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Renal Function

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by

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PREFACE

The title " Renal Function " limits the scope of the book by excluding discussion of intrarenal mechanisms. In the 40 years since Cushny's " The Secretion of the Urine " appeared renal physiologists have been much concerned with the evaluation of the respective roles of glomerular and tubular function in the production of changes in the urine, and the result has been a literature increasingly dependent on its own peculiar jargon and assumptions, and incomprehensible to general physiologists. The present work originated from a belief that complex discussions of intrarenal mechanisms have obscured a very simple fact: changes in the urine are the results of changes in a very few agents which reach and act on the kidneys. It is therefore hoped that the function of the kidneys in regulating the body fluids will be more clearly presented by describing these agents without the obscuring complexities of the intrarenal mechanisms. In effect, changes in plasma composition etc. are regarded as the input into a mysterious renal " black box ", the urine as its output; and the attempt is made to relate output to input by the direct observation of both, quite apart from ideas of how the " black box " works. The modern physiologist is well accustomed to electronic devices whose internal mechanisms are understood only by the electronic specialist, but which can be used after careful comparison of input and output in the process of calibration.

It seems that the first purpose of a monograph in this series is to provide teachers and advanced students with an account of a specialized topic fuller than can be obtained in text books and more concise than reviews. The general physiologist requires direct narrative, together with sufficient indication of the kind of evidence and argument which have led to it; and will be confused by controversial debate. A direct narrative in a controversial subject involves the personal opinions of the author, which has been justified in prefaces to previous monographs in this series by pointing out that these are monographs, not reviews, and should express the opinion of one worker in the specialized field. Secondly, however, an author is aware that his monograph will be read and criticised by experts, to whom he must supply sufficient

reasons for adopting one interpretation and excluding others. The arrangement of this book is intended to provide for both readers by giving in sections *A* and *B* an account with the minimum of argument, and separately in section *C* the arguments about topics of current debate.

Prefaces are written just after the author has completed his task, when he may be expected to have strong views on the literature of his subject. I have been staggered by the number of papers, appalled by the poor quality of many of them, confused by contradictions of fact and bewildered by arguments which try to fit doubtful experimental results into preconceived theory. Preparing this monograph has involved critical selection of what appears experimentally sound, which is not always the work most extensively publicised. A strong general impression has been that the accuracy attained in renal investigation is much less than might be expected from the apparent simplicity of the processes of collection and analysis of urine, and that failure to appreciate the limitations of experimental data has led to much unsound speculation. In this monograph a deliberate attempt has been made to keep the speculations close to experimental justification, and thus the conclusions are often in the nature of first approximations. Description of the main mechanisms makes, however, a good beginning.

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During the preparation of this book departmental colleagues, Physiological Society Editors and the publishers have been tolerant and helpful and many authors have readily agreed to the use of their figures as indicated in the legends. Acknowledgement of permission to reproduce published figures is due also to the Editors of the following journals: *Acta physiologica Scandinavica; American Journal of Medicine; American Journal of Physiology; Annals of the New York Academy of Sciences; Biological Review of the Cambridge Philosophical Society; Clinical Science; Journal of Applied Physiology; Journal of Clinical Investigation; Journal of Physiology; Proceedings of the Royal Society, B; Quarterly Journal of Experimental Physiology.*

CONTENTS

Section A

AGENTS WHICH ACT ON THE KIDNEYS

EXPLANATION of the object and arrangement of this book can usefully be combined with definition of the particular meaning with which three words will be used: *circumstances* under which urine flow and composition is changed; *agents* which act on the kidneys; *intrarenal mechanisms*.

It is an obvious statement that the volume and composition of the urine is continually changing in response to changes in the environment and activity of the animal. Exercise, change in posture, intake of food and water are all *circumstances* under which the urine changes.

Ingestion of food however does not define what actually reaches the kidney to cause changes in the urine; it is a *circumstance* producing, for example, increased urinary excretion of urea; the *agent* which acts on the kidneys appears to be the plasma concentration of urea, which is increased. Ingestion of water is a *circumstance* which increases the volume of the urine; the *agent* appears to be the blood content of neurohypophysial antidiuretic hormone, which is decreased.

