussion of tubular function tests to one or two recent observations which have practical value, mainly because of their simplicity.

In 1917, 90 years after Bostock's pioneering observation, Addis noted that the urine-to-plasma urea concentration ratio fell with declining function.² Four years later, Van Slyke and his coworkers introduced the term "renal clearance", defined as the volume of plasma required to furnish that quantity of a substance excreted in the urine in unit time.³ This was a key concept in the subsequent development of renal function measurement, and in the measurement of GFR in particular. Rehberg⁴ in 1926, first measured the clearance of creatinine and suggested that it might provide a measure of GFR, but it was left to Homer Smith and his students, in a series of now classic reports, to define the full potential and limitations of clearance studies as a means of investigating renal function. Smith's monograph "The kidney"⁵ remains the definitive account of clearance methodology and is required reading for anyone with a serious interest in the subject.

Since the excretion of *any* substance found in both urine and blood can be expressed as a clearance, it follows that a substance whose clearance is equal to the GFR must fulfil certain requirements. These are:

- 1 The concentration of the substance in glomerular filtrate must be the same as in plasma water—that is, the substance must be freely filtered.
- 2 It must not be secreted by the tubule.
- 3 It must neither be reabsorbed by the tubule nor leak back through it.

If these requirements are met, it follows that the filtration rate and the excretion rate must be identical. Since the filtration rate of any freely filtered substance is equal to the GFR multiplied by its plasma concentration, and the excretion rate is expressed as urinary concentration multiplied by urine flow rate it follows that, taking inulin as an example:

$$GFR \times P_{in} = U_{in} \times V$$
 (1)
where P_{in} and U_{in} represent the concentrations of inulin in plasma and urine respectively, and V is the urine flow rate.

Dividing both sides by P_{in} :

$$GFR = \frac{U_{in} V}{P_{in}} \quad (2)$$

Using this formula, clearance is expressed in the same units as V —for example, ml/min, l/day etc—that is, volume of plasma per unit time. Numerous substances have been investigated for their suitability as markers for GFR measurement. Smith⁵ has summarised the evidence in favour of inulin, a fructose polymer, and has clearly established its place as an ideal compound for this purpose, at least in adults with normal renal function. It should be remembered that the GFR cannot be measured directly in humans, and that the validation of methods for its estimation is always indirect. The usual way in which a new substance is evaluated for this purpose is by simultaneous comparison with inulin; if clearance rates for the two substances are the same at all levels of function, it is generally accepted that GFR is being measured.

The clearances of two endogenous compounds—namely, urea and creatinine, have been used extensively as indices of the GFR.

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Urea clearance underestimates the GFR due to passive back diffusion from the tubular fluid to the plasma. The proportion of filtered urea so reabsorbed is inversely proportional to the flow rate through the distal tubule, so that the lower the urinary flow rate the greater the degree to which urea clearance underestimates the GFR. Conversely, during water diuresis such that the flow rate exceeds 2ml/min (in adults), the urea clearance levels off at about two thirds of the GFR.³ If this condition is met, urea clearance can be used as a reasonably acceptable measure of the GFR using the appropriate correction factor, but in clinical practice it has been superseded by more accurate methods. Incidentally, the dependency of urea clearance on the flow rate explains the rise in blood urea concentration seen in water-depleted patients; under these conditions the clearance, and hence the excretion, of urea falls even if a normal GFR is maintained.

Creatinine clearance somewhat overestimates GFR, due to some secretion of creatinine by the proximal tubule. If the plasma concentration is raised to extremely high levels by infusion of exogenous creatinine the ratio of "true" creatinine clearance to inulin clearance falls from 1.4 when plasma creatinine is in the normal range to 1.1 when it is artificially raised to 120 mg/dl (about 10 000 μmol/l), the curve relating creatinine clearance to inulin clearance approaching unity as an asymptote.⁶ Further evidence for the tubular secretion of creatinine is provided by the effect on this ratio of the tubular poison phlorizin, which renders the creatinine and inulin clearances almost equal. The matter is further complicated by difficulties in the laboratory measurement of creatinine, since the standard alkaline picrate reaction also measures so-called "non-creatinine chromogens" in plasma, spuriously lowering the calculated clearance. Thus the errors due to tubular secretion and to estimation of non-creatinine chromogens in plasma tend fortuitously to cancel one another out, with the result that creatinine clearance based on measurement of total chromogens is sufficiently close to inulin clearance for most clinical purposes.

