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Preface

This is the first volume to appear in English exclusively. As pointed out in the Preface to Volume 3, English has become the 'lingua franca' in medicine and we are happy to contribute to the international understanding among surgeons by subscribing to this attitude. This, however, should not be confused with a denial of the cultural riches of the many European languages.

Volume 4 is concerned with the hemodynamic responses to blood loss and injury in general and with the pathophysiology of the kidney as well as of the liver in shock. It should offer quite a series of pertinent information all related to the various 'low flow states', a matter of continuous concern to the surgeon.

J. Bull offers solid ground to the clinician for the evaluation of blood loss and its pathogenetic significance. The provocative contribution of C. Brun and O. Muncк might surprise the reader—as it did the editor—by giving a 'heavy blow' to some ever repeated half truths. Those who appreciate careful experimental work in the dog laboratory will enjoy L. Smith and U. P. Veragut's paper. The work on dogs is not presented without pointing out the differences between man and dog. This makes this paper particularly valuable also to the clinician interested in shock problems related to the liver.

M. Allgöwer

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Pathophysiology of the Kidney in Shock and in Acute Renal Failure

Circulatory Responses to Blood Loss and Injury

The Liver and Shock: Initiating and Perpetuating Factors

Prog. Surg., vol. 4, pp. 1–34 (Karger, Basel/New York 1964)

Pathophysiology of the Kidney in Shock and in Acute Renal Failure

Claus Brun* and Ole Munck, Copenhagen**

CONTENTS

I. Introduction

Since the rediscovery in World War II of acute renal failure following crush injuries and other traumata an increasing interest has been taken in this disease and it is evident that the entity is by no means associated exclusively with war and other mass catastrophies. The origin of the cases seen today differ considerably from case to case and may even vary from country to country. Added to the cases of crush injury—today mainly produced by road accidents—are considerable numbers seen following surgical procedures with superimposed complications, and cases following infected abortions. Clinically indistinguishable from these cases are the

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patients with renal failure following inhalation of carbontetrachloride. This widely used cleaning agent, found in many households because its potential toxicity is not realized, is responsible for considerable numbers of acute renal failure.

The treatment of acute renal failure has been improved tremendously since the days of the London 'Blitz'. The two most important factors are probably the increased understanding of fluid balance problems leading to present days very strict fluid allowances and the advent of treatment by dialysis.

One aspect of acute renal failure is largely unchanged since the rediscovery of the syndrome in 1941: the knowledge of its pathogenesis and the pathophysiological mechanisms involved in the cessation of urine production is still scarce and open to speculation.

The present review describes methods for estimating renal function and their application to cases of acute renal failure.

II. Some Clinical Methods for Measuring Renal Function

Clearance methods

Since the kidney has many different functions it is obvious that no single renal function test can give an adequate expression of all these functions. Some of the available tests measure different functions and all tests should thus not necessarily show parallel changes. This lack of equivalent reduction can sometimes be seen in acute renal diseases, while in most chronic renal diseases there is a relative uniform reduction of all measurable functions.

The most important function of the kidney is to maintain the composition of the body fluids at a constant and normal level. A failing renal function will be reflected in the composition of the body fluids, and it is thus possible to detect a reduction of renal function just by examining the blood alone—at least when the reduction has reached a considerable degree. The determination of urea, NPN or creatinine in the blood (or preferably in serum) is daily routine in every laboratory and is mainly a test of the glomerular filtration rate.

Examination of the urine alone can also be informative in evaluating renal function. The determination of urinary specific gravity or osmolarity following a period of dehydration will give

information on the renal capability of creating an osmotic gradient. This is mainly a test of tubular function as is also the determination of the excreted amount of PSP in the urine after i.v. injection of a known dose of PSP.