In addition to *circumstances* under which the volume and composition of the urine is changed and *agents*, which act on the kidneys, *intrarenal mechanisms* are involved: the final urine is the result of glomerular filtration, tubular reabsorption or secretion, ion interchanges etc. In this book intrarenal mechanisms are not of particular concern; for example, in Chapter I the effect on the urine of a fall in plasma protein concentration is described without any attempt to decide whether the intrarenal mechanism consists of an increase in glomerular filtration rate. Reference to intrarenal mechanisms, however, sometimes helps the description. The distinction between *circumstances* under which there are changes in the urine, *agents* which act on the kidneys and *intrarenal mechanisms* is important and not always appreciated in speculative discussions of the control of renal function.

This first section (*A*) deals with agents which act on the kidneys. The complexities of urinary composition and the number of

circumstances under which it is altered tend to give the impression that many agents may act on the kidneys. In fact, however, agents which have been established as having actions on the kidney can be listed as in Table 1 under comparatively few headings, and even some of those included in Table 1 have no great im-

TABLE 1.—*Agents which act on the kidneys*

Composition of the blood
- Concentration of individual urinary constituents (Chapters VI, VII)
- Plasma protein concentration (Chapter I)

Arterial blood pressure (Chapter II)

Hormones
- Antidiuretic hormone of the neurohypophysis (Chapter IV)
- Adrenal cortical hormones (Chapter VIII)
- Adrenaline (Chapter III)

The renal nerves (Chapter III)

portance. Section *B* of the book attempts to account, by means of agents already described in section *A*, for the changes in urinary flow and composition which occur during normal function. Section *C* provides a dumping ground for theories which have been extensively considered in recent literature but which are either not relevant to the main argument of the book or, in the author's opinion, not adequately supported by facts. Such theories are discussed separately in order to avoid confusing the other chapters.

The argument in each chapter of section *A* is usually the same. The basis is an experimental circumstance under which urine flow and composition is changed; from procedures such as denervation of the kidneys, comparison with the effects of hormones, there is evidence that the urinary changes are due to the effect of the kidney of one agent; the urinary changes are then described as the effect of that particular agent. For example, in Chapter I the

urinary changes produced by ingestion of 0.9% sodium choride (circumstance) are described as the effect on the kidneys of dilution of the plasma protein (agent), because of evidence in the first paragraphs which shows that no other agent is acting. Attention is drawn to this first essential step in the argument as it is often almost self-evident and usually occupies only a small introductory paragraph.

In each chapter there is usually a graph relating the agent to changes in urinary composition; for example, in Chapter I plasma protein concentration to rate of excretion of sodium. The fact that the graph can be plotted is not evidence that the relationship is causative. In experiments in which 0.9% sodium chloride is ingested dilution of plasma protein, increase in the volume of extracellular fluid or plasma, increase in glomerular filtration rate are inter-related because all are proportional to the amount of saline retained in the body, and a similar relationship would therefore be obtained if any one of these factors were plotted against sodium excretion. The sole purpose of the graphs is to express quantitatively the effect of an agent already accepted as acting on the kidney.

The experiments discussed in section *A* are mostly of short duration and on conscious dogs. It avoids complications if discussions are confined to one species and the dog is the obvious choice, since there has been more work on this than any other species and there is also the advantage that operative procedures like denervation of the kidneys can be used. As far as possible each chapter is provided with an account of parallel findings in human subjects. Section *A* is mostly based on experiments lasting for only a few hours. In short experiments control values are more readily established and the results thus achieve greater accuracy than in experiments lasting for several days such as are more considered in section *B*. Also in short experiments there is not time for the effects of the primary agent to set up secondary changes in other agents which act on the kidneys.

I

PLASMA PROTEIN CONCENTRATION

THIS chapter describes the effect on the urine of changes in the plasma protein concentration, based on experiments in which dilution of the plasma protein resulted from ingestion or infusion of " physiological saline ", i.e. 0·9% sodium chloride or mixtures of sodium and potassium salts more closely resembling the ionic composition of plasma.

