Selection, presentation, and interpretation of biochemical data in renal failure

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The physicians task is to classify his patient’s conditions to predict their course and to take effective action at the most appropriate time. Biochemical measurements often assist them as a series of measurements to assess the development of a disorder and the prognosis or as a single measurement to assess a function or allocate the patient to a disease category (diagnosis). The proper selection, presentation, and interpretation of data is an important part of any physician’s activity.

The display of sequential data and the manipulation of single values are very simple in mathematical terms, but the tedium of calculation and plotting has prevented large-scale application. There is, therefore, a need for quick, reliable, repetitive data manipulation and display. These are ideal, if low level, tasks for a computer. We will not discuss the computing aspect further, but instead concentrate on the aims and advantages of data manipulation and display in the particular context of the detection and management of renal disease. Initially, we will consider the handling of sequential data which are collected from the majority of patients attending renal clinics. Then we will discuss the evaluation of single measurements collected to assess renal function.

Sequential data

Laboratory results in a sequence are most often viewed singly in relation to a few previous results and are not carefully scrutinized for trends or patterns partly because they are not tabulated. Sequential data are increasingly available from laboratory systems as a cumulative report. However, in our opinion a graphical display of sequential data is essential for interpretation, because the irregular intervals between results make it difficult to assess patterns or trends even from tables. Manipulation of the data before display can also have advantages. The use of statistical analysis to evaluate trends or patterns is considered elsewhere in this issue.

Display. The introduction of time converts data from a series of snapshots into a film, which is best observed as a sequence and not as individual frames. As a simple example of the advantages of the display of data, Figure 1 shows the changes in the serum creatinine in two renal transplant patients whose renal function deteriorated when they were given a diuretic for the fluid retention associated with an acute rejection episode.

The deterioration was reversed after withdrawal of the drug, either immediately (top panel) or after an interval of about 1 month (lower panel). The relationship between drug exposure and the renal deterioration is obvious on the display but might well have been missed without it.

Diuretics of various kinds are commonly prescribed for patients with chronic renal failure or after renal transplantation (particularly at the time of acute rejection). Renal impairment due to the drugs can be easily obscured by other events and may not be associated with obvious signs of an allergic response [1]. (In the examples we provide only patient 2 showed an eosinophilia). In addition, some delay may occur before the toxic effects of the drug are recognized (perhaps in patient 2 because of initial high-dose steroid therapy), or before an improvement in renal function occurs after the drugs have been withdrawn. A further example of this “dead time” is the 1-week delay before renal function improves when mefenamic acid is stopped in patients in whom it has caused renal failure [2]. These intervals of “dead time” are important in clinical management.

Manipulation to linear trends. Transformed plasma creatinine. The response to diuretic withdrawal in patient 1 (Fig. 1) is easily detected when the data are displayed because there had been a steady increase in serum creatinine beforehand. A change is most easily detected when it is superimposed on an obvious and easily recognizable trend. In addition, if trends or patterns are defined in the data, it may be possible to extrapolate the data to important thresholds and “action limits.” The type of trend or pattern is not critical, but rectilinear changes with time are the easiest to interpret and use [3].

A plot of the reciprocal or the logarithm of serum creatinine against time in progressive chronic renal failure is often rectilinear (Fig. 2) [4, 5].

The two transforms, logarithm and reciprocal, have different implications (see Appendix). A linear decrease in the reciprocal with time implies a constant rate of decline of the GFR, with a constant number of nephrons failing in unit time. On the other hand, a linear increase in the logarithm of the serum creatinine with time indicates a constant fractional decline in the GFR, with a fixed proportion of surviving nephrons failing in unit time. In Figure 2 the reciprocal changes more linearly with time than the logarithm, and indeed the trend in the logarithm suggests some acceleration in the loss of renal function beginning in December 1980. A sequence which is linear as the reciprocal must be nonlinear as the logarithm, and this nonlin-
replacement therapy may well become necessary, and plans can be made
for the data or by an appropriate calculation, of the time when renal
function can be made aware, by extrapolation of
information in it. It is a guide to the clinical effect of any fall in
creatinine or its transform remains the most useful index of
renal function [7].

