RENOVASCULAR HYPERTENSION | STAMEY

# Renovascular Hypertension

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Baltimore 1963

THE WILLIAMS & WILKINS COMPANY

Library of Congress Catalog Card Number 63-13821

Composed and printed at
Waverly Press, Inc.
Mt. Royal and Guilford Aves.
Baltimore 2, Md., U.S.A.

# PREFACE

The recent introduction of a technique for obtaining meaningful and reproducible ureteral catheterization data has made it possible for the first time to study differential renal function in a quantitative manner. This approach, which compares simultaneously a diseased kidney with its contralateral normal or less diseased kidney in the same *milieu intérieur*, would have pleased Claude Bernard. There are at least two major advantages to renal function studies performed by ureteral catheterization when this method is compared with the classical technique of collecting urine from the bladder.

One advantage of ureteral catheterization is a hemodynamic quantitation. For example, the extraordinary variation in renal blood flow from one normal person to another makes it virtually impossible to know if any absolute value is pathological or normal. Renal plasma flow in normal men varies from 491 to 817 ml/min per 1.73 $m^2$ of body surface area, but these values include only 68 per cent of the normal population (one standard deviation). Ninety-five per cent of the normal population (two standard deviations) includes individuals with diverse values ranging from 326 to 980 ml/min which is a variation of 300 per cent. If a patient with diastolic hypertension has a total renal plasma flow of 800 ml/min, it is impossible for an investigator to state that flow is normal when a few months or years previously the value may have been 1000 ml/min. The advantage of measuring renal plasma flow by ureteral catheterization is that the differences between two kidneys in the same person are less than 15 per cent in the majority of the population.

A more important advantage of ureteral catheterization studies is the opportunity to study subtle differences in water and electrolyte transport in the nephron of the diseased kidney. These studies have led to our description of excessive reabsorption of water and sodium in the ischemic nephron. Renal ischemia (reduced blood flow to functioning renal tissue) can be recognized and *defined* in new functional terms based on changes in water and sodium transport. These changes in transport of sodium and water are produced by a reduced volume of glomerular filtrate presented to nephrons previously carrying larger volumes of filtrate. Measurement of these changes can be made only when a diseased kidney is compared with the contralateral normal or less diseased kidney. It cannot be made when the standard method of collecting urine from the bladder is used.

Our observations of the *Functional Characteristics of Renovascular Hypertension* were reported in *Medicine*, **40:** 347, 1961 (Chapter II, this book). These studies indicated that reduced renal plasma flow is important and that it produces the

characteristic functional defect: a proportional reduction in the volume of glomerular filtrate causing excessive water and sodium reabsorption, primarily in the proximal tubule. Since these observations were published in *Medicine*, our laboratory has made a number of studies on several related subjects in the renovascular hypertensive field: (1) ureteral catheterization studies on patients with bilateral renal artery stenosis; (2) subsequent changes in renal plasma flow to the contralateral nonoccluded kidney after nephrectomy and the relationship of these changes to the fall in blood pressure; (3) collateral circulation to the ischemic kidney; (4) renal vein extraction ratios of *p*-aminohippurate; (5) further observations on the relationship between changes in the volume of glomerular filtrate and reabsorption of water and sodium in the human nephron—observations that suggest a vital relationship between small changes in the volume of glomerular filtrate and the tubular handling of sodium and water; and (6) the relationship of the *macula densa* in transferring tubular changes in sodium concentration to the juxtaglomerular cells.

There is a large gap between the basic renal physiologist and the practicing physician interested in diseases of the urinary tract. The physiologist is frequently unaware of the clinical problem, and the physician is equally unaware of the quantitative techniques available to increase his knowledge of the patient's disease. The Urea-PAH test may partially help the physician to bridge this gap between physiologist and physician because the proper treatment of the hypertensive patient requires an understanding of renal plasma flow, glomerular filtrate, excessive water reabsorption, and the determinants of urine flow. For this reason, the Introduction is devoted to a few basic principles which may help the physician to understand the subsequent chapters rather than accept some magical and arbitrary figures which indicate the presence or absence of disease. The concept of renal plasma flow, based on the Fick principle, is developed in an illustrative manner which will make the ensuing data more meaningful to the practicing physician. The approach throughout this research is to compare the diseased kidney with the contralateral kidney in the same *milieu intérieur*; therefore, certain simplifications are possible from the standpoint of renal transport. These concepts are included in the Introduction.

In chapter 1 the important historical investigations and beliefs are reviewed that have characterized the sometimes turbulent and contradictory relationship between the kidney and the hypertensive patient and renal blood flow. The reader may find this historical and editorial presentation helpful because recognized authorities on the kidney and hypertension do not believe there is an etiological relationship between renal blood flow and hypertension.

Chapter 2 is a reproduction of the article in *Medicine* with the addition of several radiographical and pathological studies which were omitted from the original publication because of limited space. The more recent investigations on renovascular hypertension are included as separate chapters (chapters 3–8).

