The Urinary Function of the Kidney

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To

EDWARD FREDERICK ADOLPH

revered teacher

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A. V. W.

Foreword

By making available this informative and thought-provoking book, my colleague, Dr. A. V. Wolf, has performed a brilliant and timely service to those who wish to keep abreast of the developments in renal physiology and related fields. Many investigators and clinicians are dissatisfied today with questionable hypotheses that have gained widespread acceptance, largely through a process of repetition. They will welcome the opportunity to revise outmoded concepts regarding body fluid and electrolyte metabolism in health and disease.

Dr. Wolf draws from his own extensive background as investigator and teacher and from the abundant literature on the subject. His original integration of established facts, old and new, advances the reader's ability to understand variations in volume and composition of urine under different conditions. The quantitative view stressed by the author is of great import; it is particularly practical in the treatment of the problems of thirst, diuresis, and steady states. Dr. Wolf has keen insight into the needs of the physiologist, the clinician, and the pharmacologist. He clarifies such intricate subjects as the regulation of body volumes as compared to body concentrations; the problems of absolute and relative dehydration and hydration; renal regulations; and the endocrine relationship to urine volume and composition. His classification of edemas should gain universal acceptance.

Many, like myself, will appreciate the author's singling out of commonly employed terms that are ambiguous or meaningless and his efforts to replace them with logical and exact expressions. This example in semantics might well be heeded by those who plan reviews of other topics in the biological sciences.

The monograph is documented with the most extensive bibliography thus far published in this field; its value to the investigator is obvious. I was pleasantly impressed by the arrangement and structure of the book. Text and illustrations are well balanced and there is a useful system of cross references.

I consider myself privileged to have been called upon to introduce Dr. Wolf's "The Urinary Function of the Kidney." It is a much needed, refreshing review; a book that seems destined to achieve the status of a classic.

Harold C. Wiggers, Ph.D.

Albany, N. Y.
May, 1950

Preface

THE experimental partitioning of glomerular and tubular functions which has appeared feasible in recent years, and which depends upon the behavior of substances supposed to be susceptible of unique renal processing, has led to a characteristic pattern of thinking about renal function. In this pattern, renal excretion is conceived at once in terms of that euphonious synonym, *clearance,* and in terms of the more obvious anatomy and topology of the kidney. Many see in this the substantial basis for a modern theoretic physiology, forthright in its methods and happily attractive to the analytically minded.

There is another pattern of thinking which differs in that it emphasizes regulation rather than excretion. It is described here as the urinary function of the kidney. Those who share this view do not imagine it is the final aim of the kidney to "clear" things, nor do they sound other insistent notes of orthodoxy. In the regulatory view, excretion is only one thermodynamic facet of the total effort of the kidney. The urine is regarded as a physiologic unit, sui generis, whose formation and removal permit the body to maintain its substance and volume in the face of continuous and varying activity of other emunctories, and of paths of intake. Thus, what the kidneys do represents the difference between what must be done to maintain normal living states and what is being done to this end by all extrarenal activities.

Basically, the two concepts deal with the same problems but, for example, where the concept of clearance stresses the independence of separate excretory systems for substances like water, sodium, and bicarbonate, the concept of regulation stresses an interdependence in varying degrees between these systems. Little has been done so far to harmonize the differences between these two views. One trouble seems to be that renal physiology suffers from a paucity of facts which have meaning for other fields. It is partly in this regard that I have tried to integrate aspects of renal function, water balance, and electrolyte metabolism in ways which seem to me instructive or provocative. If there seems to be an untoward preoccupation with the vicissitudes of urinary flow it comes not simply by predilection but by way of the desire to bring into some order an agglomerate of information which has been long neglected for the more glamorous fields of renal physiology.

It is difficult for me to avoid some mention of the curious multiplicity of hypotheses which afflicts renal physiology, since it is my belief that few deserve consideration for having breadth. Except for some few detached scientists, most investigators usually observe only what their minds are prepared to observe, and dwell on those facts which best fit their ideas, to the exclusion of others. The effect has been to engender perennial oversimplifications. Too many delude themselves that their experiments have demonstrated this or that functional relation, and lack of space in our scientific journals appears to protect hypotheses from suffering sustained and calculated attack.

Viewed historically, hypothesizing about the kidney seems to have little more validity for having stemmed from authority. Certain important critical views of even learned renal physiologists are unimpressive in retrospect. Much has been said, for example, of the too great defensive strength of an old "secretion" theory and we were once cautioned to take no refuge there until the resources of a "reabsorption" theory were exhausted. But what flights of fancy were sustained along with the stubbornly persistent belief in the latter theory at a time when it was manifestly at odds with sober evidence. Investigators still feel impelled to generate appealing hypotheses concerning the precise measurement of glomerular filtration, renal water conservation, or the independence of tubular reabsorptive processes even though these ideas are contingent and possibly unverifiable. Fortunately, they have just enough substance to stimulate further research.

