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# GLOMERULAR FILTRATION RATE AND CREATININE CLEARANCE

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## Glomerular filtration rate

The concept of renal clearance was introduced by Möller, McIntosh & Van Slyke in 1929, although the clearance formula was already devised twelve years previously by Thomas Addis. Renal plasma clearance is the ratio between the urinary excretion rate and plasma concentration of a specific substance. This is equivalent to the virtual volume of plasma completely cleared of the substance in the time interval considered. Clearance is not a rate in the sense of quantity excreted per unit time. Rate can vary while clearance remains constant if the excretion rate is proportional to the concentration in blood as is the case with the glomerular filtration of a low molecular weight, non-protein bound, non-electrolyte. The definition of renal clearance does not imply how a substance is handled by the kidneys and it is only by the use of compounds with specific renal excretion characteristics that measured clearance values express different partial functions of the kidney.

A substance used in the assessment of glomerular filtration rate (GFR) should be:

1. metabolically inert and excreted exclusively by glomerular filtration i.e. neither reabsorbed nor secreted by the renal tubules;
2. non-toxic and should not alter renal function when infused in quantities which permit adequate quantification in plasma and urine;
3. freely filtrable through glomerular capillary membranes i.e. neither protein bound nor large enough to be held back in the process of ultrafiltration;
4. easily quantitated in plasma and urine with a high degree of accuracy.

The excretion rate of such a substance will increase in proportion to the serum concentration (first order kinetics) and the measured clearance is thus independent of the plasma concentrations obtained.

### *Relevance to drug studies*

The relevance of GFR is two fold; the renal clearance of drugs tends to parallel GFR; secondly many drugs alter GFR either reversibly as a result of haemodynamic change or permanently as a manifestation of toxic damage. The determination of the renal clearance of drugs and the adjustment of dosage to take account of impaired clearance will be considered in sequence later. Similarly the use of GFR as a measure of global kidney damage will be considered alongside other methods of detecting nephrotoxicity. The chief purpose of this contribution is to describe the methods available for the determination of GFR as a measure of a pharmacological response. Secondary effects on the handling of sodium and of water will be deferred to the second and third contributions to this series.

### *Inulin clearance*

Only the fructose polysaccharide inulin seems to fulfil all the criteria listed above and the renal plasma clearance of inulin is generally accepted as the standard reference for the GFR in all vertebrates (Shannon & Smith, 1935; Smith, 1937). Direct proof of the equivalence of GFR to the clearance of inulin has recently been provided by animal experiments (Gutman, Gottschalk & Lassiter, 1965). Use of the renal plasma clearance of exogenous creatinine as originally suggested by Rehberg (1926) was abandoned because of a great overestimation of GFR due to a large tubular secretion of creatinine (Shannon, 1935).

The practical procedure in the determination of inulin clearance is described in Table 1 which also contains methodological references and normal values. The age dependent decrease according to Davies & Shock (1950) is shown in Figure 1.

Although the clearance of inulin provides a correct measure of GFR two problems remain. The procedure is time consuming and tedious demanding an intravenous infusion to a constant serum level. The methods of measuring inulin in serum and urine are laborious and cumbersome, although the method of incubation with β-indolyl-acetate has been adapted for automatic analysis using a Technicon Autoanalyser (Dawborn, 1965). Measurement of inulin clearance has therefore only been used to a minor extent in clinical medicine and its use in drug research

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**Table 1** Determination of inulin clearance

*Procedure*:
Priming dose: 3–5 g inulin in 50 ml 0.9% saline i.v.
Continuous dose: 25–50 mg/min in 0.9% saline
Equilibrium period: 1 h
Urine collection: Preferably 3 periods of 0.5 to 1 h
Plasma sampling: In the middle of each period
Plasma concentrations should be around 300 mg/l
Inulin distributes in about 16% of total body weight (extracellular fluid)

