RECENT ADVANCES in UROLOGY

By

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With the assistance of specialist contributors

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It is becoming increasingly difficult to read all of the ever-growing volume of urological literature, and is even more difficult to decide what constitutes a real clinical advance. This book deals only with aspects of urology in which new data are accumulating, or in which recent progress has occurred. The author and his colleagues, who have contributed to the work have attempted to discuss these changes rather than to review recent literature.

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PREFACE

THERE are very few surgeons to-day who could honestly claim to feel equally confident when operating inside the skull, the thorax and the abdomen. This is not due to the fact that surgical techniques are becoming more difficult or more numerous, but rather to the fact that the indications for each operation are becoming more selective, while the alternative and the ancillary methods of treatment are becoming more complex.

The surgical technique of an operation is generally much easier to master than the indications for its use, and it is not the operative surgery which is becoming specialized so much as the study and treatment of the surgical pathology. Nowhere is this more true than in urology.

It is becoming increasingly difficult to read all of the ever-growing volume of urological literature, let alone glance through the general surgical journals as well. It is even more difficult to decide from the literature what constitutes a real clinical advance rather than an addition to our scientific knowledge. Although most of this scientific knowledge will inevitably lead to further clinical advances in due course, such advances are not a continuous process. There are long periods during which, from the patients' point of view, there are no advances, even though our data on the particular subject may be increasing rapidly.

This book deals only with aspects of urology in which new data are accumulating, or in which recent advances have occurred. My colleagues, who have contributed to the work, could all be regarded as specialists within a speciality, and I am extremely grateful to them for their co-operation. We have attempted to discuss recent advances rather than review recent literature, and would apologize for omissions and commissions which may appear obvious to all in a few years' time.

I wish to express my thanks to the many authors who have allowed me to use their illustrations and blocks, while I am particularly grateful to Miss Freda Wadsworth, the medical artist at the Institute of Urology, for the outstanding quality of her illustrations.

My thanks are also due to Mr. E. Stride, A.I.B.P., of the Photographic Department, Hillingdon Hospital, and to Mr. R. E. Bartholomew, A.I.B.P., A.R.P.S., of the Photographic Department in the Institute of Urology, for the X-ray and other photographic reproductions throughout the text.

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MEDICAL PROBLEMS IN UROLOGY

by

A. R. HARRISON

PHYSIOLOGY

IN health, the volume and composition of the extracellular fluid remains virtually constant, largely due to the activity of the kidneys. However, although the stability of the internal environment depends on renal function the converse is partially true for if there are gross disturbances of the body fluids, from whatever cause, then renal function may suffer. It is necessary to have some knowledge of the physiology of the kidneys and the body fluids in order to understand and treat renal failure. Only an outline of these extensive subjects can be given here, with more emphasis on the important advances than on the well established facts.

Renal Function

The kidney in performing its regulatory function is required to excrete metabolic end products, foreign substances and surplus normal constituents of the body fluids, and in addition to conserve substances such as glucose, amino-acids, water and electrolytes which are necessary to the body. The urine formed will therefore be, at one and the same time, both more and less concentrated than the blood plasma in respect of different solutes.

Knowledge of renal physiology has not changed in broad outline since Marshall showed that tubular excretion occurred and Cushny's theory of filtration and reabsorption was finally modified. Since then, however, many of the details of renal function have become clearer and quantitative measurement of different aspects of function has become possible.

It is convenient to consider renal function in three stages; renal

blood flow, glomerular function and tubular function. Before doing so it may be as well to remind the reader of the principle of clearance tests, which figure prominently in researches in renal physiology.

If the concentration of any substance in the urine is U mgm./ml., and the rate of urine formation is V ml./min., then $U \times V$ mgm. of this substance are excreted per minute.

If, at the same time, the plasma concentration of this substance is P mgm./ml., then $\frac{U \times V}{P}$ ml. of plasma must have been cleared of the substance per minute.

Renal Blood Flow

There is a very large renal blood flow. Smith *et al.* (1938) showed that, when present in low concentrations in the plasma, the substance diodrast appeared in the urine at such a rate that about 700 ml. of plasma must have been cleared of it per minute. Sodium p-amino-hippurate (PAH) was shown to be cleared at the same rate and these clearance rates were thought to represent the total renal plasma flow. Warren *et al.* (1944) were able to make simultaneous analyses of arterial and renal vein blood by catheterisation of the renal vein and show that PAH was virtually removed from the blood in one passage through the kidney. This confirmed the hypothesis that the PAH clearance is a measure of renal plasma flow.