No special hypothesis, much less theory, of renal function is proposed in this book. If it tells the reader that, in the writer's opinion, clearance analysis is, in general, as empirical as other analysis and that the illusion to the contrary is the dry rot of modern renal physiology, it nevertheless treats these differing contentions side by side. The writer admits freely that he does not always know when he is rationalizing his own persuasions, or applying without warrant his limited experience, or otherwise indulging the Idols of the Cave. In consequence (and not by perversity alone) the following pages are occasionally agnostic where to others the physiological faith seems clear.

It is a pleasure to declare here my indebtedness to some of those who helped to fructify this work—to Dr. Harold C. Wiggers, Professor of Physiology and Pharmacology of the Albany Medical College, for his warm and effective encouragement; to Agnes E. Mullin and Wilma Whitney, faithful technicians who have contributed to the original researches reported herein and to dreary tasks of checking references and other bookish things; to Dr. Herta R. Leng, Associate Professor of Physics of the Rensselaer Polytechnic Institute, for enlightening discussions of urinary physics; to Marion F. Dondale and Helen A. Fraser, librarians of the Albany Medical College Library, who caused the accumulation of reference material to appear almost painless; to Charles H. Tracy, for adapting so many diagrams as figures for this book; and to my wife, Orietta, who helped to make whatever is, scrupulous.

Financial support from the U. S. Public Health Service made possible the original research reported here on fluid transfers among interstitial compartments and the function of the plasma as a conductor of fluid. Grants from the Dazian Foundation for Medical Research (which supported in 1945–1946 much of the work reported here and elsewhere, and which has come generously to my aid once again), from the Winthrop Research Fund of the Albany Medical College, and from the Department of Physiology and Pharmacology of the Albany Medical College defrayed part of the cost of publishing this book.

A. V. Wolf, Ph.D.

Albany, New York
May, 1950

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CHAPTER I

The Urinary Function in Water Balance and Fluid Transfer

1.1. One of the useful abstractions of theoretic physiology is the balance concept. Perhaps the simplest definition of a balance is the expression

$$\text{Balance} = \text{Gain} - \text{Loss}$$

An organism in balance is defined as one that maintains constant, within measured limits, the contents of one or more specified body components[16]. In practice a state of balance must be defined arbitrarily except under unusual experimental conditions. Intakes (gains) are not physiologically constant or uninterrupted; neither are outputs (losses). We often call the "normal" or the usual state one of balance, that is, *zero* balance, and we choose elapsed intervals of observation so that in the normal state the balance formula equates to zero. If, in this chosen interval, intake (and, therefore, rate of intake) is greater than output (or rate of output), the balance is called positive. When output exceeds intake, then conversely, the balance is called negative. In mammals, intake is usually intermittent and output continuous. The usual balance obtains when neither intake nor output is forced, when there is neither privation nor manipulative procedure, and where sufficiently long periods (usually 24 hours) elapse so that rhythms of feeding and sleeping shall be minimized.

Zero balance is a critical equilibration point. With respect to water a man comes into zero balance at meal times, when we suppose he has no excesses or deficits (positive or negative loads, respectively). If he then loads himself with water by forced ingestion or infusion, regulatory mechanisms come into play to reduce the water load to zero. In the absence of excessive sweating, the reduction of a large positive water load is usually, and mainly, accomplished through renal action, that is, urinary flow augments. A negative load of water or absolute dehydration usually calls forth a compensatory mechanism in the form of reduced urine flow which favors the restoration of water balance by decreasing the difference between intake and output.

1.2. *The Water Balance Statement in Man.* Table I provides an account of the water balance which might be found in an average man in some temperate environment, and the traffic borne by the various paths of intake and output. Its division of intakes and outputs into obligatory and facultative portions emphasizes the extensible nature of the water balance which can be attained at greatly different levels of water exchange. The *obligatory urine volume* is defined by Ambard and Papin[37] as that minimal volume of urine compatible with the excretion of the solid material contained therein. It forms daily even when fluids or food intake may be zero. Its rate of formation is the *obligatory urine flow.* The *facultative urine volume* is any excess above the obligatory urine volume, determined by ingestion, and supposedly

TABLE I

A water balance statement for normal man (cc. per 24 hours).