*Measurement*:

| | |
|---|---|
| Reaction with diphenylamine | Corcoran & Page (1939)<br>Bojesen (1952) |
| Reaction with resorcinol | Roe *et al.* (1949)<br>Schreiner (1950) |
| Reaction with anthrone | Young & Raisz (1952)<br>Führ *et al.* (1955) |
| Reaction with β-indolylacetic acid | Heyrovsky (1956)<br>Dawborn (1965) |

*Normal values*:
GFR in males (= inulin clearance) ml $min^{-1}$ 1.73 $m^{-2}$
= 152.2 − 0.96 × Age (years) (Davies & Shock, 1950)
Females: 10% lower in comparable age groups.
(Goldring & Chassis, 1956; Bröchner-Mortensen, Giese & Rossing, 1969)

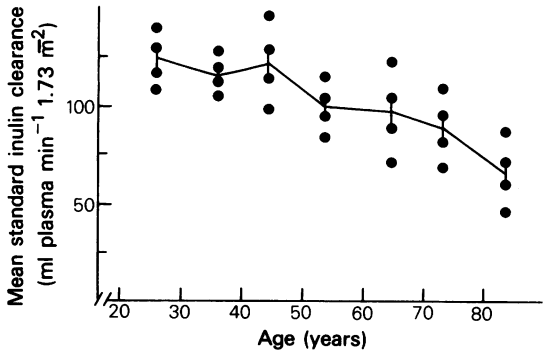


**Figure 1** Age-related decline in inulin clearance (glomerular filtration rate) after Davies and Shock (1950). ● ●s.d. of distribution, ●—● s.d. of mean.

has also been restricted. Examples of the use of inulin clearance in drug studies can be found in the papers of Steiness (1974) and Dubb *et al.* (1978).

*Endogenous creatinine clearance*

Several other substances were examined as substitutes for inulin and in 1937 Popper & Mandel suggested endogenous creatinine which is continuously introduced at a constant rate into the blood stream. It was hoped that the low concentration of endogenous creatinine in contrast to the high concentration attained by exogenous infusion would less involve the tubular secretory system thus making the clearance more equivalent to the true GFR. Unfortunately, it was at that time impossible to measure the low concentration of endogenous creatinine in plasma. A year later however Miller & Winkler (1938) succeeded in this and the clearance of endogenous creatinine became widely applied in clinical and scientific work as the standard procedure for the assessment of GFR. Today it is still the most used parameter of renal function in drug research despite the appearance of more specific methods.

Several authors have compared creatinine clearance with GFR measured as inulin clearance. While a few found a close approximation (Miller & Winkler, 1938; Steinitz & Türkand, 1940; Brod & Sirota, 1948; Tobias, McLaughlin & Hopper, 1962; Bennett & Porter, 1971), most have demonstrated that endogenous creatinine clearance is an inaccurate estimate of GFR (Miller *et al.*, 1952; Mandel *et al.*, 1953; Berlyne *et al.*, 1964; Lavender, Hilton & Jones, 1969; Kim *et al.*, 1969; Skov, 1970; Hagstam *et al.*, 1974). The discrepancy is particularly pronounced in subjects with low GFR values and is undoubtedly due to an increasing tubular secretion of creatinine with increasing serum creatinine. Creatinine clearance thus overestimates GFR and particularly so in subjects who most need precise evaluation of renal function. A second problem is that the original alkaline picrate method of Jaffe does not measure creatinine only but also many other substances. This grossly overestimates the concentration of creatinine particularly in blood. These so-called non-creatinine chromogens which include uric acid, glucose,

fructose, acetone, pyruvic acid, acetoacetate and ascorbic acid can exaggerate the concentration of creatinine by as much as 20% (Mandel & Jones, 1953; Doolan, Alpen & Theil, 1962; Young *et al.*, 1972). It has been argued that the overestimation of the plasma creatinine concentration which increases the denominator in the clearance formula is cancelled out by tubular secretion which increases the numerator. This is a spurious argument as the two errors are not correlated and direct measurements comparing different methods for evaluation of plasma creatinine have demonstrated that the best approximation of creatinine clearance to inulin clearance is obtained when using true serum creatinine (Healy & Graeme, 1968).