For a more exact evaluation of the renal function, or if the object is to detect a minor functional reduction, it is generally necessary to examine blood as well as urine. This is done e.g. in the determination of the clearance of some preformed or injected substance. By clearance is understood the amount of blood which each minute is cleared of the substance in question. It is calculated by dividing the amount of substance in question excreted in the urine per minute by the corresponding concentration in the blood. Since most substances are not completely cleared from the blood by one passage through the kidneys, clearance is a theoretical concept which designates the volume of blood which contains the amount of substance excreted by the kidneys per minute.

On the choice of renal function tests

The choice of a renal function test depends primarily on what kind of information is desired. In some cases the problem is to find out if a given patient has a renal function which is normal or only slightly reduced, or if the functional impairment is so serious that special precautions have to be taken in the treatment of the patient. To this end a determination of serum creatinine is adequate since patients with a 50 per cent or more reduction of the renal function will have an elevated serum creatinine. In clinical surgery a serum creatinine thus can be used as a screening test to select those patients where special attention to renal water and electrolyte losses is a matter of necessity if the postoperative period is to be handled safely. The determination is simple to carry out, and the result is independent of dietary protein intake and of normal variations in urine flow.

If the problem is a different one, namely to find out whether or not a patients kidneys are involved at all in a disease so that even a slight reduction must be found, a determination of serum creatinine is not sufficient because no significant rise in this value can be expected before an about 50 per cent reduction has been reached. To demonstrate a mild degree of renal functional impairment or to get precise quantitative information a clearance determination is

necessary. In clinical work a 24 hour endogenous creatinine clearance should in most cases be the method of choice since it is simple to carry out and less subject to extrarenal factors and to collection errors than e.g. the one hour urea clearance or the PSP excretion test.

A number of clearance methods are available for a more detailed study of the different renal functions.

The most important of these is the inulin clearance which with reasonable assurance can be taken to express the glomerular filtration rate. Other non-preformed substances such as thiosulphate and mannitol have clearances of about the same order of magnitude but are subject to some degree of tubular secretion or reabsorption. If an accurate determination of the glomerular filtration rate is needed, e.g. for studies of renal pathophysiology, inulin clearance is the method of choice. Of the preformed substances in the blood only creatinine has a clearance which nearly equals inulin clearance. In man this is true only of the so-called endogenous creatinine while exogenous creatinine seems to be excreted partly by tubular secretion.

Renal blood flow *in normal* kidneys can be measured by the clearance of paraaminohippurate (PAH) since this substance is practically extracted quantatively from the blood by one passage through the kidneys. In the damaged kidney the extraction of PAH may be low and the clearance of PAH is no longer usable as an expression of renal blood flow. For routine clinical work none of the clearance methods mentioned—except the endogenous creatinine clearance—is of any practical value.

In the daily routine clinical work it may be useful to remember that a fair estimation of the glomerular filtration rate can be had from a determination of serum creatinine in non-anuric patients. Fig. 1 shows 64 corresponding values of serumcreatinine and inulin clearance from 42 patients with different kinds of renal disease including: acute and chronic glomerulonephritis, pyelonephritis, diabetic nephropathy, nephrotic syndrome and the diuretic phase of acute renal failure. The inulin clearances vary from normal to very low values and, as expected, it can be seen that the serum creatinine rises when the inulin clearance decreases. The drawn line represents the equation:

$$\text{Inulin clearance} = \frac{61}{\text{Serum creatinine}}$$

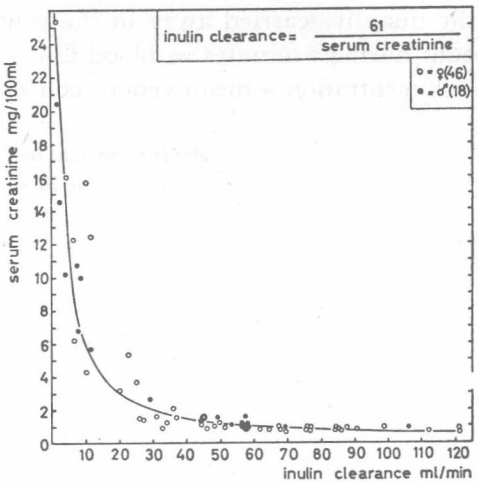

Fig. 1 64 corresponding values of serum creatinine (Jaffé chromogen) and inulin clearance in 42 patients with different kinds of renal disease including acute and chronic glomerulonephritis, pyelonephritis, diabetic nephropathy, nephrotic syndrome and the diuretic phase of acute renal failure.