The Appendix contains the procedural details for the technical performance of the Urea-PAH test at the cystoscopy table as well as the directions for the laboratory determination of *p*-aminohippurate. The postcystoscopic morbidity resulting from transient ureterovesical edema is discussed in detail. Although

these directions, with exemplary calculations in the Appendix, will not interest those individuals versed in elements of renal physiology, the primary purpose of the Appendix is to help the physician and the clinical laboratory technician who may be unfamiliar with these procedures.

This book is addressed to all physicians interested in the problem of hypertension; the general practitioner, the internist, the urologist, the vascular surgeon, and the diagnostic radiologist. The studies on sodium and water reabsorption in the nephron and their relationship to changes in the volume of glomerular filtrate concern the basic renal physiologist, especially those investigators who have been interested in the so called "glomerular tubular balance." These studies on the interrelationship among the volume of glomerular filtrate, sodium reabsorption, the *macula densa*, and the juxtaglomerular cells have led to a new proposal which may explain the direct relationship between blood pressure and renal hemodynamics. Our findings on the collateral circulation to the ischemic kidney, especially the finding that this collateral circulation is preglomerular, are of interest to the renal anatomists who have long thought in terms of "end-arteries." The importance of this preglomerular collateral circulation in potential revascularization of the ischemic kidney will be apparent.

In essence, this is a book about the kidney in *man*. A separate chapter on experimental renal hypertension is not included; nevertheless, animal investigations which have contributed to or sometimes confused the basic issues with which our studies are concerned will be referred to in considerable detail.

# CONTENTS

# INTRODUCTORY CONCEPTS

Two aspects of renal physiology, renal plasma flow, and the reabsorption of water in the nephron, are of major importance if the data presented in this book are to be understood and properly interpreted. A different, and hopefully simpler approach is presented here because the writer remembers too well when $(U \times V)/P$ was an unnecessarily difficult and confusing equation.

## Renal Plasma Flow (RPF)

The conceptual difficulties with the word "clearance," which will be considered later in this section, can be avoided if blood flow is first developed in terms of the Fick principle. The blood flow through any organ may be determined by the Fick principle if the rate of excretion of a substance and the concentration of this substance in blood entering and leaving the organ are known.

For example, consider an imaginary problem of measuring blood flow to the hand with the Fick principle. Suppose that a hand excretes a large and constant amount of salt which is equally distributed through whole blood and that large amounts of distilled water can be washed across the hand to collect the salt. In Figure 1a, sodium (Na) is washed from the hand at a rate of 10 mEq/min, which is the *excretion rate* of Na from the hand. It does not matter whether the 10 mEq of Na is collected in 100 ml, 1000 ml, or 10,000 ml because the excretion rate is still 10 mEq/min. If the arterial concentration of Na is known ($A_{Na}$), for example, 1 mEq/ml, and *if there is no Na in the venous return from the hand,* then the rate of blood flow to the hand must be 10 ml/min for 10 mEq/min of Na to be washed from the hand. Thus, the calculation for blood flow in Figure 1a is:

$$\text{Total blood flow} = \frac{\text{excretion rate (mEq/min)}}{\text{conc. in artery (mEq/ml)} - \text{conc. in vein (mEq/ml)}} \tag{1}$$

$$= \frac{10 \text{ mEq/min}}{1.0 \text{ mEq/ml} - 0.0 \text{ mEq/ml}} = 10 \text{ ml/min.}$$

This measurement, under the circumstances of complete Na extraction from the artery in Figure 1a, not only represents *total* blood flow moving between the artery and vein, but also indicates the blood flow to *sodium excreting tissue.* It is therefore, much more than a simple measurement of total blood flow to the hand.

In Figure 1b, 50 per cent of the Na excreting tissue of the hand is replaced with fibrous tissue which cannot excrete Na but requires the same amount of

blood. If that half of the arterial blood perfusing the Na excreting tissue of the hand is completely cleared of Na (venous concentration = 0.0 mEq/ml), and if the Na concentration in the other half of the arterial blood perfusing the fibrous tissue remains unchanged (venous concentration = 1.0 mEq/ml), then the final concentration of Na in the total venous blood from the hand is 0.5 mEq/ml. Under these circumstances, only 5 mEq/min of Na is washed from the hand (Figure 1b). However, the *total* blood flow moving into and out of the hand, as calculated by the Fick principle, is exactly the same in Figure 1b as in Figure 1a. The excretion rate, 5 mEq/min, divided by the actual Na concentration available for excretion ($A_{Na} - V_{Na}$), 0.5 mEq/ml, equals the same *total* blood flow as in Figure 1a (10 ml/min). However, it is not the *total* blood flow that is important. If studies similar to those shown in Figure 1a have established that the Na excreting tissue is capable of completely eliminating all of the Na in a single passage of the blood (at least within a certain range of arterial concentration), then blood flow to the hand based on Na excreting tissue is clearly 50 per cent less in Figure 1b than 1a:

$$\frac{\text{Excretion rate}}{A_{Na}} = \frac{5 \text{ mEq/min}}{1 \text{ mEq/ml}} = 5 \text{ ml/min.}$$

Thus, although application of the Fick principle produces data on *total* blood flow to the hand, if the excreted substance is completely extracted from the arterial blood, then the excretion rate divided by the arterial concentration also represents blood flow to specialized functional tissue regardless of the total blood flow in and out of the hand. It is apparent that measurements based on blood flow to functioning tissue are more important than measurements based on total blood flow.