Newer, more specific methods have emerged (Table 2), but they are all more difficult and have not yet gained widespread use compared to the colorimetric ones.

Creatinine excretion is increased by a high protein diet and serum creatinine is acutely increased after eating cooked meat. This results in an overestimation of endogenous creatinine clearance if calculated from a single fasting specimen (Pasternack & Kühlbäck, 1971; Jacobsen *et al.*, 1979). Creatinine excretion is also increased by intensive physical exercise (Doolan *et al.*, 1962) and a considerable day to day, within-subject variation in creatinine excretion has also been demonstrated with a coefficient of variation of 10 to 15% (Greenblatt *et al.*, 1976). Hilton *et al.* (1969) found no correlation between the degree of proteinuria and the ratio between inulin and creatinine clearance. Although normally carried out over 24 h it has been shown that a one hour urine collection gives comparable results provided bladder emptying is complete (Richardson & Philbin, 1971).

Reviews of the use and limitations of creatinine clearance have been made by Doolan *et al.* (1962) and by Bjornsson (1979). References to measurements of creatinine and inulin clearances in children are given in the papers of Arant, Edelmann & Spitzer (1972) and Rudd *et al.* (1980).

An intriguing phenomenon is that the tubular secretion of creatinine can be blocked by various drugs. This imposes limitations on the use of creatinine clearance to measure drug effects on renal function (Young, Pestamer & Gibberman, 1975). Examples include triamterene, spironolactone, amiloride, cimetidine and trimethoprim (Berglund, Killander & Pompeius, 1975; Dubb *et al.*, 1978; Larsson, Bodemar & Kågedal, 1979). It is important to realize that the impression of decreased renal function conveyed by creatinine clearance measurement in such circumstances is false as revealed by an unchanged renal function when GFR is evaluated by $^{51}$Cr-EDTA or inulin clearance.

### $^{51}$*Cr-EDTA clearance*

The inulin and creatinine methods share a serious drawback in that they depend on meticulous urine collection. This is difficult to obtain without bladder catheterization which can rarely be ethically justified in research. The problem can be circumvented by using a different approach based on the disappearance from serum of a substance solely eliminated by glomerular filtration. The method is equivalent to the well known way of measuring the clearance of drugs (Tucker, 1981). Early methods used thiosulphate (Vorbruger, Riedwyl & Reubi, 1969) and inulin (Rose, 1969) but the approach gained popularity with the introduction of radiolabelled substances easy to quantitate in plasma. The substances used include $^{57}$Co-cyanocobalamin (Breckenridge & Metcalfe-Gibson, 1965), the urological contrast agents $^{131}$I-diatrizoate (Morris *et al.*, 1965) and $^{125}$I-iothalamate (Skov, 1970; Groth & Tengström, 1977), and the metal chelates $^{140}$La-DTPA (Funck-Brentano, Lellouch & Leski, 1967) and $^{51}$Cr-EDTA (Garnett, Parsons & Veall, 1967). The methods have been

**Table 2** Methods of measurement of creatinine in plasma and urine

| | |
|---|---|
| 1. Jaffe's reaction (Folin-Wu technique) | Bonsnes & Taussky (1945)<br>Brod & Sirota (1948) |
| 2. Adaptation of autoanalyser | Technicon Method (1963) |
| 3. Adsorption of true creatinine to Lloyd's reagent | Haugen & Blegen (1953)<br>Owen *et al.* (1954) |
| 4. High-pressure liquid chromatography | Chiou *et al.* (1978)<br>Lim *et al.* (1978) |
| 5. Enzymatic assay | Moss *et al.* (1975) |
| 6. Ion exchange chromatography | Weatherburn *et al.* (1978) |
| 7. Mass fragmentography | Björkhem *et al.* (1977) |

*Normal adult values:* (Based upon total chromgen analysis of creatinine)
Males: Creatinine clearance (ml/min) = 143.5 − 1.095 × age (years)
Females: Creatinine clearance (ml/min) = 119.5 − 0.915 × age (years)

(Bjornsson, 1979)

reviewed by Bianci (1972) and Cohen (1974). $^{51}$Cr-EDTA in particular became the preferred substance due to its reliability and the extremely high correlation with inulin clearance (Bröchner-Mortensen, Giese & Rossing, 1969; Lavender *et al.*, 1969; Chantler *et al.*, 1969; Hagstam *et al.*, 1974).