	Intakes		Outputs		
	Obligatory	Facultative	Obligatory	Facultative	
Drink	600	600	600	600	Urine
Water in food (preformed)	700	0	400	0	Skin
Oxidative water of food (potential, metabolic)	300	0	400	0	Lungs
			200	0	Feces
Subtotals	1600	600	1600	600	Subtotals
Total	2200		2200		Total

independent of physiological requirement. In the balance statement we observe a 600 cc. obligatory "drink" intake offset by the obligatory urine volume of 600 cc. since the sum of the water contained in the normal food intake, plus the "potential" water of food which arises from its oxidation, offsets the obligatory outputs of skin, lungs, and feces.

Oxidative or "metabolic" water[12] is nearly proportional to the calorific value of food, 1000 Calories yielding about 100 to 140 grams of water. The total water requirement is roughly equal to 1 cc. per Calorie. During starvation almost no exogenous water is required by the body. Dogs, for example, ingest only one-quarter the usual amount of water upon interspersed days when no food is given[12, 602].

Richter[905] states that the average voluntary daily intake of water in rats, cats, dogs, monkeys, and man is 1142 cc. per square meter of surface area, that is, is proportional to metabolic rate and surface area rather than body weight. However, Adolph[16, 19] finds, for mammals varying in size from elephant to mouse, that the rate of water intake varies with the 0.88 power of the body weight, the heterogonic equation being

$$i = 0.010B^{0.88} \tag{1}$$

where i is rate of water intake in grams per hour and B is body weight in grams.

In a hot, desert environment the facultative water output of the skin in the form of sweat may amount to several liters daily[20]. Similar water loss through the feces occurs in diarrhea. In these instances a water balance can be struck through appropriate adjustments in the intakes, chiefly by drink which is obligated in larger quantities. Clinically it becomes difficult to manage the water balance account of an individual as his condition deviates from the physiological normal, especially where the extent of the excess or deficit is not well known or the magnitude of output is not accurately gaged. For example, in most fevers no sweat is produced in the early stages in spite of a considerable rise in body temperature[629] whereas profuse sweating is a regular symptom of the defervescent stage. In hyperthermia the basal metabolic rate increases about 13 per cent per degree C. A rough approximation, based on a water loss of one cc. per Calorie, suggests an increased loss of 13 per cent more water per degree C. of fever. The proportionality between energy metabolism and insensible loss has been reviewed by Peters[841]. The physiology of balance suggests for therapy that we create small positive water loads to cover deficits beyond the immediate requirements, and so long as mechanisms of water output retain sufficient total integrity, our attempts to restore a working balance will not appear clumsy. However, the difficulties of artificially achieving balance are increased as regulatory mechanisms become impaired. If the urinary function of the kidney is reduced too far, any therapy aimed at establishing balance becomes, in some way, the wrong therapy.

1.3. *Water Intoxication.* Many substances, if administered rapidly and steadily, accumulate in the body as toxic loads. Often the rate of growth of a load decelerates as excretion rate approaches intake rate but occasionally the kidneys become unable to cope with a rapidly developing load. They suffer a diminished ability to excrete, and load growth is accelerated. Either of these conditions can be found when water is taken in rapidly and the syndrome of water intoxication may occur. Rowntree[916] has described this syndrome. In various mammals, it is characterized by restlessness, asthenia, polyuria, pollakiuria, occasional hematuria[410], diarrhea, salivation, frothing at the mouth, nausea, retching, vomiting, tremor, muscle twitches, ataxia, tonic and clonic convulsions, collapse, stupor, coma, and death in cardiac failure. There is hemodilution, including a decrease in serum crystalloids. Oliguria is occasionally present. The condition can be acute or subacute, lasting for days (§6.3). It can be prevented and usually cured by the administration of intravenous hypertonic sodium chloride or by oral administration of salt.

According to Smyth, Deamer, and Phatak[1010] neither water retention in the body nor hemodilution are the most essential features of so-called water intoxication. They considered the convulsive symptoms to be more closely associated with loss of systemic chloride by way of the gastric secretion and the resulting alkalosis, noting that the loss of chloride by way of the kidneys is only about one-tenth the total loss while the greater loss is by way of vomitus. In the absence of vomiting, as in the rabbit, the water in the stomach takes up chloride so the loss of this ion is effectively the same. In this way chloride falls below its renal threshold in the plasma and is withheld from the urine, but its subthreshold concentration does not prevent its diversion from blood to stomach. Atropinized dogs do not develop symptoms of water intoxication so readily presumably because gastric loss of chloride is minimal. Although these authors suggested that the effect of sodium chloride in relieving symptoms is so dramatic as to make it appear that chloride is more important than water in the syndrome, this is based on no quantitative evaluation of the relative importance of salt and water. "Heat cramps" or "miner's cramps"[20] present a picture similar to that of water intoxication. Since these are relieved by salt or saline they may constitute a type of water intoxication in which, instead of an absolute hydration or positive load of water in the body, there is a negative salt load. Further, urea diuresis, which is not highly chloruretic, is said to alleviate the symptoms of water intoxication. It is difficult to avoid the conclusion that both conditions are closely dependent on a lowered ratio of salt to water in extracellular fluids.