Unfortunately, even when blood flow is based on excretion rates of a substance completely eliminated in a single passage of blood through an organ, there is no way to decide whether the reduction in blood flow is a *true* reduction to functioning cells (ischemia) or a reduction secondary to *loss* of functioning cells.* For example, in Figure 1b, the 50 per cent reduction in blood flow to the hand, based on Na excreting tissue, occurs because there is 50 per cent less Na excreting tissue. The actual blood flow to the Na excreting tissue *per se* (the lower half of the hand in Figure 1b) is not reduced and is the same as in Figure 1a.

In Figure 1a, all of the Na has been extracted from the arterial blood, *i.e.*, the extraction is 100 per cent complete. This extraction is best expressed as a ratio, the symbol of which is $E_{Na}$ :

$$\begin{aligned} &\text{Extraction ratio of Na } (E_{Na}) \\ &= \frac{\text{conc. in artery (mEq/ml)} - \text{conc. in vein (mEq/ml)}}{\text{conc. in artery (mEq/ml)}} \qquad (2) \\ &= \frac{A_{Na} - V_{Na}}{A_{Na}} = \frac{1 - 0}{1} = 1. \end{aligned}$$

* There is no way to decide on the basis of an *absolute* value. As will be seen, however, when one kidney is simultaneously compared to the contralateral kidney, the finding of reduced renal plasma flow accompanied by excessive water reabsorption indicates a true reduction in blood flow to functioning nephrons. When reduced plasma flow occurs because of reduced secreting tissue (Figure 1b), excessive water reabsorption, in comparison to the contralateral kidney, is absent.

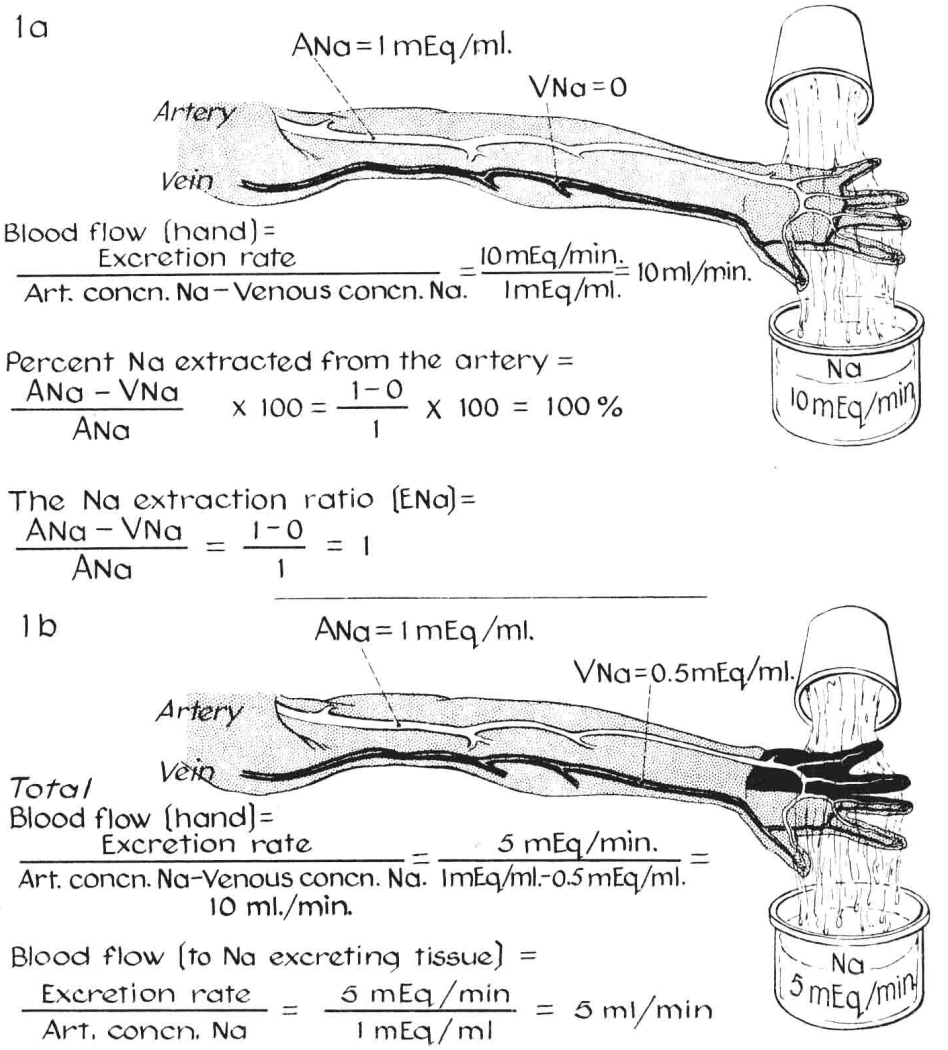


FIG. 1*a*. An imaginary hand that excretes sodium.