EDTA clearance and other methods which avoid the need for urine collection can be performed by the constant infusion technique or by the single injection technique. The latter is much simpler and its precision is equivalent to the more cumbersome constant infusion method (Hagstam *et al.*, 1974). Different variations of the single injection technique have been used; the total body clearance may be calculated by dividing the total area under the plasma concentration/time curve into the dose given (Nosslin, 1965; Aurell, 1965); area may be calculated assuming single or double exponential decay (Chantler *et al.*, 1969) or from only a few measured concentration values. Even a method using only a single blood sample has been suggested (Fisher & Veall, 1975). External counting over the head (Funck-Brentano, Lellouch & Leski, 1967), heart (Ram, Holroyd & Chisholm, 1969) or whole body after shielding the bladder and kidney (Oberhausen & Romahn, 1968) have also been used.

The principle described by Nosslin (1965) in which the complete area under the plasma curve is determined by successive integrations is the most accurate and satisfactory. The method, however, demands a large number of data points. Alternative approaches have therefore been investigated and it has been demonstrated that calculations from the final slope of a curve using only a few samples can be used. The clearance so obtained overestimates GFR but corrected values for total body clearance and hence renal clearance of $^{51}$Cr-EDTA can be obtained (Bröchner-Mortensen, 1972; Bröchner-Mortensen & Rödbro, 1976b). The difference between total and renal plasma clearance of $^{51}$Cr-EDTA is due to a small extrarenal elimination. Most authors have found that renal plasma clearance of $^{51}$Cr-EDTA underestimates GFR; the correction factor is about 1.10. Table 3 gives details for measuring and calculating GFR from a single injection of $^{51}$Cr-EDTA and a few plasma samples. The necessary corrections are independent of the renal function holding true in all conditions except severe oedema. The precision of this method has been thoroughly studied and compared with other methods of measuring GFR (Bröchner-Mortensen & Rödbro, 1976*a*).

Examples of drug studies using $^{51}$Cr-EDTA clearance are found in the papers of Larsson *et al.* (1979), Hoffman *et al.* (1980) and Dutt, Moody & Northfield (1981).

GFR is depressed by many drugs influencing renal haemodynamics, in particular many antihypertensives, as reviewed by Pedersen (1979) and Bjornsson (1979). Glucocorticoids can substantially increase GFR by an unknown mechanism (George, 1974) and GFR is also increased in hyperthyroidism and depressed in primary and secondary hypothyroidism (Ford *et al.*, 1961).

*Estimation of GFR from serum creatinine*

In daily clinical routine even the single injection technique of $^{51}$Cr-EDTA is too difficult and several authors have tried to establish alternative methods based upon simple and easily accessible clinical and laboratory data. Serum creatinine by itself is the most used simple parameter of renal function and is valuable as an expression of relative change of renal function (glomerular or total) in the individual subject e.g. in drug toxicity studies. In order to get an impression of the absolute value of GFR an early approach was to divide an average value of creatinine production by a measured serum creatinine or read GFR directly from a curve depicting the relationship between clearance and serum creatinine (Effersöe, 1957; Doolan *et al.*, 1962; Kassirer, 1971). These methods, however, are still marred by the discrepancy between creatinine clearance and inulin clearance just as they also suffer by ignoring the large variation in the production and hence urinary excretion of creatinine. Creatinine is an endproduct from muscle creatine phosphate metabolism and its production varies greatly depending on the weight, age and sex of the patient. The creatinine production is closely related to body weight and in particular to muscular development. The production in females is about 90% of that in males of the same age and weight and it decreases with age in both sexes (Kampmann *et al.*, 1974; Cockcroft & Gault, 1976; Rose *et al.*, 1976).