For simplicity we have presented the data as if creatinine excretion and probably production were constant in progressive renal failure, but there is, in fact, a consistent decline in the amount excreted each 24 hr. This, and the implausibility of independent single nephron failure as the unit of function or dysfunction, undermines the interpretation of changes in serum creatinine (or its transform) as changes in GFR. However, GFR is difficult to measure precisely in advanced renal disease and is variable according to posture. For example, (Fig. 3) serum creatinine or its transform remains the most useful index of renal function [7].

It could be argued that information is lost when only the transform is used. The “illness” effect of a slowly progressive fall in GFR is presumably due to the increase in the blood concentration of “uremic toxins,” which are usually excreted by glomerular filtration. The degree of retention of these substances and of illness will in general parallel the increase in the untransformed plasma creatinine. The value obtained for the plasma creatinine is used for the two distinct pieces of information in it. It is a guide to the clinical effect of any fall in GFR, and, used as a reciprocal, it is a guide to the GFR. The pattern of change in these two measurements in progressive renal failure (Fig. 4), emphasizes the accelerating clinical deterioration when function was lost at a steady rate, both patient and chemistry showed dramatic changes when the GFR reached very low levels although the rate of renal functional deterioration was unchanged.

The transformation of other biochemical measurements. It has been pointed out recently that the transformation and display of biochemical measurements other than the serum creatinine may be of clinical value in the management of patients with chronic renal disease [8]. Serum alkaline phospha-

carity would suggest an accelerating deterioration of function at high values of plasma creatinine (at a fixed rate of decline of GFR, the fraction of nephrons failing increases as the GFR decreases).

Conversely, a curvilinear plot of plasma creatinine may be linear when the data are transformed as the logarithm. In the patient illustrated in Figure 3 an apparent amelioration in the rate of decline of GFR is shown by the reciprocal plot. This makes the interpretation of the effect of a therapy introduced late in progressive renal failure difficult, if not impossible, from serial plasma creatinine measurements.

The inevitable differences in the reciprocal and logarithmic transform are important. For the purpose of detecting change and making predictions, both transforms should be calculated and displayed, and the one rendering the better straight line of time should be used. This empiricism is justifiable as the transform is used solely to define the trend and make prediction. Deviations from a rectilinear trend allows the early detection of intercurrent causes of renal deterioration, such as drug toxicity or renal vein thrombosis, as described above. The ability to detect small deviations from a trend restores a belief in causality. There is so much “noise” in clinical affairs that the relationship between a change in data and a definable event or cause can easily be lost. Changes which would otherwise be overlooked may, however, be clear cut after transformation and display, and demand an explanation. In addition to this detection of added events, the transforms of serum creatinine allow the course of renal failure to be viewed at a glance, and both the clinicians and patient can be made aware, by extrapolation of the data or by an appropriate calculation, of the time when renal replacement therapy may well become necessary, and plans can be made [6].

Fig. 1. Serial measurements of serum creatinine in two renal allograft recipients.
Each data point represents a single reading of serum creatinine, and the triangles high dose steroid therapy. In patient 1 (top panel) the second acute rejection episode responded to corticosteroids, but thereafter a slow decline in renal function occurred. A thiazide diuretic was prescribed for the fluid retention accompanying the rejection episode, and when this was discontinued, renal function progressively improved. In patient 2 (lower panel) there were several acute rejection episodes, which initially appeared to respond to extra corticosteroid therapy but were followed by progressive renal impairment. A loop diuretic prescribed for fluid retention at the time of one of these episodes was associated with a marked eosinophilia, which disappeared when it was withdrawn. Renal function significantly improved after a short delay, during which no other measures were taken.
The changes of serum creatinine with time in a patient with polycystic renal disease and progressive renal impairment. When plotted as a reciprocal (middle panel), a rectilinear decline in GFR is apparent, but in the logarithmic transform (lower panel) the plot is curvilinear. However, there appears to be a significant change in slope occurring in December 1980 which might indicate an intercurrent cause of accelerated decline in renal function. In fact no change in management was made at this time, and the clinical status of the patient was stable.