FIG. 1*b*. Fifty per cent of the Na excreting tissue in the hand in Fig. 1*a* is replaced with fibrous tissue which cannot excrete sodium but requires the same blood flow.

When the extraction ratio equals 1, complete extraction has occurred and none of the substance is leaving the organ in the vein. The extraction ratio of Na in Figure 1b is 0.5. The percentage of sodium extracted from the artery is simply the extraction ratio × 100. In Figure 1a:

$$(3)\quad \text{The \% Na extracted} = \frac{A_{Na} - V_{Na}}{A_{Na}} \times 100 = \frac{1 - 0}{1} \times 100 = 100\ \%.$$

For Figure 1b, the percentage of Na extracted is 0.5 × 100 or 50 per cent.

Because we are interested in a functional measure of renal blood flow rather than total blood flow, the determination of renal vein concentrations is not very useful. Nevertheless, in chapter 6, total blood flow to both kidneys (utilizing

renal vein sampling) has been measured by the Fick principle. For this purpose, it is apparent from equations (1) and (2) that calculations are the same by using equation (1), excretion rate/($A_{Na} - V_{Na}$), to calculate flow, or, by leaving out the venous concentration in equation (1) and dividing by the extraction ratio ($E_{Na}$) from equation (2):

$$\frac{\text{Excretion rate}/A_{Na}}{E_{Na}} = \text{total blood flow.} \tag{4}$$

Simplifying, equation (4) becomes the same as equation (1):

$$\frac{\text{Excretion rate}/A_{Na}}{(A_{Na} - V_{Na})/A_{Na}} = \frac{\text{Excretion rate}}{A_{Na}} \times \frac{A_{Na}}{A_{Na} - V_{Na}} = \frac{\text{Excretion rate}}{A_{Na} - V_{Na}}.$$

In other words, if the excretion rate of a substance and its arterial concentration is determined on one occasion, the total blood flow can be calculated by determining the extraction ratio a short time later and dividing the term excretion rate/$A_{Na}$ by $E_{Na}$ (the extraction ratio).

Except for chapter 6, measurements of blood flow (actually plasma flow) throughout this book are based on the excretion rates of *p*-aminohippurate (PAH) divided by the concentration of PAH in the plasma. Direct sampling of the kidney is unnecessary because the venous concentration is virtually zero. It was this possibility of complete extraction of a substance from the blood into the urine that led H. Smith *et al.* to study the excretion of various hippuric acid derivatives (94). From their studies, *p*-aminohippuric acid, which is almost completely extracted, has become a universal measure of functional renal blood flow. Because the renal venous concentration of PAH is negligible, the excretion rate of PAH in mg/min (U × V in the clearance formula, in which U is the concentration of PAH in mg/ml and V is the urine flow rate in ml/min) divided by the arterial concentration of PAH in mg/ml (P in the (U × V)/P clearance formula) is equivalent to renal plasma flow (plasma flow rather than blood flow because PAH is extracted from the plasma and not whole blood).* It is apparent that under conditions of a constant infusion of PAH, the arterial concentration is the same as the peripheral vein concentration, and, for this reason, a simple, antecubital venous sample suffices. The Fick principle for renal plasma flow based on PAH becomes:

$$\begin{aligned}\text{Renal plasma flow} &= \frac{\text{excretion rate of PAH}}{A_{PAH} - V_{PAH}} \\ &= \frac{\text{U(mg/ml)} \times \text{V(ml/min)}}{A_{PAH}\ \text{(mg/ml)} - V_{PAH}\ \text{(mg/ml)}} = \frac{U \times V}{A_{PAH} - 0} \\ &= \frac{U \times V}{P} = \frac{\text{U(mg/ml)} \times \text{V(ml/min)}}{\text{P(mg/ml)}} = \text{ml/min.}\end{aligned} \tag{5}$$

Even when PAH appears in the renal venous blood in renal disease (see chapter 6), unless the investigator is interested in total renal blood flow which includes

* *Renal blood flow* to tissue secreting PAH = $\frac{\text{renal plasma flow}}{1 - \text{hematocrit}}$.

blood supply to nonfunctioning tissue, it is useless to determine the renal venous concentration of PAH. It is not the Fick calculation of total blood flow that is important but rather the simple functional measurement of the excretion rate of PAH divided by the plasma PAH $((U \times V)/P)$.