The line is calculated by means of the method of least squares as the curve which correlates best with the values found. The accuracy of this estimation of the glomerular filtration rate is of course not high, but if the glomerular filtration rate is reduced by more than about 50 per cent and the serum creatinine value consequently increased above the upper normal value, the equation is very useful as a 'rule of thumb' for estimating renal function. Since the normal value of inulin clearance is of the order of magnitude 100 to 125 ml/min, the resulting figure can roughly be taken as percentage of normal filtration rate.

Measurement of renal blood flow

The renal blood flow in man (from which the oxygen consumption may be calculated) can be determined by using FICK's principle (FICK, 1870) which may be stated as follows:

The amount of a substance taken up by the tissue per unit of time is equal to the quantity brought to the tissue by the arterial

blood minus the quantity carried away in the venous blood, i.e.: Absorbed amount during t minutes = blood flow (in ml/min) · t · (mean arterial concentration – mean venous concentration)
or

$$\text{blood flow (in ml/min)} = \frac{\text{absorbed amount per minute}}{\text{absorbed amount per ml perfused blood}} \quad (1)$$

For most purposes the direct FICK method is employed, i.e. the absorbed amount can be directly determined, as in measurements of the cardiac ourput from the total body oxygen consumption, and in determinations of renal blood flow using p-aminohippuric acid (PAH). When inert gases are employed, it is only possible to determine the amount absorbed by the tissue indirectly by calculations based on the inert gas content of the blood draining from the tissue. The indirect FICK method has been used to measure the cerebral blood flow and the renal blood flow employing either nitrous oxide or radioactive krypton as the inert gas.

The analysing and blood and urine sampling techniques are described by SMITH, GOLDRING AND CHASSIS (1938); BRUN, HILDEN AND RAASCHOU (1947); LASSEN AND MUNCK (1955); BRUN *et al.* (1955).

The p-aminohippuric acid method

The renal blood flow can be calculated by dividing the amount of a certain substance excreted through the kidneys per minute by the amount of the substance excreted per ml blood perfusing the kidneys (VAN SLYKE, RHOADS, HILLER AND ALVING, 1934).

The general formula for a substance x is:

$$\text{Blood flow} = \frac{U_x \cdot V}{A_x - R_x} \quad (2)$$

where the flow is in ml/min.
U_x = concentration in urine of x in mg/100 ml,
V = urine flow in ml/min,
A_x = concentration of x in arterial blood,
R_x = concentration of x in renal venous blood.

The blood flow of the kidneys can be determined either by means of natural components of blood and urine, such as urea and creatinine, or by substances injected into the organism and excreted

through the kidneys such as inulin, diodrast and PAH. Extensive investigations have shown that PAH is the most suitable (SMITH, 1951), and it is nowadays the most commonly used compound for determinations by the direct FICK method.

The plasma flow of both kidneys is obtained by inserting the plasma concentrations of PAH (A_{PAH} and R_{PAH}) in formula 2. The total renal blood flow (RBF_{PAH}) can be calculated from the plasma flow by correcting for the haematocrit value (H), as PAH does not penetrate the human red cell in vivo (SMITH, 1951:

$$RBF_{PAH} = \frac{U_{PAH} \cdot V}{(A_{PAH} - R_{PAH})\,(I - H)} \text{ ml/min} \qquad (3)$$

The PAH-method gives a good estimate of renal blood flow in normal subjects and in patients with only moderately decreased renal function (coefficient of variation about 10 per cent). In cases of acute renal failure the method is very inaccurate due to the small arterio-venous PAH-difference (coefficient of variation about 90 per cent).