O'Connor (1955, 1958) has given reasons for attributing to dilution of the plasma protein the urinary changes which are about to be described. They are prevented if protein is added to an infusion of saline (Bojesen, 1954); they occur unaltered after denervation of the kidneys and differ in time course and nature from the effects of any hormones known to act on the kidneys; they occur in the absence of changes in the plasma concentrations of sodium, chloride or other ions. In brief, the immediate effects of the ingestion of 0·9% sodium chloride cannot be accounted for by the agents described in the other chapters of this section; whereas, as will be seen below, they can be related to changes in the plasma protein concentration. Consequently it is possible in this chapter to describe the renal effects of fall in plasma protein concentration (agent) by describing the urinary changes produced by ingestion of saline.

THE EFFECT IN THE DOG OF 0·9% SODIUM CHLORIDE

Sodium Excretion. The most obvious effect of the ingestion of an isotonic solution of sodium chloride is to increase the rate of excretion of sodium and chloride, but the extent and characteristics of the increase may present different pictures illustrated by the examples of Figs. 1 and 2.

Fig. 1 shows the urinary changes produced by 100–250 ml. of saline by stomach tube or intravenous infusion in a dog which had received on the days before the experiment no sodium salt except the 15 m-equiv/day contained in the diet; this type of response was particularly described by O'Connor (1958). Sodium excretion

was increased (line *UV*); the volume of the urine (line *V*) did not increase much above 0·1 ml./min; the increased rate of excretion of sodium was mainly due to an increase in the concentration of sodium in the urine (line *U*).

On the other hand Fig. 2 shows the response to the ingestion of saline when the dog had been given doses of 300 ml. of 0·9% sodium chloride on the days before the experiment and a final

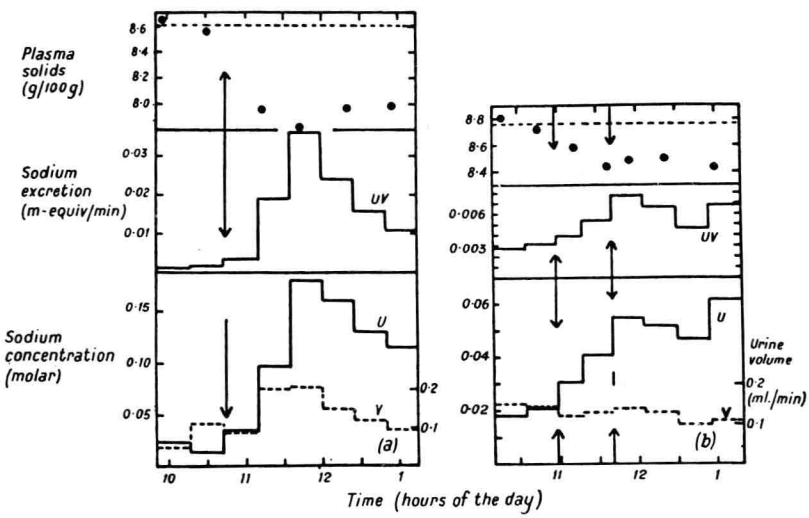

Fig. 1. *Effect of dilution of plasma protein*

Urinary excretion of sodium by a dog (*a*) following the administration of 250 ml. of 0·88% sodium chloride by stomach tube at the time marked by the arrow, (*b*) following the intravenous infusion of 100 ml. of 0·85% sodium chloride at 2·33 ml./min during the period between the arrows. No priming doses of saline had been given (O'Connor, 1958).

priming dose of 200 ml. about four hours before the test dose, the response to which is shown in the figures; this type of response was particularly considered by O'Connor (1955). Due to the priming doses of saline, the initial rate of excretion of sodium in each of the two experiments of Fig. 2 was about 0·1 m-equiv/min and this was raised by the infusion or administration of 350–400 ml. of saline by stomach tube to 0·5 m-equiv/min (line *UV*); in this type of response the increased excretion of sodium was due to an increase in the volume of the urine (line *V*) with practically no change in the urinary sodium concentration (line *U*).