Alkaline phosphatase is widely used as an index of renal osteodystrophy, particularly secondary hyperparathyroidism, and as an index of the response of the disorder to parathyroidectomy or vitamin D metabolites [9]. The reciprocal or logarithm of the serum alkaline phosphatase often changes linearly with time during treatment (Fig. 5), and this gives a number of advantages in patient management. Extrapolation of the data for example, gives a prediction of the time at which the serum alkaline phosphatase value will return to the normal range. Dangerous hypercalcemia is most likely to occur at that time and can then be prevented by reduction of the drug dosage. When there is no risk of hypercalcemia, unnecessary clinic visits may be avoided. The rate of decline of serum alkaline phosphatase may also be useful as an indicator of an optimum dosage of vitamin D metabolites. We found a mean half time of 3.3 weeks in 11 patients during treatment with 1-alpha hydroxycholecalciferol, and this may be used for the assessment of treatment in new patients.

Pattern. The display of sequential biochemical data may create a series of more complex patterns, which nevertheless, may appear repeatedly and, therefore, have to be considered seriously. A well known example is the “spike” in the serum creatinine after an acute renal transplant rejection (Fig. 1). The recognition and use of patterns in data are of particular importance as they may be the only available approach in complex clinical situations. There are less well recognized patterns of change in the serum alkaline phosphatase after renal transplantation. Some typical patterns are shown in Figure 6. The bone heals in a year or more after transplantation whereas the renal osteodystrophy had taken much longer to develop. The changes during healing may be characteristic for the predominant type of renal osteodystrophy (say osteitis fibrosa or osteomalacia) present beforehand, particularly where healing occurs against a background of constant immunosuppression and stable renal function. In a dialysis population an analysis of the patterns may characterize the predominant bone disease in a particular unit and indicate the impact of prophylactic treatments [10].

The use of patterns to describe complex clinical events is one example of the benefit of organizing and presenting data at an appropriate level of simplification. On the other hand, a complex and mixed biological phenomenon may by chance fit a simple mathematical function. Logarithmic transformation of the data of Manuel et al [11] on the proteinuria which follows renal transplantation, for example, shows a simple linear decline of proteinuria with time (Fig. 7). However, the underlying events are complex, with the contribution of albumin to the proteinuria decreasing with time and the “tubular” component increasing [11].

Consideration of the single measurement

When interpreting biochemical measurements, it is commonly assumed that the value of the measurement is proportional to the function or severity of the disease being assessed, however, such linear relationships are rarely verified. Interpretation is most simple when the reported information derived from biochemical measurement is not only proportional to the function which is being assessed but also directly related to it and in our
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view the presentation of information with any other relationship will involve unnecessary, and potentially dangerous, mental gymnastics. The analytical result should be regarded as no more than raw material, which should be manipulated mathematically in any way which simplifies interpretation and enhances the information contained within the stated result.

Plasma concentrations of urea and creatinine are routinely used as single measurements in the assessment of GFR, and they are generally regarded as necessary screening measurements for patients admitted to an acute general hospital. The results are often viewed suspiciously as the plasma urea may be determined largely by factors other than the GFR. The plasma creatinine is considered by many to be a crude measure of GFR in young people with further limitations in the elderly. These limitations may be less when data is correctly considered, furthermore, direct but complex measurements such as creatinine clearance, themselves have less well recognized limitations and may in practice be less precise than the simple measurements.

Assessment of GFR in young adults. The view that the plasma creatinine can give only a crude and insensitive assessment of GFR, even in young people, is based on several observations and conclusions: (1) The plasma creatinine is insensitive to a reduction in GFR. (2) A direct measurement of GFR is more precise than an indirect assessment such as the plasma creatinine. (3) The plasma creatinine is determined by body size, as well as by the GFR. (4) A direct measure of the GFR is essential for certain clinical uses (such as the assessment of drug dosage). (5) The plasma creatinine is increased by recent meat intake.

These last three criticisms can be answered: A recent intake of meat is an avoidable event, a direct measure of GFR is not necessary for the adjustment of drug dosage, and there is no evidence that body size is a major determinant of the plasma creatinine [12].