The renal vein blood is not entirely free of PAH in the normal kidney. The extraction ratio is slightly less than 1.0 with an average $E_{PAH}$ of 0.92 in the normal kidney. The renal vein is expected to contain some PAH because the kidney is composed also of nonsecretory tissue such as fibrous tissue, calyces, vessels, capsule, and pelvis. Thus, about 8 per cent of the blood supply to the kidney perfuses tissue which does not secrete PAH. Eight per cent is a surprisingly low figure. For every 500 ml/min of renal blood flow, only 40 ml/min supplies tissue which does not perfuse the proximal tubule, the site of PAH secretion. Smith was the first to emphasize that equation (5), $(U \times V)/P$, is a *functional* measurement of renal plasma flow. With Smith's analogy (93), if a cannula is placed between the artery and vein at a point just inside the hand, an arteriovenous fistula is produced (Figure 1a or 1b). Although blood flow measurements based on the *functional* excretion of Na by the hand are reduced in proportion to the amount of shunted blood, this decrease in blood flow will not be detected by application of the Fick principle in which venous concentration corrections are used or by mechanical techniques in which blood flow is measured along the artery going to the hand. If an electromagnetic flowmeter is applied to the artery, changes in blood flow produced by the arteriovenous fistula inside the hand cannot be detected. It is also impossible to detect functional changes in blood flow diverted from the hand if flow is measured by direct collection of the venous return from the hand. Because the primary interest is in blood flow changes to *functioning tissue*, and not direct flow along major arteries, the important measurement is the indirect PAH method $((U \times V)/P)$. A number of recent publications on renal hypertension and blood flow (9), based on direct mechanical estimates of renal blood flow, are open to the serious criticism that renal blood flow was not measured to functioning renal tissue.

## Plasma Clearance

Equation (5) is derived exclusively from the Fick principle and a negligible concentration of PAH in the renal vein. However, equation (5) not only represents renal plasma flow, but also indicates the rate at which plasma is cleared of PAH. At least some of the confusion associated with the word "clearance" is caused by abbreviated methods of expression. The words "inulin clearance" or "PAH clearance" are used when neither inulin nor PAH is cleared of anything. The correct usage is the "*plasma* clearance of inulin" or the "*plasma* clearance of PAH." The usual symbols are $C_{IN}$ for the "clearance of inulin" and $C_{PAH}$ for the "clearance of PAH." These symbols are misleading for the beginning student in renal physiology; the clearance concept would be understood more readily if these abbreviations were preceded by the letter P. By introducing P, the symbols become $P_{CIN}$ and $P_{CPAH}$, which serves to emphasize that it is the plasma which is cleared of inulin or PAH. However, the letter P is unnecessary because the kidney, in its excretory function, is involved solely in clearing the

*plasma*, with the single exception of urea when it is equally proper to refer to the whole blood clearance. Although the symbols $C_{IN}$ and $C_{PAH}$ will be used throughout this book, the concept of a clearance is easier to understand if one remembers that it is the *plasma* clearance of inulin that is important and *not* the inulin clearance.

The plasma clearance of any substance, then, is the volume of plasma required to supply the quantity of that substance excreted in the urine in 1 minute's time. When the substance is PAH, the volume of plasma represents renal plasma flow to functioning kidney tissue, *but only because the renal vein concentration of PAH is negligible in the Fick equation.*

When the substance cleared from the plasma is inulin, the volume of plasma cleared in 1 minute's urine represents the glomerular filtration rate (GFR). The validity of identifying the plasma clearance of inulin with GFR is based on the evidence that the only method by which inulin reaches the urine is through simple filtration at the glomerulus and that inulin is neither reabsorbed with postglomerular reabsorption of nephron filtrate, nor is additional inulin added to the tubular fluid by secretion from the postglomerular blood supply. The evidence for this unique role of inulin is summarized in chapter 3 of H. Smith's book, *The Kidney* (95). Because inulin only reaches the nephron in the ultrafiltrate from the glomerulus, and because subsequent events in the nephron neither add to nor subtract from the original quantity of filtered inulin, the volume of plasma cleared of inulin must represent the rate of glomerular filtration. It follows that the plasma clearance of inulin also represents the rate at which water filters into the nephron because the glomerular filtrate is primarily plasma water by volume.