**Table 3** Routine method for $^{51}$Cr-EDTA clearance measurement

1. Patient should stay in bed throughout the investigation period. Fasting is not necessary.
2. 100 $\mu$Ci $^{51}$Cr-EDTA in 0.9% saline is injected intravenously.
3. Radioactivity of standard solution and plasma samples obtained at 3, 4 and 5 h is measured in a well counter.
4. The 'one-slope' area under the curve is calculated by dividing the intercept by the rate constant of the regression line.
5. Clearance ($Cl_1$ = final slope clearance) is found by dividing the dose by the area found in 4.
6. The final slope clearance ($Cl_1$) is transformed to total body clearance ($Cl_t$) by the formula $C_t = 0.9908\ Cl_1 - 0.0012\ Cl_1^2$.
7. GFR is found by subtracting 3.7 ml/min from $Cl_t$ and multiplying by 1.10.

All the corrections can be combined in a single formula: $GFR = ((0.9908\ Cl_1 - 0.0012\ Cl_1^2) - 3.7) \times 1.10$.

(Bröchner-Mortensen (1972) and Bröchner-Mortensen & Rödbro (1976a))

Creatinine clearance decreases with age and is lower in females than in males (Kampmann *et al.*, 1974; Cockcroft & Gault, 1976). These changes are in accordance with those previously described for inulin clearance (Tables 1 and 2). Serum creatinine, on the other hand, is almost unchanged by increasing age as creatinine production and renal function decline in parallel although no feedback control mechanism has been established (Dubach, Metz & Schmid, 1967).

Allowance for these factors can be combined in a nomogram (Figure 2) or formula presentation making it an easy procedure to estimate creatinine clearance from the serum creatinine, age, sex and weight of the patient (Siersbaek-Nielsen *et al.*, 1971; Cockcroft & Gault, 1976; Rowe *et al.*, 1976; Lott & Hayton, 1978; Bjornsson, 1979). Estimates so calculated correlate well with measured endogenous creatinine clearance (Cockcroft & Gault, 1976) and the error of about 20% is equivalent to that involved in the determination of creatinine clearance from an apparent 24 h urine collection. It is the method of choice with regard to rapid clinical assessment of renal function and is particularly useful with regard to drug dosage adjustment in renal insufficiency (Dettli, 1976; Mawer, 1976).

Serious miscalculation can be the result of neglect of the age-dependent decrease in renal function as shown in Table 4. Serum concentration half-times of gentamicin were measured in three age groups. Good agreement was obtained between measured $T_{1/2}$ and $T_{1/2}$ calculated from estimated creatinine clearance (Figure 2) and distribution volume. The assumption of a fixed ratio between $T_{1/2}$ and serum creatinine (perhaps the value for the middle-aged group) would clearly exaggerate $T_{1/2}$ in the young and underestimate $T_{1/2}$ in the elderly (Lumholtz *et al.*, 1974).

The above mentioned methods cannot be used in postoperative conditions, in severe uraemia, in extreme obesity or in the weakened paralysed patient as the creatinine production relative to body weight in