The major remaining argument against the plasma creatinine, especially in young people, is that it is insensitive to a decline in GFR. This conclusion is based on the well-established relationship between plasma creatinine and GFR in health and disease, which is that a substantial reduction in the GFR is associated with relatively little increase in the plasma creatinine (Fig. 8). The relative clinical usefulness of any two methods of assessment depends, however, on the frequency of abnormal values for each measurement in a group of patients with renal function impairment. That frequency depends on the variation in each measurement, as well as on the difference in the mean values. This variation is relatively greater for the creatinine clearance than for the plasma creatinine (Table 1). Our calculations indicate clearly that the frequency of abnormal values will be greater when plasma creatinine is used to look for renal dysfunction than it is when the creatinine clearance is used [13]. For example, in a group of unselected young people who each lose 25% of the average GFR, the frequency of a raised plasma creatinine would be 38% and the frequency of low creatinine clearance would be 21%. Doolan, Alpen, and Theil [12] and Tobias, McLaughlin, and Hopper [14] in 1962 separately reported the relation between plasma creatinine and creatinine clearance illustrated in Figure 8. They each concluded that the creatinine clearance is preferable among their patients with renal disease; there were some with a low creatinine clearance but a “normal” plasma creatinine. Duarte, Elveback, and Liedtke [15] have made similar observations and drew the same conclusions. In all three studies, however, there are even more
patients with "raised" plasma creatinine but a "normal" creatinine clearance [13]. All the observations, therefore, support the conclusion that in practice, in contrast to theory, the plasma creatinine is more useful than the creatinine clearance in detecting a fall in GFR largely because of the error in measuring creatinine excretion due to difficulties of urine collection, even when patients are in a hospital.

When the measurement of creatinine clearance, or of plasma creatinine, indicates that the GFR in a patient is low, and that the results are outside the limits of the reference range, then the patient probably has renal disease. The question which then arises is by how much the GFR has been reduced in that individual as a result of the disease. The problem in providing an answer is the uncertainty about that person's GFR before he became ill and the best guess of the original value usually made, and one which would certainly be used for a group of patients, is the mean value of the range in healthy young persons. The individual's GFR, of course, could have started from any value within the reference range. We suspect that often the person is assumed to have a GFR that began at the bottom of the reference range, which is the smallest possible change, rather than from a GFR at the top of the range, which would be the largest possible change. The best estimate is the difference between the observed value and the mean of the reference range; the confidence limits of this estimate are the range of the reference values. The magnitude of the uncertainty can be illustrated with examples based on the standard data for young men shown in Table 1. A young man is found to have a creatinine clearance (single estimate) of 60 ml/min, compared with a reference range for single estimates of 70 to 170 ml/min, and a plasma creatinine of 180 μmoles/liter compared with a reference range of 64 to 116 μmoles/liter. The reduction of GFR estimated as the ratio of the observed to the mean value in healthy men would be 50%. However, the range of the possible reduction given by the variation of the reference range is 15 to 65% based on creatinine clearance, and 36 to 65% based on plasma creatinine. Even if error and variability in the individual patient could be abolished (Table 1), the range of the possible reduction would be 30 to 61% based on creatinine clearance, and 39 to 62% based on plasma creatinine.

The difficulty in assessing the magnitude of the change in the individual is the uncertainty about the value when he was well. This rarely discussed uncertainty is a major limitation in our ability to assess changes in GFR. If sequential values are unavailable, it means that only crude interpretations are possible, and this would be the case even if the measurement of the GFR in the individual was precise. For this reason alone, the single nature of plasma creatinine is as adequate as an assessment of GFR. What is required with the result, and is not often provided, is some measure of the uncertainty or certainty that there is a change from health in that individual.

If the plasma creatinine is measured, there is an advantage in using the reciprocal of the value as an index of the GFR, since this is more directly related to GFR and changes in the same direction as GFR.

The plasma urea and the blood urea nitrogen are regarded as very crude indices of the GFR and are being replaced rapidly by the plasma creatinine. In the young chronically ill adult the plasma urea is possibly as reliable as the plasma creatinine, which is why it has continued as a screening procedure for chronic renal disorder. In the acutely ill patient a raised plasma urea is often not associated with a rise in plasma creatinine (a fall in GFR) and is more usually due to an increased rate of urea production.

