RECENT ADVANCES IN RENAL DISEASE

The Proceedings of a Conference held in London at the Royal College of Physicians of London 22nd-23rd July 1960

EDITED BY M. D. MILNE

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PARTICIPANTS

CHAIRMEN

Sir Robert Platt, Bt.	President of the Royal College of Physicians
The Lord Evans	The London Hospital
R. A. McCance	Professor of Experimental Medicine, University of Cambridge
J. McMichael	Professor of Medicine, Postgraduate Medical School, London

SPEAKERS

D.A.K. Black	Professor of Medicine, University of Manchester
C.E. Dent	Professor of Human Metabolism, University College Hospital Medical School, London
H.E. de Wardener	St. Thomas's Hospital Medical School, London
D. Edwards	University College Hospital, London
P. Freedman	St. George's Hospital, Tooting Grove, London
C.J. Hodson	University College Hospital, London
W.W. Holland	Medical Research Council, Statistical Research Unit, London School of Hygiene and Tropical Medicine
R.C. Jackson	Princess Mary's Royal Air Force Hospital, Halton
A.M. Joekes	St. Mary's Hospital, London
Lavinia W. Loughridge	Postgraduate Medical School, London
M.D. Milne	Postgraduate Medical School, London
K. Owen	St. Mary's Hospital, London
M.L. Rosenheim	Professor of Medicine, University College Hospital Medical School, London
G.A. Smart	Professor of Medicine, University of Durham
A.G. Spencer	St. Bartholomew's Hospital, London
J.R. Squire	Leith Professor of Experimental Pathology, University of Birmingham
S.W. Stanbury	The Royal Infirmary, Manchester
C. Wilson	Professor of Medicine, London Hospital
O.M. Wrong	University College Hospital Medical School, London

President's Opening Remarks

Fellows and Members of the College: First of all let me say what a great pleasure it is to me to welcome you again to the College to this which is our Fourth Scientific Conference and particularly to welcome one or two of our most distinguished fellows from overseas. Now I have not really anything to say in introduction except perhaps just two or three minor things. In the first place you may like to know that the subject was not of my choosing, though I shall be very interested to hear both the speakers and the discussion. Now we have heard a number of suggestions about subjects for further conferences and I am of course still open to receive those suggestions. We have had a number of suggestions as to how we can most fairly arrange these conferences when they are over-subscribed but we have not really had any suggestions as to how the conference should be run and therefore I take it that the general lines on which they have been run in the past have been satisfactory to the audience and you will see that this particular conference is designed on what is now becoming the usual pattern. It is divided into a number of sections, which those of you who can read do not need me to tell you about, and the speakers have been chosen of course with the usual great care which will be obvious to you, I am sure, during the course of the conference. Success of conferences depend as much upon those who come to hear, and particularly to discuss, as they do upon the chosen speakers and I do hope that you will not hesitate to get up in the discussions. Because the publication of these conferences has been really a popular feature of them. We have to record the discussions, and I hope that this will not put you off getting up and saying whatever you wish to say and I hope that you will move towards the centre to the microphone when you enter in the discussion and that you will give your name before speaking. If you do not I am sure that our first Chairman, upon whom I am now going to call, will keep you in order. So I have great pleasure now in asking Dr. R.A. McCance if he will take over for this first session.

PROFESSOR McCANCE: Well, one of the great joys, of course, in being asked to take the chair at a conference of this kind is the privilege: but the other is the opportunity it gives one to learn, and I am looking forward very much indeed to this morning. I am going to be rather strict about timing and names because I think it adds to the enjoyment of the people who have to speak last if they are not worried all the time that they are going to be crowded out. So I will ask the first speaker to begin now, and that is my old friend Dr. Douglas A. K. Black and he is going to talk about Normal Function. And this morning the whole subject will be Renal Function and Structure.