Why, then, has creatinine clearance acquired such a bad name in recent years? The problem lies not with creatinine clearance as such, but with the 24-hour urine collection on which most clinical estimates are based. Since the urine flow rate forms part of the clearance formula, it is apparent that an accurately timed urine specimen is indispensable for an accurate clearance. Given that bladder catheterisation is not routinely acceptable, and that bladder emptying cannot be relied upon to be complete, a large volume of urine is desirable in order to

minimise errors due to incomplete voiding. An extended collection period is one obvious way to do this; hence the popularity of the 24-hour method. In fact, reliable 24-hour collections are extremely difficult to obtain, especially in children, and the reproducibility of the 24-hour creatinine clearance is poor. Large urine volumes can also be obtained by other means, of which the simplest is water diuresis. If the patient drinks 600-800 ml water per square metre body surface area (about 20 ml/kg/body weight), equivalent to 1-1.5 l for an adult, the ensuing diuresis allows three or four separate voidings of reasonable volume over the next 1-2 hours if the diuresis is maintained by further drinks equal in volume to the voided specimen at the end of each collection period. Independent clearance calculations are then made on the basis of each individual urine specimen, the average of the resulting estimates being taken as the overall result. If this technique is used, a perfectly adequate clinical estimate of GFR is obtained, as shown in children by Arant *et al.*⁷ Exceptions include patients with obstructed or dilated urinary tracts, in whom the problem of reliable urine collection is magnified, and those whose clinical condition precludes the administration of a water load. When the GFR is severely reduced (inulin clearance < 25 ml/min/1.73 m²) creatinine clearance substantially overestimates GFR⁸ because the proportion of non-creatinine chromogens diminishes as plasma true creatinine rises, thus unmasking the inherent overestimate due to tubular secretion.

In recent years a number of exogenous substances have been investigated as substitutes for inulin (Table) which is an inconvenient material to use being poorly soluble in water and tedious to measure in the laboratory. It is clear on the basis of several studies^{9 10} that Polyfructosan S, a synthetic fructan of smaller molecular size than inulin, is an excellent alternative being freely soluble in cold water. Various labelled chelates of EDTA and DTPA (diethylenetriamine pentacetic acid), notably ⁵¹Cr EDTA, fulfil the criteria well and the latter preparation is now widely used in the UK, although usually by means of a different technique discussed below. Sodium iothalamate, labelled

Substances whose clearance approximates GFR
 (*indicates preferred where high accuracy is required)

-
- Urea
 - Creatinine
 - *Inulin
 - Mannitol
 - Vitamin B₁₂
 - *Polyfructosan S
 - *⁵¹Cr EDTA
 - DTPA (various labels)
 - *Sodium iothalamate (¹²⁵I, ¹³¹I, or "cold")
-

either with ^{131}I or ^{125}I , has been shown to be an excellent choice^{11 12} and "cold" (ie, non-radioactive) sodium iothalamate (Conray) can also be used, being estimated in plasma and urine by fluorimetry.¹³ In short, if it is desired to estimate GFR by the classical technique using an exogenous, infused marker, there is an abundance of suitable substances and the choice is probably best made on the basis of convenience of laboratory measurement, which will vary according to local practice. It should be possible to achieve a coefficient of variation of about 5% using any of these markers, provided that satisfactory urine collections can be made. The fact that this is not always possible has led to a continued search for methods of measuring the GFR without the need for timed urine collections. Two partially successful solutions to this problem have been found.

The first is known as the infusion clearance, described by Earle and Berliner in 1946.¹⁴ The principle is very simple: if a compound such as inulin is infused at a constant rate, an equilibrium condition will be reached in which the infusion rate equals the excretion rate and plasma concentration is steady. Since the excretion rate forms the numerator in the classical clearance formula (equation 2 above), substituting the infusion rate for it should yield the same value for clearance but without the need for urine collection. The technique is somewhat laborious, although less so than the standard method, and it probably represents a useful advance particularly in the context of certain types of clinical research.¹⁵

The second method, or group of methods, for measuring clearance without urine collection involves the analysis of the rate of disappearance from the plasma of an injected bolus of a suitable chemical. Assuming that all the injected marker is eventually excreted in the urine, renal clearance is calculated as the total dose injected divided by the area under its plasma disappearance curve (Fig. 1). Inherent in the method is the need to calculate the area below the curve from the smallest possible number of blood samples, and this is the Achilles' heel of the technique. Best known are the formulae based on the two compartment model of Sapirstein,¹⁶ originally worked out for creatinine in the dog, and various simplified versions of it, notably that developed by Chantler and coworkers.¹⁷ The latter requires three blood samples and, using ^{51}Cr EDTA, yields an excellent estimate of GFR for most purposes. The method is not reliable in patients with oedema or serous effusions which cause delay in the equilibration of the marker in body fluids, in individuals with severely reduced glomerular filtration because the slope of the curve following plasma concentration is too flat, and (perhaps) in small infants. It also progressively overestimates

GFR at values above 90 ml/min/1.73 m².