**Plasma creatinine as an assessment of GFR in the elderly.** The published surveys on plasma creatinine show that it is
remarkably constant with advancing age in adults, although men have in general higher levels than women at any age. There is, by contrast, no doubt that the average creatinine clearance and the inulin clearance decreases with age, and this has been observed in longitudinal and cross-sectional studies [16]. The constant plasma creatinine in the face of declining creatinine clearance must indicate a fall in creatinine production, and this has been attributed to the reduction in muscle mass known to be present in the elderly. This explanation, although generally adopted is unlikely, both because the reduction in muscle mass is probably insufficient, and because it seems unlikely that a perfect match of declining muscle mass and renal mass would occur by chance. The constancy of the plasma creatinine is so remarkable that it is tempting to regard it, or something associated with it, as a controlled variable, with feedback control of either the rate of creatinine production, or of compensatory hypertrophy in the kidney as nephrons are lost.

Whatever the explanation, the constancy of the plasma creatinine in the presence of a fall in GFR rules out the plasma creatinine alone as a measurement of GFR in the elderly. Yet a direct measurement of GFR is often unavailable in the elderly because of the difficulties in obtaining a complete urine collection. One alternative is to use the mean GFR of a group of healthy persons of the same age as the patients. These values can be presented as a simple table, either in absolute units or as a percentage of the value in men aged 45 (Table 2). The values represent the most precise information we have, and the error in assuming that each person in a group is at the mean is probably no greater than the error of the estimate of the GFR if we had measured it as the creatinine clearance. This table could be used to estimate the GFR in a patient whose plasma creatinine was within the range seen in healthy persons. If the plasma creatinine exceeds the upper limit of this range then the GFR must be less than expected for the patient’s age. The extent of this reduction in GFR can be estimated from the ratio between the patient’s plasma creatinine and the average plasma creatinine in the healthy person. A plasma creatinine x times the average value in healthy persons suggests that the GFR is reduced to 1/x of the value expected at the patient’s age.

Unlike the plasma creatinine the plasma urea increases with age in adults, but the increase is less than expected from the decline in GFR, presumably because the urea load (determined by protein intake) and/or the percentage tubular reabsorption of urea is reduced. The GFR is therefore adequate to meet the usual demands for urea excretion in the elderly, but any increase in the urea load can lead to a dramatic increase in plasma urea. Any fall in GFR in the elderly leads to a rise in the plasma urea relatively greater than the rise in the plasma creatinine. This discrepancy will be exaggerated in the elderly when there is extra muscle wasting because of disease or poor nutrition, as this will lead to a further reduction in creatinine production and plasma creatinine at a given GFR. It is, therefore, particularly difficult in the elderly to interpret the combination of a raised plasma urea and a normal or nearly normal plasma creatinine. There is a need to identify some naturally occurring component of plasma, the concentration of which is
determined by GFR alone at any age. Serum $\beta_2$ microglobulin has been proposed to fill this need, but it can be increased as a result of increased production as well as by reduced renal clearance. Other low molecular weight proteins are under investigation.

The assessment of GFR for the adjustment of drug doses. One reason for estimating the GFR in patients of any age is the need to adjust, when GFR is low, the dosage of drugs which are largely excreted through the kidney. This is particularly important in the elderly, because of the age-related reduction in GFR. Direct measurement of GFR is imprecise and indeed impossible in many clinical situations. Formulae are available for the estimation of GFR from plasma creatinine, age, and body size. Some of the formulae used are complex and most conveniently handled by a computer. Increased complexity does not, however, necessarily bring a real and useful increase in precision, particularly when there is such wide variation between persons in the kinetics of any drug, and in the toxic drug levels. A simple approach will probably suffice. The age-related reduction in GFR can be estimated from data as in Table 2, and the disease-related reduction in GFR can be estimated from the increase in plasma creatinine. These two factors can be used to give an estimate of the steady-state level of the drug if the patient was given a standard dose. This estimated value can be compared with the toxic threshold level for the drug, and, if necessary, a lower dose can be chosen. Take, for example, a 75-year-old man with a plasma creatinine of 250 $\mu$moles/liter. The age-related reduction in GFR is 62% so that for this reason alone the steady-state drug level on a standard dose would be 1.6 (1/0.62)-fold that of a young man. There is also a disease-related fall in GFR as indicated by the rise in plasma creatinine, and this alone would increase the drug level by a factor of 2.5 (250/100). The two factors combined increase the drug level by a factor of 4 ($2.5 \times 1.6$). The potential for using a computer to store either the simple age-related data and the plasma creatinine to GFR relationships, or the programs to perform the complex kinetic calculations proposed by others, should increase the frequency with which appropriate dose modifications are made.