CONTENTS

President's Opening Remarks		Page ix
RENAL FUNCTION AND STRUCTURE		
Chairman - R.A. McCance		
Normal Function	D.A.K. Black	3
Tests of Renal Function	O.M. Wrong	11
Renal Biopsy	A.M. Joekes	23
Discussion		28
ACUTE RENAL FAILURE		
Chairman - R.A. McCance		
Course and Prognosis	M.D. Milne	35
The Artificial Kidney	R.C. Jackson	54
Discussion		63
THE NEPHROTIC SYNDROME		
Chairman - Lord Evans		
Functional Pathology	J.R. Squire	71
Lumpus Nephritis	P. Freedman	90
Renal Amyloidosis	L.W. Loughridge	98
Discussion		109
Treatment in Adults	G.A. Smart	112
Treatment in Children	W.W. Holland	123
Discussion		131
PYELONEPHRITIS		
Chairman - Sir Robert Platt, Bt.		
The Nature of Pyelonephritis	M.L. Rosenheim	137
The Micturating Cystogram	D. Edwards	145

Diagnosis and Treatment — H.E. de Wardener — 157

Discussion — 166

METABOLIC ASPECTS OF RENAL DISEASE

Chairman - Sir Robert Platt, Bt.

Inborn Errors of Renal Tubular Function — C.E. Dent — 173

Renal Osteodystrophy — S.W. Stanbury — 181

Discussion — 194

HYPERTENSION AND THE KIDNEY

Chairman - J. McMichael

Radiological Investigations in Renal Hypertension — C.J. Hodson — 201

Clearance Studies in Unilateral Renal Disease — A.G. Spencer — 208

Medical Treatment — C. Wilson — 220

Surgical Treatment — K. Owen — 229

Discussion — 240

Index — 247

Normal Function

D. A. K. BLACK

This is an exciting, and in some ways a difficult time to present an outline of renal physiology to a conference of physicians. Exciting, because the past decade has seen the gradual piling up of evidence which favours a radically new concept of urine-formation put forward by Wirz and his colleagues in 1951. Difficult, because the new ideas are still mainly worked out in the normal animal, and their application to man and to clinical problems has scarcely begun. I shall try to maintain a balance between our knowledge of <u>what</u> the kidney does, knowledge which has already made substantial contributions to the management of patients; and the fascinating ideas on <u>how</u> it does it, whose clinical application lies all in the future.

The kidney has functions other than the formation of urine, to which the terms 'metabolic' and 'endocrine' have been applied. These are important in relation to hypertension, as will be discussed later in this Conference; and also in relation to erythropoiesis (Onsnes, 1959). The main job of the kidney is still the making of urine. In doing this, it is supplied with about a litre of blood each minute, a fifth of the cardiac output; of the plasma contained in this large amount of blood, again about a fifth is filtered off in the glomerular tufts, so that the raw material for urine-formation is some 120 ml./min. of a fluid containing only traces of protein and lipoid, but otherwise resembling plasma in its composition. The renal tubules must then concentrate this fluid by a factor at least five, and more commonly 100; and at the same time effect striking changes in its composition, by the selective re-absorption, and in some cases the actual secretion, of solutes.

Many years ago now, Cushny appreciated that the tubules handled solutes in two distinct ways: some substances, such as urea and creatinine, went on being excreted when their plasma concentration was low (the 'no-threshold' substances); while others, such as glucose, sodium and chloride, were excreted at higher plasma levels and retained at lower plasma levels (the 'threshold' substances). While the explanations proposed by Cushny have not stood the test of time, the phenomenon itself is of importance in clarifying the role of the kidney in homoeostasis, and is indeed the basis of Cannon's later distinction between the 'excretory' and the 'homoeostatic' (or regulatory) functions of the kidney.