Glomerular Filtration

Although actual analysis of the fluid in the capsular space, as was achieved by Richards (1938) in the kidneys of amphibia, is obviously impossible in man, it is universally accepted that at the glomerulus there is a simple physical process of filtration of the plasma through the glomerular capillaries, the fluid formed being a protein-free replica of plasma—an ultra-filtrate. The effective filtration pressure is the blood pressure in the capillaries less the opposing osmotic pressure of the plasma proteins and the pressure within the capsular space. The inulin clearance test developed by Homer Smith and his colleagues (1951), provides a method of measurement of the rate of formation of filtrate, for inulin is filtered at the glomeruli but

neither excreted nor reabsorbed by the tubules. In the healthy adult man the rate averages 130 ml./min., or over 180 litres a day. This test is acknowledged to be valid in health, and probably measures the rate of glomerular filtration in the diseased kidney, but there is a possibility that inulin might diffuse back to the blood stream through the tubular epithelium when this is severely damaged.

Tubular Function

In broad terms the function of the tubules is to modify the glomerular filtrate in such a way that excretion of the urine formed will always defend the composition and volume of the extracellular fluid in spite of the variable metabolic loads which tend continually to alter this. This implies a complexity and flexibility of function; in contrast to the simple mechanical process of filtration at the glomerulus. The tubular epithelium performs three tasks; it reabsorbs some things back to the blood stream, excretes others into the urine and, in regulating the acid-base balance of the body, synthesises new substances.

Reabsorption. Clearly most of the huge quantity of filtrate must be reabsorbed, and in normal circumstances virtually all the glucose, 99 per cent of the water and sodium and between 40 per cent and 50 per cent of the urea will be returned to the blood stream.

The modern view is that the proximal tubule is the site of reabsorption of glucose and most of the other substances that are to be retained. About 80 per cent of the water accompanies these solutes, leaving a fluid which is approximately isotonic with blood plasma. This phase has been described by Smith (1951) as "obligatory reabsorption."

Mechanisms of Reabsorption. The reabsorption of glucose requires an active transport mechanism calling for the expenditure of energy, for it proceeds against concentration gradients. Shannon and Fisher (1938) showed that the tubules can only handle a limited quantity of glucose in a given time, and when this is exceeded glycosuria will occur. This work has been extended to the reabsorption of other substances and it now appears that the tubular transport of amino-acids, phosphate, sulphate and vitamin C exhibits the same phenomenon, i.e. there is a relatively sharp limit to its

capacity. This, the maximal tubular transport capacity measured in mgm./min., is often denoted by the symbol Tm. It is of course different for different solutes, and whereas the Tm for glucose is such that at normal plasma concentrations and filtration rates all is absorbed and none is excreted, phosphate, having a much lower Tm, normally appears in the urine.

Sodium and other major electrolytes are also reabsorbed by active mechanisms limited in scope, but it is not possible to determine a Tm value for them.

Urea in contrast is returned to the blood stream by a process of simple diffusion through the tubular epithelium.

The processes so far described are comparatively rigid, and the power of fine adjustment which the kidney must possess appears to reside in the distal tubule. Here the remaining 20 per cent of the filtrate is modified so that either a concentrated or dilute urine is excreted. This implies the existence of mechanisms allowing reabsorption of water and solutes independently of each other.

Reabsorption of Water. There are two distinct phases involved in water reabsorption. As already mentioned about 80 per cent of the water of the glomerular filtrate is reabsorbed in the proximal tubule simply because of the osmotic gradients created by the active reabsorption of solutes such as glucose. This process, controlled entirely by osmotic forces, cannot vary to meet the water requirements of the body.

In the distal tubule active reabsorption of water can occur independently of solutes and it is in this stage, which Smith (1951) has called the stage of facultative reabsorption, that the necessary adjustments of the rate of water excretion take place. The mechanism is controlled by the antidiuretic hormone of the posterior pituitary and the action of this hormone is to increase the reabsorption of water but not of solutes. As a consequence of this conservation of water a small volume of concentrated urine is formed. Conversely, when the secretion of the hormone is inhibited relatively less water than solutes will be reabsorbed and a large volume of dilute urine will be excreted. The stimulus to the secretion of antidiuretic hormone is an increase in tonicity, or osmolarity, of the extracellular fluid which, in turn, is normally caused by a low ingestion of water.