Plasma clearances are not limited to substances requiring an infusion. In Figure 1a, the plasma clearance of sodium is calculated by dividing the excretion rate of Na (10 mEq/min) by the Na concentration in the plasma:

$$(6) \qquad C_{Na}\ (\text{Figure 1a}) = \frac{\text{Excretion rate}}{P_{Na}} = \frac{10\ \text{mEq/min}}{1\ \text{mEq/ml}} = 10\ \text{ml/min.}$$

However, the plasma clearance of Na in Figure 1b is *not* the same as Figure 1a, although total blood flow is 10 ml/min in Figures 1a and 1b:

$$(7) \qquad C_{Na}\ (\text{Figure 1b}) = \frac{\text{Excretion rate}}{P_{Na}} = \frac{5\ \text{mEq/min}}{1\ \text{mEq/ml}} = 5\ \text{ml/min.}$$

In summary, it should be clear that when total blood flow is calculated, the Fick principle must be used. To use the Fick principle, the renal vein concentration must be a known quantity. When the concentration in the renal vein is actually determined, any substance serves to measure total renal plasma flow whether that substance is PAH, Na, or even inulin. On the other hand, total renal plasma flow is usually not important. The Fick principle becomes a *functional* measure of renal plasma flow when the excreted substance is completely extracted from the arterial circulation perfusing the functioning tissue.

When plasma clearances are determined, the ability of the kidney to clear the plasma of any given substance is measured without reference to renal venous concentration or renal blood flow.

## Reabsorption of Water in the Nephron

It has been emphasized in the preceding section that the plasma clearance of inulin is equivalent to the milliliters of plasma water filtered per minute into the renal tubules. It was emphasized that once inulin crosses the glomeruli into the tubules, there is no further addition or subtraction of inulin in the nephron. Under these unique circumstances, the difference between the concentration of inulin in the glomerular filtrate and the concentration in the final urine is a measure of the percentage of water reabsorbed as the filtrate passes down the nephron. The average plasma clearance of inulin in a healthy adult is approximately 120 ml/min, *i.e.*, 173 L of plasma water are filtered in 24 hours. Because the total urine output in 24 hours is only 1.5 L, it is apparent that 99 per cent of the water filtered from the plasma, under conditions of average hydration, is reabsorbed along the tubule. For example, a gallon of water contains inulin in a concentration of 20 mg%. If the water is evaporated to $\frac{1}{10}$ gallon without losing inulin, the concentration of inulin in the $\frac{1}{10}$ gallon will be 200 mg%. To calculate the degree to which inulin is concentrated by evaporation, the volumes are not directly important: inulin has been concentrated by 200 mg%/20 mg% or 10 times. However, this increase in the concentration of inulin is proportional to the volume of water evaporated (or reabsorbed in the renal tubule). This relationship of the final evaporated volume to the original volume can be expressed as a percentage by the ratio $1/(200/20) \times 100$ or $\frac{1}{10} \times 100$, which is 10 per cent. Therefore, the final volume of evaporated water is 10 per cent of the original 1 gallon volume.

The nephron in Figure 2 is similar to the evaporation analogy. The concentration of inulin in the ultrafiltrate of the glomerulus is 20 mg% which is determined by analysis of the inulin concentration in plasma or serum. The concentration of inulin in the plasma (or serum) is virtually identical to the concentration of inulin in the glomerular filtrate. In Figure 2, the concentration in the urine is

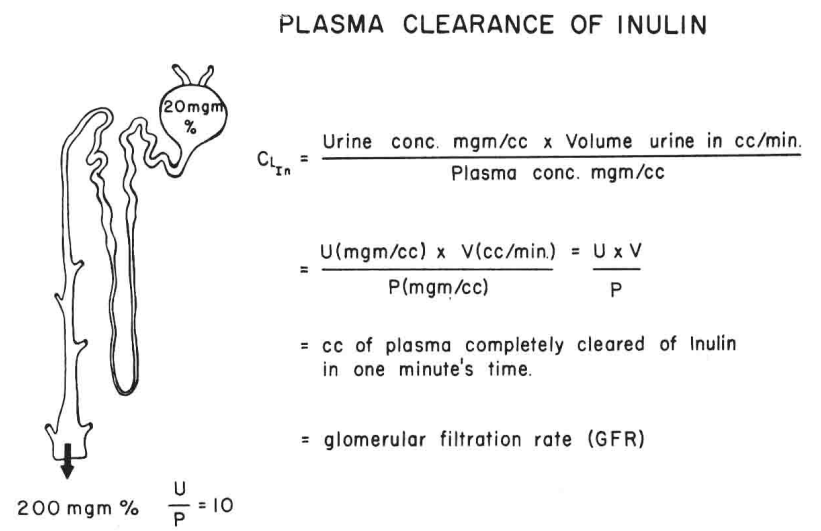


Fig. 2. A diagram of the plasma clearance of inulin and the inulin U/P ratio.