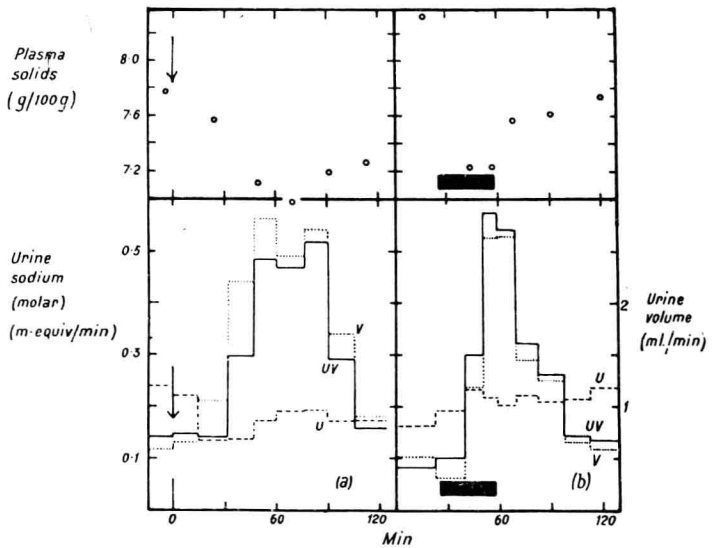

Fig. 2. *Effect of dilution of plasma protein*

The excretion of sodium by a dog (*a*) given at zero time 350 ml. 0·9% sodium chloride by stomach tube and (*b*) 400 ml. of 0·675% sodium chloride, 0·32% sodium bicarbonate by intravenous infusion in 33 min. Line *V*, urine volume (scale on right); line *U* urinary concentration and *UV* rate of excretion of sodium (scale on left). Priming doses of saline had been given on the day before and 4 hr before each experiment (O'Connor, 1955).

The increased excretion of sodium followed very soon after the entry of saline into the circulation. For example in Figs. 1*b*, 2*b* the rate of excretion of sodium rose progressively to a maximum at the end of the infusion, and in Fig. 2*b* fell from that maximum as soon as the rapid infusion was ended. In all experiments the time course of the changes in the urinary excretion of sodium followed closely the dilution of the plasma solids—any delay appeared to be less than 10 min.

Anion Excretion. Increased excretion of sodium must be accompanied by anions. In Fig. 2*b* the infusion fluid was such that there was no change in the plasma concentrations of chloride and bicarbonate; when sodium excretion increased to 0·53 m-equiv/min chloride was 0·40 m-equiv/min and the difference represents increased excretion of bicarbonate (for further discussion see p. 79). The effect of dilution of plasma protein may

thus include excretion of bicarbonate in which case the urine will become alkaline (see p. 83). The excretion of other anions, e.g. sulphate and phosphate, is a little increased (Lotspeich, 1947; Pitts and Alexander, 1944).

Potassium Excretion. Administration of 0·9% sodium chloride also produced increased excretion of potassium. Table 2 shows the changes in the urine when two doses of saline were given by stomach tube on the same day. Urines 2, 3 show changes in

TABLE 2.—*The effect in a dog of* 0·9% *sodium chloride by stomach tube* (O'Connor, 1958)

	Time	Volume ml./min	Sodium		Potassium		Urea		Plasma solids g/100g
			m-equiv/min	M	m-equiv/min	M	m-equiv/min	M	
1.	9.52–10.42	0·08	0·0013	0·017	0·0021	0·026	0·100	1·25	8·61
2.	12.00–13.15	0·12	0·017	0·14	0·0095	0·079	0·095	0·79	7·98
3.	14.31–15.11	1·12	0·28	0·25	0·017	0·015	0·115	0·10	7·61

At 10.45 250 ml. and at 13.18 400 ml. of 0·88% sodium chloride was given by stomach tube. The figures under sodium, potassium and urea give the urinary excretion (m-equiv/min) and urinary concentration (Molar).

sodium excretion of the two types described above and in each case there was a small increase in the excretion of potassium. From comparison with blank experiments O'Connor (1958) concluded that the increased excretion of potassium was only partly accounted for by diurnal variation in the excretion of potassium, and that about half the increase shown in Table 2 could be attributed to an effect on potassium excretion of the ingestion of 0·9% sodium chloride. Certainly the large increase in sodium excretion which resulted from a second dose of saline was never accompanied by a comparable increase in potassium excretion, and as the urine volume increased the urinary concentration of potassium fell.

Urea Excretion. During each of the collection periods in Table 2 the rate of excretion of urea was 0·095–0·115 m-equiv/min. In blank experiments (O'Connor, 1958) urea excretion fell by about 10% between 10 a.m. and 3 p.m. so that a small increase in the rate of excretion of urea may be attributed to the ingestion

of 0·9% sodium chloride, but the increase is too small for it to be established with any certainty. Again the increased urine volume in the third collection period of Table 2 was associated with a fall in the urinary concentration of urea. The excretion of most urinary constituents is affected in the same way as urea. Dilution of plasma protein by saline produces only small increases in the excretion of creatinine, inulin and other glomerular substances (see Chapter XVII).