Naturally there is a limit to this process of distal water reabsorption and, even when the body can ill spare water and the urine is of maximal concentration, about 600 ml. of urine must be formed in excreting a normal daily load of solutes.

The regulation of water reabsorption in the distal tubule is not the only factor controlling urine volume and concentration. If the glomerular filtrate contains an increased amount of any osmotically active solute which is not reabsorbed by the proximal tubule then the passive osmotic reabsorption of water at this site will be retarded. Furthermore, the active reabsorption of other solutes may be diminished, simply because their concentration in the tubular fluid will fall and so increase the osmotic force opposing their reabsorption. As a consequence a greatly increased flow of fluid will be delivered to the distal tubule, a flow which overwhelms the reabsorptive mechanisms in this segment. The resultant increased urine flow is termed an " osmotic diuresis."

The studies of Raporport *et al.* (1949) have shown that when an osmotic diuresis is induced by the administration of various solutes, the rate of urine formation increases as the solute load is increased but at the same time the total concentration, or osmolarity, of the urine decreases, even in subjects who have been deprived of water. However, unlike the diuresis induced by drinking a lot of water, the osmolarity of the urine can never fall below that of blood plasma.

The important fact which emerges from this concept of osmotic diuresis is that whenever the kidney has to excrete a large load of any solute there will be an abnormal loss of water and, perhaps of less importance, an abnormal loss of other solutes such as sodium.

Platt (1952) suggests that in chronic renal disease the polyuria and inability to form a concentrated urine can be explained by osmotic diuresis. In chronic renal disease the number of functioning nephrons is reduced and each will therefore have to take a larger share of the total solute load requiring excretion. Each nephron will in consequence be working continually under the stress of an osmotic diuresis, even though the total load of solutes (urea, sodium etc.) which claims excretion from the body is no greater than normal. This theory fits certain observations much better than the classical assumption that the inability to form a concentrated urine is due to

damage to the tubular epithelium. In 1892 Rose Bradford showed that polyuria occurred in dogs when much of the renal parenchyma was removed surgically. In these circumstances it is difficult to visualise damage in the tubular epithelium of the surviving nephrons.

Sodium Reabsorption. Sodium conservation is also under hormonal influences, the adrenal cortical hormones—in particular aldosterone—promoting its reabsorption. However, other factors influence the renal handling of sodium. When the intake of sodium is low its excretion is diminished and furthermore when there is a sharp reduction in the rate of glomerular filtration then sodium excretion will also fall; in both cases because a greater proportion of the filtered sodium is reabsorbed. In addition the tubular mechanisms for the excretion of acid products of metabolism allow conservation of sodium which would otherwise be lost.

Tubular Excretion

In 1923 Marshall showed that the tubular epithelium had the ability to transport phenol red from the plasma to the urine so proving the existence of tubular excretion. Later, when the glomerular filtration rate could be measured accurately, it became evident that other substances were excreted in the urine at faster rates than was possible by filtration alone. Creatinine and potassium are naturally occurring substances excreted by the tubules and many foreign substances, e.g. penicillin, are handled in the same way.

Acid-Base Regulation

Normally the acid products of metabolism exceed the basic and these are neutralised in the body-fluids by combination with base, very largely sodium, derived from bicarbonate. If the acids were excreted in combination with sodium then there would be a rapid loss of body sodium. The urine pH never drops below about 4·8, which means that the strong acids, such as H_2SO_4 are not excreted as free acids. However, in the tubule, mechanisms exist which allow excretion of acid without a loss of the fixed bases of the body. Essentially these consist of the formation of NH_3 and H^+ ions by the tubule cells. NH_3 was originally thought to be derived from urea, but it is now known to be formed from amino-acids such as

glutamine by enzymatic activity. Pitts and Alexander (1945) adduced evidence to show that hydrogen ions are formed in the tubule cells from H_2CO_3 produced from CO_2 and H_2O under the influence of carbonic anhydrase. These H^+ ions are exchanged for cations such as sodium which can be reabsorbed. This explains the excretion of $NaH_2\ PO_4$ instead of $Na_2\ HPO_4$. However, the substitution of H^+ for sodium in NaCl would leave HCl, which cannot be excreted as such, for it is a strong acid and almost completely dissociated in solution. The NH_3 formed in the cells now migrates to the urine in response to the increased hydrogen ion concentration and NH_4Cl is excreted.

THE BODY FLUIDS

A major medical advance has been seen in the improved management of the dehydrated patient resulting from a better understanding of the anatomy and physiology of the body fluids. Only a brief account of this important subject can be given here, and for a fuller description the reader is referred to the 1946 Croonian Lectures delivered by Marriott and the monograph of Gamble (1950).