200 mg%. The difference between these concentrations is expressed as the urine/plasma ratio. This ratio is more commonly abbreviated as the inulin U/P ratio. In Figure 2, the inulin U/P is 10, indicating that the filtered inulin has been concentrated 10 times. The volume of water excreted (the final urine) in relation to the volume of water filtered (the total glomerular filtrate) is expressed as:

Percentage of filtered water excreted as the final urine

$$= \frac{1}{U/P} \times 100 = \frac{1}{200/20} \times 100 = \frac{1}{10} \times 100 = 10\ \%. \tag{8}$$

The normal human kidney, under marked water hydration, can reduce the inulin U/P ratio to about 7. At this ratio, the kidney is excreting 14 per cent of the filtered water ($1/(U/P) \times 100 = \frac{1}{7} \times 100 = 14\%$). This inulin U/P ratio of 7 approaches the maximal reduction which can occur with water hydration. In fact, the illustrative example of an inulin U/P ratio of 10 in equation (8) and Figure 2 represents a marked diuresis (17.3 L of urine in 24 hours). The average U/P inulin ratio for a normal person with a 1.5 L output in 24 hours is greater than 100. Whereas, a marked water diuresis will produce an inulin U/P ratio as low as 7, an osmotic diuresis is required to obtain a reduction below 7. The osmotic diuretic partially inhibits the reabsorption of water in the proximal tubule by increasing the osmotic pressure of the glomerular filtrate. Inulin U/P ratios as low as 2 have been obtained in the dog. At this U/P ratio of 2, 50 per cent of the filtered water has been excreted!

Inulin can be used, then, as a measure of total water reabsorption as well as a measure of glomerular filtration rate. An important simplification is possible in terms of total water reabsorption. As pointed out in the Preface, there are major advantages to comparing one kidney with the other in the same *milieu*. In Figure 3 one of these advantages is illustrated. The glomerulus, except for pore size, is a nonselective filter; therefore, the concentration of inulin in the glomerular filtrate of the kidney with occlusive arterial disease is identical to the concentration of inulin in the filtrate of the contralateral, nonoccluded kidney. For this reason, total reabsorption of water can be compared in the two kidneys without reference to plasma inulin. Because the exact inulin U/P value for any one person depends on a variety of factors (the degree of hydration, the amount of endogenous antidiuretic hormone production, and the osmotic load), there is no advantage to calculating the inulin U/P ratio. If the concentration of inulin is the same in the final urine from both kidneys, then, regardless of urine volumes, the amount of total water reabsorbed per unit of glomerular filtrate must be the same for each kidney. The greater the difference in the concentration of inulin between the two kidneys, the greater will be the difference in total water reabsorption. In Figure 3* it is shown that the occlusive arterial

* The *arrows* in Figure 3 are not intended to indicate the actual sites of water reabsorption because reabsorption occurs throughout the nephron. In chapter 2, evidence will be presented that most of the excessive water reabsorption occurs in the proximal tubule, which is the part of the nephron in which 85 per cent of the filtered water is reabsorbed under normal circumstances.

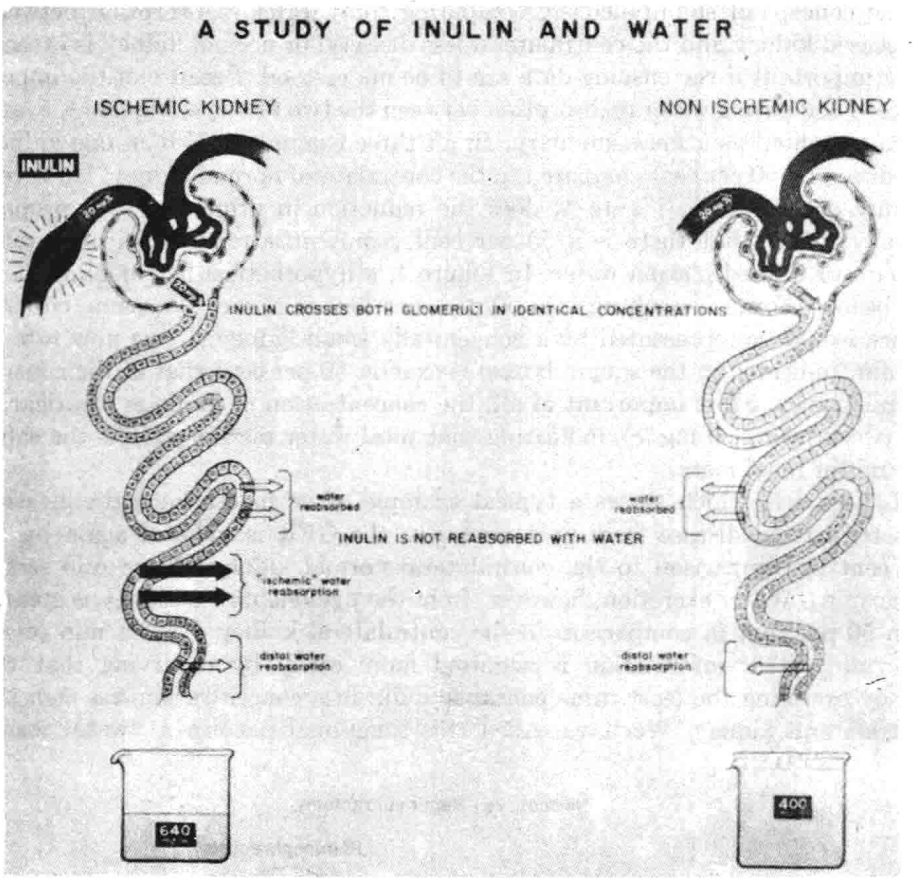


FIG. 3. A diagram illustrating the advantage of comparing total water reabsorption between two kidneys in the same person.