It is important to note that both the infusion technique and the plasma disappearance method involve an additional assumption as compared with the standard technique—that is, that the marker is not disappearing from the circulation by any route other than renal excretion, such as loss in the bile or by metabolism. This appears to be the case with regard to inulin, but requires independent validation for any other substance used in its place. Iothalamate and EDTA are probably satisfactory in this respect.

Plasma urea and creatinine concentration

Given that all clearance studies are a nuisance to perform, how much value can be placed on the plasma concentration of urea and creatinine as indices of renal function? Both rise as the GFR falls, but in the case of urea the relationship is disturbed by several other factors. This is illustrated by the fact that in the individual the range of blood urea is considerably wider than that of creatinine. The urea production rate is markedly affected by the quantity and biological quality of protein in the diet, and also by the rate of catabolism of the patient. Furthermore, as previously mentioned, the state of hydration

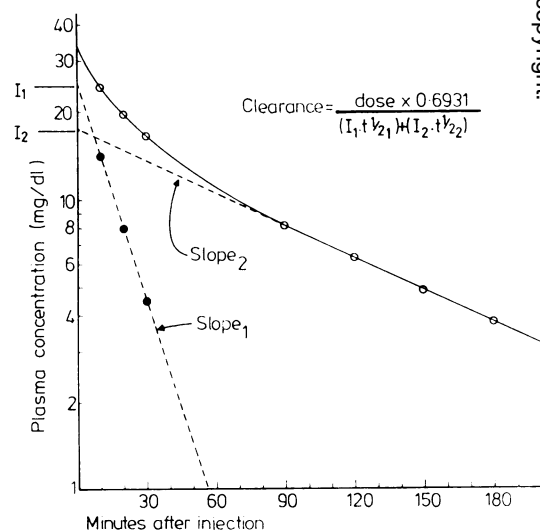


Fig. 1 The plasma disappearance curve of inulin following a bolus injection. The clearance equation is based on that derived by Sapirstein (see text). The $t_{1/2}$ terms represent the time to half the initial (I) concentration of each of the two derived * exponential curves (slopes 1 and 2). Note the logarithmic ordinate scale.

*Slope 2 is derived by extrapolation of the straight portion of the experimental curve. Slope 1 is derived by subtracting slope 2 from the experimental curve, ed.

exerts a marked effect on the urea excretion rate. Thus, while it is true that blood urea will rise as the GFR falls, it is not possible to make a useful estimate of the GFR from the plasma urea concentration alone.

The creatinine production rate, on the other hand, is relatively constant and unaffected by diet except in so far as preformed creatinine may be absorbed from cooked meat.¹⁸ Creatinine is mainly produced from muscle, and its production rate is therefore related to muscle mass. Since mass increases with growth faster than surface area, and since the GFR is proportional to surface area, the normal plasma creatinine concentration rises with body size. Normal values for plasma creatinine in relation to age are known,¹⁹ and it is possible to decide with fair confidence from plasma creatinine alone whether or not the GFR is normal. Quantitative examination of the relationship between body mass and surface area enables the following prediction to be made: GFR, corrected for body surface area, is proportional to height divided by plasma creatinine concentration. Two published studies^{20 21} have examined this relationship in children. Morris *et al.*²² using a kinetic method for measurement of plasma creatinine, which avoids interference from non-creatinine chromogens, have found that if height (cm)/plasma creatinine ($\mu\text{mol/l}$) is greater than 2.1, the GFR may be taken as normal with 95% confidence, while if the quotient is less than 1.6, it is almost certainly reduced. Analysis of values for the GFR below $90 \text{ ml/min}/1.73 \text{ m}^2$, where the fit of the relationship is better, gives the formula $\text{GFR} = 40 \times \text{height}/\text{plasma creatinine}$, the predictive value of which has been found to be a significant clinical help and has allowed a considerable saving in the number of formal GFR estimations performed. The relationship between body size and GFR in the elderly, in whom absolute GFR shows a gradual decline, is different from that which applies in childhood, and a number of formulae have been published for use in this age group.²³

Tubular function

The glomerulus has but one function: filtration. The renal tubule, in contrast, has many functions and in general these are not susceptible to examination by simple clearance techniques. Innumerable sophisticated methods have been developed for looking at specific tubular functions. For example, the specific transport systems which exist in the proximal tubule for the reabsorption of various substances can be evaluated by the use of so-called titration studies, in which the plasma concentration of the substance in question is artificially manipulated while its excretion is measured and compared with

its calculated filtration rate. A family of curves representing filtration, reabsorption and excretion can be plotted against plasma concentration, as shown here for glucose (Fig. 2); similar curves may be constructed for phosphate, bicarbonate and certain amino acids. The maximal tubular transport rate (T_m) is given by the y co-ordinate of the flat portion of the reabsorption curve, while the x co-ordinate of the point of inflexion of the curve represents the threshold—that is, the plasma concentration at which the transport mechanism is saturated and glucose begins to appear in the urine. Such studies must be interpreted with caution, since T_m and threshold values are not absolute constants and may be markedly altered by various factors, especially by variations of renal blood flow and GFR. Such elaborate investigations are rarely indicated for clinical purposes, but may occasionally be necessary to identify, for example, the proximal tubular defect in bicarbonate reabsorption which underlies the proximal type of renal tubular acidosis.²⁴ Gross defects in proximal tubular function such as are seen in the Fanconi syndrome can usually be reliably identified by quantitative analysis of a 24-hour urine specimen.