Of those substances which are truly excreted by the kidney, urea is quantitatively by far the most important. The essential features of urea excretion were established by Van Slyke and his colleagues. About half of the filtered urea appears in the urine, the remainder diffusing back through the tubule walls. At higher urine-flows, more urea escapes re-absorption, a relationship which was put on a quantitative basis by the measurement of 'urea clearance' at varying urine flow-rates. Since water is reabsorbed by the tubules to a much greater extent than is urea, the concentration of urea increases to many times that in the original filtrate. Urea is a substance of low molecular weight, and in the concentrations found in urine its osmotic activity is considerable; this effect tends to restrain the reabsorption of water and of electrolytes, so that by giving urea a diuresis can be induced. Similar effects are seen with other osmotically active substances, the phenomenon being described as 'osmotic diuresis'. The urine in this type of diuresis contains substantial amounts both of the substance given - 'the loading solute', and of other solutes; in contrast to 'water diuresis', in which solute output is almost negligible. The excretory function of the kidney is of course important in the elimination of foreign substances also, and Dr. Milne has recently drawn attention to an important mechanism of 'non-ionic diffusion' whereby the excretion of weak acids and bases may be enhanced (Milne et al., 1958). The tubule wall allows the passage of a number of such substances in the

undissociated form, but restricts the passage of the ionic form; a substance may thus diffuse from blood into the tubule lumen, and there become 'trapped' when it dissociates at the much lower pH of tubule-fluid.

The regulatory functions of the kidneys are concerned to maintain the constancy of the internal environment, so that they operate mainly on the extracellular fluid, and particularly on that large sample of it which is always being brought to them in the plasma. This regulation is obvious to us when it affects urine volume; but simple analysis shows the same type of activity in respect of osmolarity, of pH, and of individual solutes such as sodium and potassium which are important in the control of body-fluid volume. The purely descriptive literature of renal behaviour under a variety of stresses is now enormous; but it can be summarised in the general statement that the healthy kidney always tries to do the right thing, i.e. change urine composition so as to compensate for the stress. In this attempt, however, it may well be misled by partial information, derived from plasma composition; this may not characterise properly the state of affairs within the cells, as when cellular depletion of potassium is associated with a raised plasma-potassium level, e.g. in diabetic coma. In these circumstances, the kidneys may go on excreting potassium, although conservation would be a better long-term response. There are also situations in which the kidney has to compromise between multiple stresses, as in respiratory acidosis, where the elevated bicarbonate concentration of plasma calls for bicarbonate excretion and an alkaline urine, whereas the acidosis calls for increased urinary acidity. The renal response is also of course influenced by the action of hormones, of which A.D.H. and aldosterone are the most important; the balance between these hormones can also lead to apparently anomalous behaviour, as when hypertonic saline causes at one time a saline diuresis from inhibition of aldosterone production, and at another a profound antidiuresis from stimulation of A.D.H. Leaving aside these special cases, the general operation of renal regulatory function is the expected one of disposing of excesses by increased excretion, and

correcting deficits by retention. Examples could easily be multiplied, but it may be more rewarding to look at present ideas on how this is done.

It has been realised for a long time that the ability to concentrate the urine to osmolarities well above that of plasma is associated with the possession of that rather odd structure, the loop of Henle, which in mammals, but not in amphibians, is intercalated between the proximal and distal convoluted tubules. Why this should be so was inapparent, because the simple epithelium of Henle's loop did not look like a powerful osmotic engine. The revolutionary explanation suggested by Wirz, Hargitay and Kuhn (1951) was that the loop of Henle functioned, by virtue of its 'hairpin' arrangement, as a 'countercurrent exchanger'. The principle of this arrangement is indicated in Figure 1. In this,

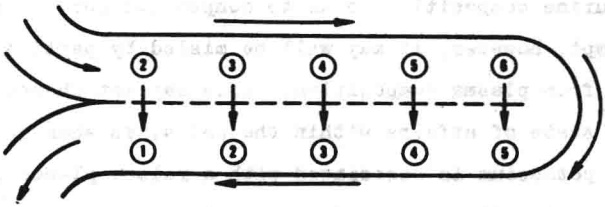

Figure 1. Diagram of a counter-current system (for explanation, see text).