The inert gas diffusion method using inhalation of the gas and sampling from artery and vein

The inert gas diffusion technique using nitrous oxide has for some years been employed for measuring the cerebral blood flow (KETY AND SCHMIDT, 1945 and 1948). In 1952 GALINIER adapted the nitrous oxide method for investigation of the renal blood flow in man.

In the investigations by BRUN *et al.* (1955), radioactive krypton 85 (Kr^{85}) was used instead of nitrous oxide. Kr^{85} allows more exact measurement and facilitates the examination. The inert gas diffusion method as used by BRUN *et al.* may be described as follows:

The subjects inhale atmospheric air containing a small amount of Kr^{85} during the period o–t (t = approximately 10 min). Kr^{85} is absorbed via the lungs, and is delivered to the various organs by the arterial blood. During the inhalation period, 6–7 sets of samples are taken continously from the femoral artery (assumed to be representative of the renal artery) and from one of the renal veins—usually the right. The concentration of Kr^{85} in the blood samples is measured and plotted against time as shown in Fig. 2.

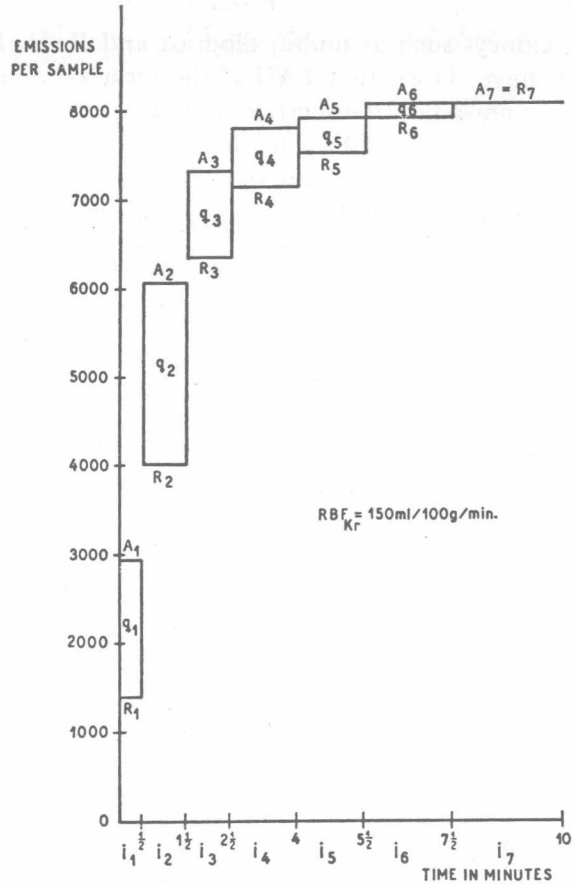

Fig. 2 Mean arterial (A_1–A_7) and mean renal venous (R_1–R_7) concentrations of krypton^{85} in the sampling intervals i_1–i_7. RBF_{Kr} indicates renal blood flow in ml/100 g/min.

Renal blood flow is calculated from the formula:

$$RBF_{Kr} = \frac{100\ R^t S}{\sum_{i=1}^{i=n} (A-R)_i - R^t} \text{ ml/100 g/min} \qquad (4)$$

where

R^t is the concentration of Kr^{85} in saturated renal venous blood

*S: the partition coefficient Kidney: blood

* S is defined as $\frac{\text{units } Kr^{85} \text{ per gram renal tissue}}{\text{units } Kr^{85} \text{ per ml blood}}$ when the tension of Kr^{85} in renal tissue equals that in the blood at normal body temperature (Lassen and Munck, 1955).

A and R are the mean concentrations of Kr^{85} in the renal artery and the renal vein
T is the mean circulation time in the kidneys.

For discussion of the details of the method see MUNCK (1958).