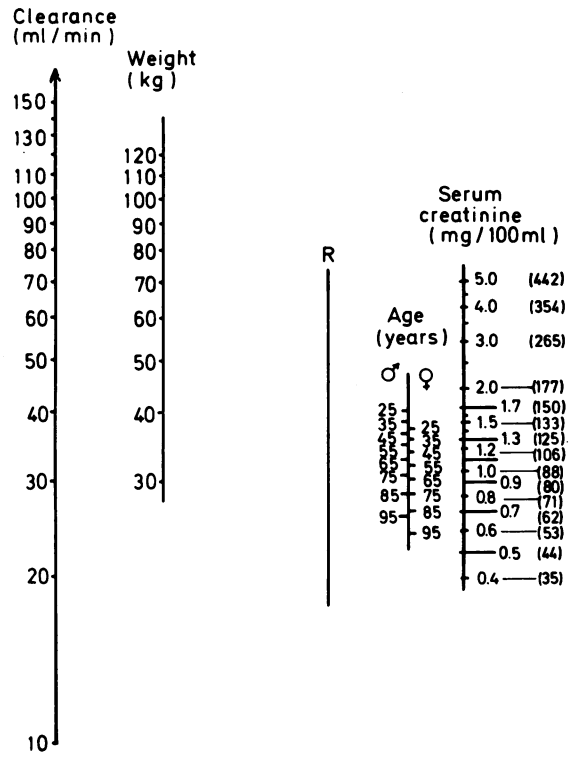


**Figure 2** Nomogram for evaluation of the endogenous creatinine clearance. Use of the nomogram: Connect with a ruler the patient's weight on the second line from the left with the patient's age on the fourth line. Note the point of intersection on R and keep the ruler there. Turn the right part of the ruler to the appropriate serum creatinine value and the left side will indicate the clearance in ml/min. Serum creatinine values in μmol/l are given within parentheses.
(Siersbaek-Nielsen *et al.*, 1971).

**Table 4** Influence of age on the disposition of gentamicin: serum concentration half-time $T_{1/2}$ may be calculated* from estimated creatinine clearance (Figure 2) and distribution volume but not from creatinine only

| Age (years) | 20–50 | 51–70 | > 70 |
|---|---|---|---|
| Number of patients | 12 | 12 | 25 |
| Serum creatinine (mg/100 ml) | 1.0 ± 0.1 | 1.1 ± 0.2 | 1.0 ± 0.2 |
| Gentamicin—distribution volume V (% of body weight) | 15.2 ± 7.8 | 16.2 ± 5.8 | 24.2 ± 5.9 |
| —measured $T_{1/2}$ (min) | 93 ± 26 | 120 ± 25 | 216 ± 60 |
| —calculated* $T_{1/2}$ (min) | 91 ± 13 | 144 ± 33 | 240 ± 52 |
| —$T_{1/2}$/creatinine (min/(mg/100 ml)) | 93 | 109 | 216 |

*$T_{1/2}$ = 0.693 × distribution volume/clearance
$T_{1/2}$ (min) = 0.693 × V × body weight (g)/(0.90 × estimated creatinine clearance (ml/min))

(Lumholtz *et al.*, 1974)

these situations is decreased. Overestimation of the creatinine clearance would result. The method is also invalid when there are rapid changes in renal function.

Creatinine is distributed in total body water (about 60% of the body weight). This corresponds with a half-time of about 4 h in a 70 kg patient with a creatinine clearance of 120 ml/min ($T_{½}$ = 0.693 × volume/clearance). Accordingly it takes about one day (5 × $T_{½}$) to reach a new steady stage after a change in renal function. This period becomes longer if the renal function is already impaired and equilibration periods up to 8 days may be anticipated in patients with severe renal insufficiency (Chiou & Hsu, 1975). Methods have been published to estimate creatinine clearance when serum creatinine is changing (Jelliffe & Jelliffe, 1972; Mawer, 1976) but these require computer programs not always available.

## Conclusion

Glomerular filtration rate (GFR) is a frequently used and valuable measure of kidney function in drug studies. Inulin clearance gives the most accurate estimate but the method is difficult and time consuming and can usually be replaced by the single injection $^{51}$Cr-EDTA technique without loss of accuracy provided careful attention is paid to correction factors. This technique seems to be the method of choice in studies on drugs and renal function. Creatinine clearance is only indicated when other more reliable methods are not available. Competition by drugs for tubular secretion should always be taken into consideration. Nomographic methods are unsuitable for drug studies but very useful in a rapid bedside evaluation of kidney function when adjusting dosage of potentially harmful drugs for patients with renal insufficiency.

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