the numerals indicate units of concentration, and an active transfer of water is postulated from the upper to the lower limb of the loop. Going along the upper limb, this will increase the concentration progressively from '2' to '6', while the arrival of this water in the lower limb will decrease concentration from '6' to '1'. The important point to notice is that throughout the loop the concentration difference <u>across</u> the dividing membrane is only unity, although the concentration difference between the open and closed ends of the loop is 5 units. This is, of course, only a model, and in the actual kidney we have vascular as well as tubular loops, and there is also some evidence that the concentration gradient is established by the active transport of sodium and not of water. It has now been established by several groups that when a concentrated urine

is being formed, the osmotic concentration in the medulla is substantially above that in the cortex; this has been shown to apply to whole medullary tissue (Gowenlock et al., 1959), to blood obtained from the papillary vessels (Wirz, 1954), and to tubule-fluid from the tip of Henle's loop (Gottschalk and Mylle, 1959). When a dilute urine is being formed, medullary hyperosmolarity is not found, and the active transport which primes the countercurrent mechanism is presumably in abeyance. The relative importance of sodium and urea as osmotically active solutes is still in some dispute, but the importance of medullary hyperosmolarity is now established. A mechanism of this type could obviously be upset in disease either by distortion of the medullary architecture, or by deficiency of protein (urea) or of sodium. It accounts for the ability to form a concentrated urine, but not for the substitution of one ion for another which is just as striking a feature of urine formation. This phenomenon of 'ion-exchange' has been established by the work of Pitts and Berliner, and has been reviewed by Pitts (1959).

The starting-point here was the demonstration by Pitts and Alexander (1945) that acidotic dogs excreted far more acid than could be accounted for by the glomerular filtrate, so that hydrogen ions must be added to the tubular fluid. It was later suggested that this addition of hydrion took place in exchange for sodium ions which were being reabsorbed; the hydrions for this process were derived from the dissociation of intracellular carbonic acid, whose availability was in turn dependent on the activity of carbonic anhydrase. The hydrion entering the tubule fluid was in part 'buffered' by phosphate and other urine buffers; in part combined with bicarbonate to form carbonic acid and ultimately $CO_2 + H_2O$; and in part combined with ammonia to form ammonium ion. Interference with carbonic anhydrase activity, or with any of the later processes of disposal of hydrion in tubular fluid, can lead to anomalies in the acidification of the urine. The process of urine acidification has generally been located in the distal convoluted tubule, but Ullrich and his colleagues have now been able to show by direct sampling that

ion-exchange continues in the collecting-duct system of hamsters (Hilger et al., 1958).

It has become apparent that sodium and hydrion are not the only participants in ion-exchange processes in the renal tubules. It is even possible that the great bulk of cations and anions are reabsorbed in exchange respectively for hydrion and hydroxyl ion, which then form water. The position has been most clearly established in respect of potassium by Berliner and his colleagues (1951). By a most ingenious analysis of the effects of a carbonic-anhydrase inhibitor and a mercurial diuretic on the excretion of hydrion and potassium, they were able to conclude that hydrion and potassium were each added to the tubule fluid in exchange for sodium, and that their excretion by this mechanism was sometimes reciprocal. In this way, urinary acidification could be influenced by the level of potassium excretion, and conversely. There is a good deal of evidence to suggest that filtered potassium is reabsorbed in the proximal part of the tubule, and that the potassium appearing in the final urine represents the product of ion-exchange for sodium in the distal tubule.