In contrast to the PAH-method the inert gas diffusion method gives accurate values when the renal function is very low (coefficient of variation about 10 per cent), and the error of the method is high for normal blood values (coefficient of variation about 30 per cent).

The inert gas diffusion method using intraarterial injection of the gas dissolved in saline and external counting

This method has recently been described by KEMP, LADEFOGED *et al.* (1963). About 10 mC krypton^{85} or 1 mC xenon^{133} dissolved in 5 ml isotonic saline are injected into the renal artery. The build-up and subsequent clearance of radioactive gas from the kidney is measured by a scintillation detector covered by a wide angle collimator connected to a ratemeter and a recorder (Fig. 3).

The desaturation or clearance of indicator from the kidney is due to the wash-out by arterial blood. There is practically no recirculation of the radioactive substance. The diffusion of Kr^{85} and Xe^{133} is sufficiently rapid to maintain equilibrium between the tissue and the venous blood leaving that tissue at any time. These features explain that the clearance curve is a reflection of the blood flow only.

By conventional graphical analysis it is possible to find one fast component and at least one slow. According to autoradiographic studies by THORBURN *et al.* (1963), the fastest component can be identified as the blood flow of the renal cortex. According to the calculation of KETY (1951) the renal cortical blood flow is given by

$$\text{Flow} = \frac{\log_n 2}{T\,½} \cdot S \text{ ml per g per minute} \qquad (5)$$

where S denotes the tissue:blood partition coefficient which is approximately 1, and T ½ is the half time of the fast component. The accuracy of the method is about 10 per cent.

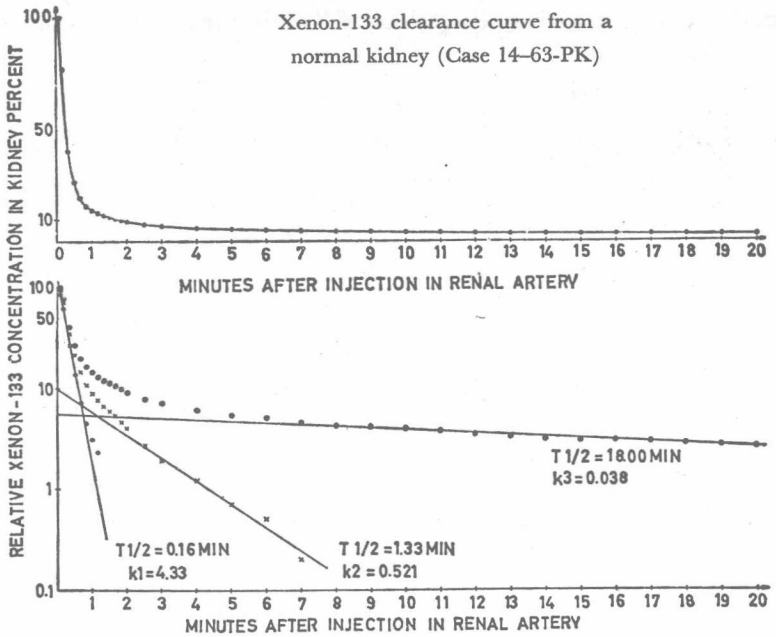

Fig. 3 The disappearance rate of Xenon^{133} from the kidney of a normal person after injection in the renal artery. On the upper curve the ordinate is linear, in the lower logarithmic. Assuming a kidney: blood partition coefficient of one, k_1 gives the renal cortical blood flow in ml/g/min, and k_2 and k_3 corresponds to medullary flows.

Indicator dilution methods

This principle can be applied in two ways, either by single injection technique or by continuous infusion technique.

A. Single injection technique:

A known amount of dye (I) is injected rapidly into the renal artery. Blood is drawn continuously from the renal vein at a known flow rate (f) and passed through the cuvette of a modified oxymeter. The area (S) delineated by the recorded concentration curve is measured and compared with that of a calibration curve (s) obtained after a known amount of dye (i) has been injected directly into the recording system (Reubi *et al.*, 1962).