Urine Volume. To complete the description of the effect of ingestion of saline, here regarded as the effects of fall in plasma protein concentration, further reference must be made to the changes in the urinary volume. In dogs given their test dose after preliminary doses of saline, the urine volume and rate of excretion of sodium usually increased together as in Fig. 2*a*. In about a third of the experiments, as in the example of Fig. 16*a*, urine volume increased to 3–4 ml./min 30–40 min after the test dose of saline and then fell in the next 20 min to below 2 ml./min. In such responses the rate of excretion of sodium and chloride followed a course similar to that of Fig. 2 so that at the time of the greatest diuresis urinary excretion of sodium and chloride was still rising. During the initial diuresis the urinary concentration of sodium and chloride fell to about 0·05 M. Responses like that of Fig. 16*a* may be regarded as consisting of the usual response of increased sodium excretion with the addition during the first 60 min of a polyuria resembling a brief water diuresis. The resemblance to a water diuresis is suggested also by the finding of O'Connor (1950) that the high urine flow of the first hour can be abolished by small infusions of extract of the posterior lobe of the pituitary (Fig. 16*b*). A similar " water diuresis " following the ingestion of saline has also been observed in man (p. 12).

Relationship between sodium excretion and plasma protein concentration. In experiments like those of Figs. 1, 2 and Table 2 the total solid content of the plasma (i.e. dry weight expressed as g/100g water) was determined as a quick method of following changes in plasma protein. Total solids in plasma include about 0·9 g/100g of sodium salts which does not change appreciably when saline is given and also about 1 g/100g of solids other than protein (fats, lecithin, etc.), which will be diluted along with the

protein. For comparison with determinations of plasma protein a simple adjustment is merely to subtract 2 g/100g from the values of plasma solids. Often determinations of plasma protein are based on measurements of specific gravity, which means that the published values are derived by an equally arbitrary formula.

It is apparent from Figs. 1, 2 that changes in sodium excretion follow a similar time course to the curve showing the dilution of the plasma solids and any delay is no more than 10 min. Because

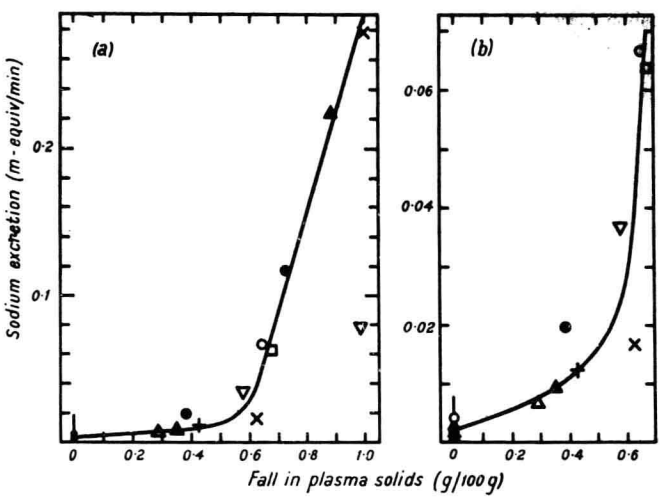

Fig. 3. *The relationship between sodium excretion and plasma solid content in eight experiments on one dog*

A separate symbol is used for each experiment. (*a*) and (*b*) show the same data, but the ordinate scale of (*b*) is more open to show the lower part of the curve more clearly (O'Connor, 1958).

there may be some small delay, quantitative comparison is best made during urine collection periods like those in Table 2 when neither the urine nor the plasma solids were changing rapidly. In Fig. 3 the results of 8 experiments on the same dog are plotted, the rate of excretion of sodium as ordinates and the fall of plasma solids below the initial value on each day as abscissae. With the exception of one aberrant value, the points lie in relation to the curved line drawn by hand in Fig. 3 and curves of similar shape, with similar scatter of the individual observations were also found by O'Connor (1958) with 2 other dogs. A similar curve (Fig. 7) was also found by Bojesen (1954). The shape of the curves may