We would emphasize however, that these complex calculations may have little advantage over the simple ones and have the disadvantage that the principles involved are obscure. To teach the principles and the simple calculations may be a more effective method of decreasing drug toxicity in the elderly and especially in those with renal disease.

Summary. There is more information in biochemical laboratory data than is generally appreciated; much can be gained by display and manipulation of data.

Table 1. Standard data for plasma creatinine and creatinine clearance in young men (drawn from a review of nine publications [1])

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<th>Plasma creatinine $\mu$moles liter$^{-1}$</th>
<th>Creatinine clearance ml min$^{-1}$</th>
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<td></td>
<td>90</td>
<td>120</td>
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<td>SD</td>
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<td>Total</td>
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<td>Within person</td>
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<td>Biological</td>
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<td>Between persons</td>
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Patients with renal disease are often under regular clinic review so that many will have sets of sequential data. Display of these data, which requires a computer if it is to be routine, will reveal patterns and define trends which could be otherwise missed or inadequately assessed. Trends are most useful if they are recti-linear and several transforms of the data should be tried to achieve this aim; for plasma creatinine the usual transforms are the reciprocal and the logarithm. The choice of transform is based on usefulness and not on any prior assumption about the underlying pathophysiology.

More frequently, however, all that is available is a single measurement, typically the simple plasma creatinine rather than the more complex creatinine clearance. The problem is to balance simplicity against precision and decide what the needs and the reliability of the interpretations of the data are. There is an advantage in manipulation of the data and comparison with standard data; and the possibilities were discussed for the plasma creatinine; these tables are ideally suited to a laboratory computer. It was suggested that complex calculations so easily achieved with a computer should be avoided unless they bring real gains, since complexity tends to hide the basic principles involved.

Appendix

The relationship between GFR and serum creatinine concentration is given by equations (1) and (2) (see below), where for simplicity UV is assumed to be the constant in time. Equation (1) gives the proportionality between the reciprocal of serum creatinine and GFR.

When empirically there is a linear relationship between the reciprocal of serum creatinine and time, it is described by equation (3). The letter $b$ is a constant and $a$ the slope of the line. By simple substitution from equation (1), we can find the change of GFR with time [equation (4)], and a value for the slope of the line, $a$; that is, $a = 2/t_{1/2}$. It should be noted that $t_{1/2}$ is not a constant but the time for the plasma creatinine to fall to half the initial value.

Where the logarithmic transform of serum creatinine is linear with time, then equation (5) holds, which by development in equation (6) and (7) gives an expression of the change of GFR with time [equation (8)] and a value for $a$; that is, $a = 0.693/t_{1/2}$. In this instance the $t_{1/2}$ is the time interval necessary for any value on the curve to be halved.

<table>
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<th>Age</th>
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<tr>
<td>Women</td>
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<tr>
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<td>86</td>
<td>75</td>
<td>62</td>
<td>50</td>
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<tr>
<td>Women</td>
<td>84</td>
<td>73</td>
<td>62</td>
<td>50</td>
<td>40</td>
<td>28</td>
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| Men  | 98     | 88     | 70     | 64     | 45     | 35     |
| Women| 76     | 74     | 60     | 49     | 41     | 34     |
| Men  | 100    | 86     | 75     | 62     | 50     | 37     |
| Women| 84     | 73     | 62     | 50     | 40     | 28     |

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Abbreviations used in the equations are: GFR, glomerular filtration rate at time \( t \); GFR\(_0\), glomerular filtration rate at \( t = 0 \); U, urine creatinine concentration; V, urine excretion rate; P, serum creatinine at time \( t \); P\(_0\), serum creatinine at \( t = 0 \).

\[
\begin{align*}
(1) & \quad GFR &= UV/P = K \times 1/P \\
(2) & \quad \ln\ GFR &= \ln\ K - \ln\ P \\
(3) & \quad 1/P = b - at = 1/P_0 - at \\
(4) & \quad GFR = GFR_0 - K at \\
(5) & \quad \ln\ P = at + b = at + \ln\ P_0 \\
(6) & \quad \ln\ GFR = \ln\ K - (\ln P_0 + at) \\
(7) & \quad = \ln\ GFR_0 - at \\
(8) & \quad GFR = GFR_0 \cdot e^{-at}
\end{align*}
\]

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