Two aspects of distal tubular function deserve mention since they are of more than occasional clinical relevance: the excretion of non-volatile acid and the concentration and dilution of urine.

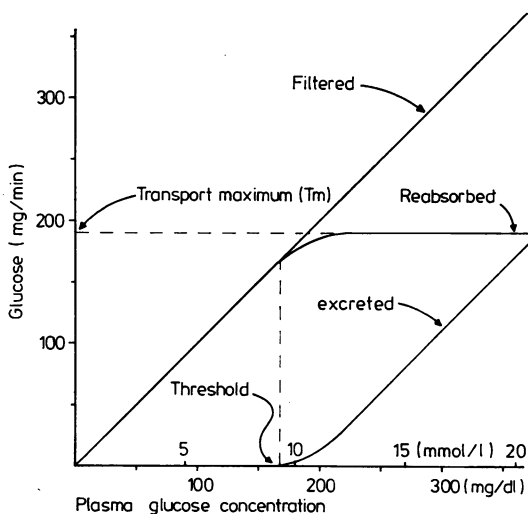


Fig. 2 A normal glucose titration curve. The line for glucose filtered is calculated from $\text{GFR} \times \text{plasma glucose}$, and the GFR is assumed to be 100 ml/minute . The curve for glucose reabsorbed is derived by subtracting glucose excreted from glucose filtered.

In order to maintain external balance for hydrogen ion at normal blood pH the distal tubule must secrete hydrogen ion against a concentration gradient. Failure to achieve this results in type 1 or distal renal tubular acidosis. This function may be definitively tested by stressing the tubule by loading the patient with ammonium chloride and measuring the output of acid derived from it as the sum of titratable acid and ammonium; the protocol described by Wrong and Davis²⁵ is generally accepted as the standard method. A test of this type is indispensable for the accurate diagnosis of incomplete acidification defects and their variants. However, it is time-consuming and often unpleasant for the patient, and for the detection of complete distal renal tubular acidosis a procedure described by Halperin and coworkers in 1974²⁶ may avoid the necessity for acid loading and deserves to be more widely known. As long ago as 1952 Kennedy *et al*²⁷ observed that CO₂ was generated in alkaline urine, and subsequent work has shown that this depends on the secretion of hydrogen ion in the presence of excess bicarbonate. In the presence of normal hydrogen and potassium ion exchange for sodium in the distal tubule, when urine is alkaline the urinary PCO₂ is considerably higher than that of blood, whereas in distal renal tubular acidosis where there is a defect of tubular hydrogen ion secretion the difference virtually disappears. The only prerequisite is a urinary pH above 7.4, which is easily achieved by a suitable oral dose of sodium bicarbonate. The dividing line between normal and abnormal values is clear cut, and the test represents a useful advance in the investigation of patients suspected of having renal tubular acidosis. There are several well known tests of renal concentrating ability, including water deprivation, the administration of pitressin or synthetic arginine-vasopressin, and measurement of free water clearance after water loading or free water reabsorption after mannitol loading. These procedures are well described in standard texts and will not be discussed further, save to point out that they are all difficult, demanding of both patient and staff and may occasionally be dangerous. It is pertinent to draw attention to the fact that examination of a few random urine specimens collected at different times of day, without any water restriction or other invasive manipulations, yields in most normal subjects at least one urine of osmolality 900 mosmol/kg or of specific gravity 1.027 or better, criteria sufficient in themselves to exclude a defect in urinary concentrating capacity. I suggest that this is a highly desirable preliminary to the performance of any of the more difficult and unpleasant tests previously mentioned.

Although urinary concentration is a specific

function of the loop of Henle and the distal tubule, it is important to remember that it is also dependent on the delivery of sufficient chloride to the ascending limb of the loop, since this is the site which drives the countercurrent multiplier system of the medulla. As GFR falls the amount of chloride reaching the distal nephron falls proportionately until, in advanced chronic renal failure, it must almost all be excreted to maintain external balance for salt; little or none is therefore available for reabsorption in the loop, severely restricting both concentrating and diluting capacity. Thus the achievement of normal maximal urinary concentration absolutely requires a normal or near normal GFR.

Which, in essence, is precisely what John Bostock observed in 1827.

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