Anatomy and Physiology

The body fluids exist in two main compartments—intracellular and extracellular, and the latter can be further divided into the interstitial fluid and the blood plasma. All these fluids are watery solutions, the intracellular water being about 40 per cent, the interstitial about 12–15 per cent and the plasma water about 5 per cent of the total body weight.

Water moves freely between all compartments and there is also a free interchange between the plasma and the interstitial fluid of all solutes except the plasma proteins. The plasma and interstitial fluid will therefore have essentially the same composition.

Substances entering into metabolic processes within the cell must be able to enter or leave it. Nevertheless, the cell membrane behaves as though it is impermeable to the major electrolytes of the body fluids, in that quite different concentrations of these are maintained on either side of it, presumably by processes needing energy

expenditure. The composition of the extracellular fluid is therefore quite different from that of the fluid within the cell though, since the cell membrane is permeable to water, they will have the same total osmolarity. The approximate composition of each is shown below:

Extracellular Fluid (E.C.F.)				Intracellular Fluid (I.C.F.)			
Cations		Anions		Cations		Anions	
Na	142 mEq./l	Cl	103 mEq./l	K	157 mEq./l	PO_4	113 mEq./l
K	5 ,,	HCO_3	27 ,,	Na	14 ,,	Protein	74 ,,
Ca	5 ,,	SO_4	1 ,,	Mg	26 ,,	HCO_3	10 ,,
Mg	3 ,,	HPO_4	2 ,,				
		Organic acids	6 ,,				
		Protein	16 ,,				

Units of Measurement

In reporting on the chemical analysis of body fluids it is obviously advantageous to express the concentration of the various electrolytes in terms of their chemical equivalence to each other rather than by their actual weights. The equivalent weight of a substance is the weight which will combine with or displace one gramme-atom of hydrogen, and a milli-equivalent is 1/1000th part of this.

The equivalent weight of monovalent elements such as Na^+, Cl^-, K^+ is equal to their atomic weight. In divalent elements such as Ca^{++} or Mg^{++} it will be half the atomic weight and so on.

Thus 23 mgm. of Na or 35 mgm. Cl will each be 1 milli-equivalent. To convert milligrammes per 100 ml. into milli-equivalents per litre, multiply by 10 to give milligrammes per litre, then divide by the atomic weight of the element concerned and finally multiply by the valency, i.e.:

$$\text{mEq/l} = \frac{\text{mgm./100 ml.} \times 10}{\text{Atomic wt.}} \times \text{Valency.}$$

The osmotic force exerted by ions will be independent of their valency so that a divalent ion will have the same osmolar value as a monovalent one.

The adoption of these units of measurements for body fluid electrolytes is almost universal, but as yet the more familiar units of grammes and milligrammes are still commonly used in describing fluids used in replacement therapy; a complication which adds to the difficulty of computing how much of a particular intravenous fluid should be given to replace total body deficits.

Body Fluid Disturbances

Deficiency of the body fluids, i.e. dehydration, can be caused by a lack of water, of electrolytes or "salt" and by a combination of both. In practice the combination of water and salt loss is most commonly seen but conditions approximating to isolated water or salt deficiency can exist, and their effects are different. Experimental work on salt depletion by McCance (1936, 1938), and the clinical work of Nadal *et al.* (1941), have led to a much better understanding of the effects of these different forms of dehydration. These effects will be described separately for, although the separation may be somewhat artificial from a clinical standpoint, this method of presentation facilitates explanation and understanding of the principles involved.

Effects of Water and of Salt Lack

Before either of these is considered, two points need emphasis:

The immediate effects of both water and salt lack are borne by the extracellular fluid (E.C.F.) but the changes which occur in this rapidly induce alterations in the intracellular fluid (I.C.F.).

At first the kidney attempts to defend the tonicity of the E.C.F. at the expense of volume though later this defence fails and changes in tonicity occur.

Water Lack. The body can only economise in water to a limited extent and, if none is ingested, there are inevitable daily losses of about 1 litre from the skin and respiratory tract and 600 ml. in the urine, these being counterbalanced by only 400–500 ml. of water obtained from metabolic processes. In water deficiency the initial effect is that the E.C.F. becomes hypertonic. Water therefore passes from the cells into the E.C.F. to restore osmotic equilibrium and cellular, as well as extracellular, dehydration will occur.