lesion reduces the volume of glomerular filtrate (*i.e.*, the glomerular filtration rate). Nevertheless, the concentration of inulin in the filtered plasma water is 20 mg per cent in both glomerular filtrates. This reduction in the volume of glomerular filtrate must reduce the rate of flow of the filtered water down the nephron and, therefore, give the tubular cells a longer time to act on the filtrate. The tubular epithelium, in response to the slowing of the glomerular filtrate, produces the characteristic functional defect of the ischemic kidney: an excessive reabsorption of water (640 mg% inulin) when compared with the contralateral kidney (400 mg% inulin). The diagnostic pattern in Figure 3 (60% reduction in urine flow with a 60% increase in the concentration of inulin) is compatible with either segmental renal ischemia and a contralateral normal kidney, or bilateral fibromuscular hyperplasia with greater ischemia to one kidney than the other, or bilateral nephrosclerosis ("essential" hypertension) with a disparity in the degree of nephrosclerosis in the two kidneys. These functional patterns will be considered in detail in chapters 2, 3, and 7.

The concept of simultaneously comparing total water reabsorption between a diseased kidney and the contralateral less diseased or normal kidney is exceedingly important if the ensuing data are to be understood. Because of the importance of comparing water reabsorption between the two kidneys, Figures 4, 5, and 6 are presented as a final summary. In all three examples, GFR in one kidney is reduced by 50 per cent compared to the contralateral normal kidney. However, in only one instance (Figure 4) does the reduction in urine flow rate proportionally reflect that there is a 50 per cent *comparative* reduction in the total amount of filtered plasma water. In Figure 4, a hypothetical heminephrectomy has been performed resulting in a 50 per cent loss of tissue. The same circumstance would be represented by a congenitally small kidney. Urine flow rate in cc/min (indicated in the square boxes) is exactly 50 per cent that of the contralateral kidney. Most important of all, the concentration of inulin is identical in the two urines (200 mg%), indicating that total water reabsorption is the same per unit of renal mass.

In Figure 5, which shows a typical example of normotensive patients with unilateral renal disease from pyelonephritis, the GFR is reduced again by 50 per cent in comparison to the contralateral normal kidney (30 cc/min *versus* 60 cc/min). Water excretion, however, from the pyelonephritic kidney is greater than 50 per cent in comparison to the contralateral kidney (3⅓ cc/min *versus* 6 cc/min). This information is acquired more easily by observing that the kidney excreting the least urine contains inulin in a concentration *less than* the contralateral kidney. We have called this functional pattern á "water losing

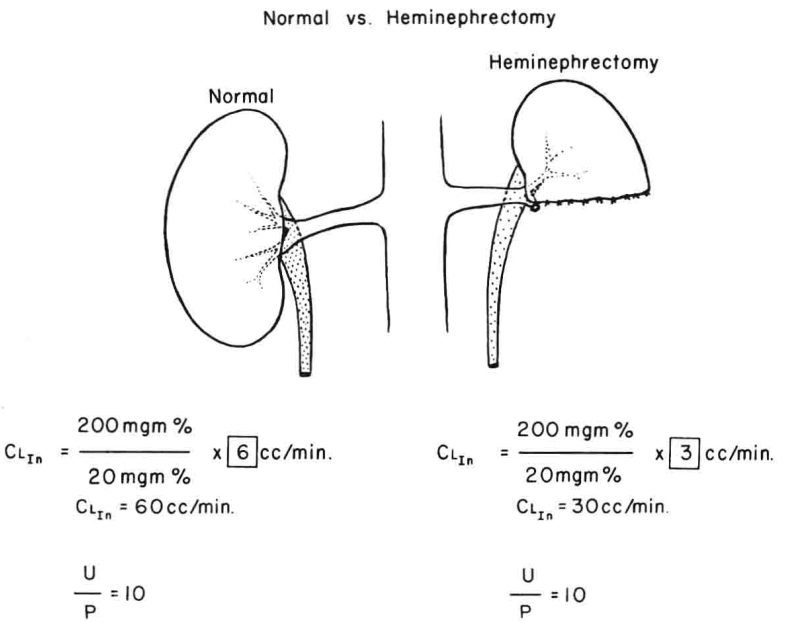


FIG. 4. A hypothetical heminephrectomy compared to a contralateral normal kidney in a normotensive patient. Total water reabsorption per unit glomerular filtrate is the same in the two kidneys. Differences in urine flow rates exactly reflect the differences in GFR.