All this is somewhat remote from the teleological concepts of an earlier day, such as the selection by the tubules of an 'ideal reabsorbate'. We are indeed a long way from understanding how the kidneys work, but we are beginning to see some kind of pattern which has at least the merit of taking account both of anatomical arrangements, and of cellular activities such as ion exchange which must be general in the body, and not limited to the kidney. The revival of micro-puncture studies, and the use of histochemical techniques, have begun to tell us with more precision where things happen. An approximate 'lay-out' of some of the processes which go to form urine is given in Figure 2. This diagram is of course concerned only with the main stream of urine formation, and omits many substances of whose handling a good deal is known, substances important in themselves, but making only a negligible contribution to total urinary output, such as glucose or uric acid. Still less have I tried to include substances such as inulin or diodone, which have

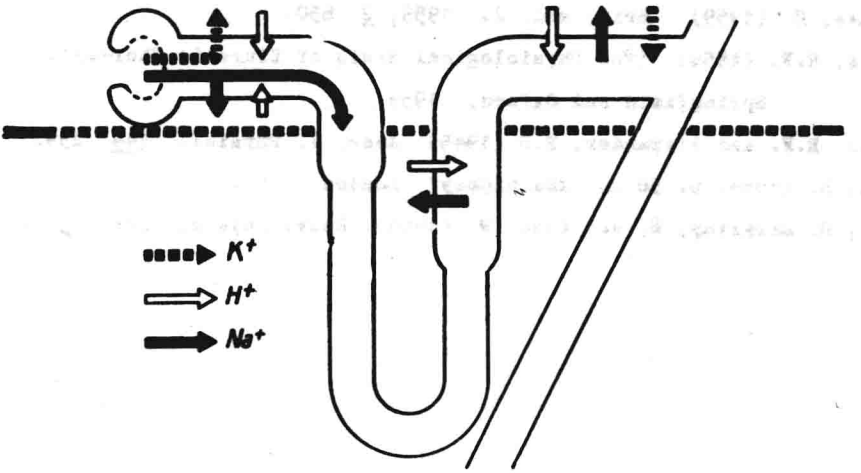

Figure 2. Diagram to indicate the spatial arrangement of some of the processes concerned in urine-formation. In the proximal tubule, the greater part of filtered Na, and probably all the K, are reabsorbed; there may be some entry of H (and OH) into the tubule at this level, and neither aldosterone nor ADH is known to be involved. The thick part of Henle's loop is a likely site of active Na reabsorption in exchange for H; this process is in part or whole responsible for 'medullary hyperosmolarity', and it may be influenced by aldosterone. In the distal tubule, and probably also in the collecting tubules, exchange of Na for both K and H goes on probably under aldosterone control, and the K content and acidity of the urine are determined here. In the production of a concentrated urine, medullary hypersmolarity is set up, and the ADH allows the diffusion of water from the distal tubular system, including the collecting ducts. (The diagram is that of Morel, 1957).

taught us a great deal about the operations of the kidney, but which it normally never encounters.

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Tests of Renal Function

O. M. WRONG

Medical and physiological literature abounds with tests of renal function. As physicans we are mainly concerned with tests that tell us something about prognosis - not so much the length of survival alone, but the hazards attendant on that survival and how they may be prevented and life prolonged by knowledge of the state of renal function. Many of the measurements described in physiological textbooks have little place here. What value is it, for instance, to know the maximum tubular reabsorption of glucose? But some other tests which might seem equally abstruse to the uninitiated are of help. I have chosen to describe a few tests of fairly general application, with particular emphasis on some I use myself.

Glomerular filtration rate Convention demands that I start with the glomerulus. It is certainly very helpful to have some idea of the glomerular filtration rate, both in making a diagnosis of the type of renal lesion present and in forecasting prognosis. At present the inulin clearance is the most accurate measure of glomerular filtration and it is the standard against which other methods should ideally be assessed. However, on this side of the Atlantic we seldom measure inulin clearance. The technique is tedious, but a more important drawback arises from the fact that inulin is a foreign substance which has to be given parenterally. It is difficult to maintain a constant blood level however carefully it is administered, yet the blood level must be constant for each clearance period if the result is to mean anything. Consequently most authorities shorten the periods of urine collection to 10 - 20 minutes and catheterize their subjects to ensure that these small collections are complete (Smith, Goldring and Chasis, 1938). Many of us believe that cathet-