Several authors have described water intoxication in human subjects. Positive water balance with primary elevation of intake is seen in psychiatric polydipsia. The case is reported[63] of a dementia praecox patient who drank excessive quantities of water with resulting convulsions and coma, but with subsequent recovery. Death in convulsions has followed a cholecystectomy when 9 liters of water were absorbed by proctoclysis within 30 hours[529]. Reduction of urinary water output together with elevation of water intake has also been studied. McQuarrie and Peeler[759] have induced grand mal seizures readily in epileptic subjects under pituitary antidiuresis by excessive water loading. These effects are prevented by sodium chloride administration and are thus correlative with water intoxication.

1.4. *Susceptibility and Resistance to Water Intoxication. Renal-Adrenal Relations.* Gaunt[409, 410] has shown that after adrenalectomy in rats, diminution in the ability to sustain a water diuresis occurs along with an increased susceptibility to water intoxication. There is a delayed intestinal absorption of water as well as delayed excretion of absorbed water. After large doses of water there is a lowering of plasma chloride and the hematocrit rises sharply, the latter probably reflecting an osmotic swelling of erythrocytes in their hypotonic medium. The body temperature falls sharply, providing an excellent measure of the extent of water intoxication in normal and adrenalectomized animals.

Adrenal cortical extract and desoxycorticosterone acetate exert a protective action against water intoxication[352, 407]. Large doses of these in normal rats will prevent intoxication which would otherwise occur with large water intakes. Whole cortical extract appears to be better in this regard than DCA, and compound E (17-hydroxy-11-dehydrocorticosterone) was found three times as effective as DCA. The amorphous fraction is only weakly effective when compared with whole extract of equal potency in maintaining life in the adrenalectomized dog.

Resistance to water intoxication is also raised in rats by giving water orally in increasing but nontoxic doses for 5 days[660]. Such resistance is not entirely dependent on the characteristically increased rate of diuresis (§8.7) since with vasopressin toxic symptoms are less at given water loads.

1.5. *Water Deprivation.* Just as renal activity can fail to prevent water intoxication, it can also be ineffective in neutralizing dehydrating influences. McCance and Young[752] found that human subjects who had lost up to 7 per cent of their body weight in three or four days could, following large doses of sodium or potassium chloride in relatively small volumes of water (18 g./500 cc. water and 12 g./100 cc. water, respectively), sustain a diuresis which led to a fall in the urine:plasma osmotic pressure ratio. Thus, as water excess does not carry the insurance of compensatory renal excretion, neither does water deficit necessarily bring restriction of urinary flow; and the composition of the urine is not necessarily conducive to the maintenance or restoration of normal plasma concentration. In fasting there is an initial diuresis and an increased negative water balance during water deprivation[1148]. On a standardized diet daily water output depends on salt intake, within limits, and is possibly regulated by factors other than plasma concentration.

1.6. *Equilibration.* Excesses or deficits of water, when carried to extremes, elicit renal responses which no longer follow the physiological pattern. When an excess of water becomes too great, diuresis may fall off[476, 1171]; and we may believe this to be some acknowledgement of overwhelming stress. When deficits of water become too great or salt excesses relatively too large, the kidneys, instead of further increasing urinary concentrations of minerals, may decrease them and at the same time increase water output[752, 886]. Both actions appear inconsistent with what might be supposed desirable and, indeed, there seems to be no theoretical justification for regarding either of these actions as favorable to the body economy. In a larger sense, however, the dipsogenic effect (§6.4, 7.12) here would be expected to favor the ingestion of water which in turn would tend to restore salt-water balances. It would not be surprising if such processes become explicable in some future science of "metaphysiology" whose subject matter deals with the laws of stress beyond the physiological.

In contrast to renal decompensations which are revealed only after sufficient provocation, the normal or physiological pattern is patently calculated to undo the effects of lesser provocation. There are well defined limits of excess or deficit within which renal and allied responses vary in some proportion to the stresses applied and undo or minimize strains. The equilibration diagram of Adolph[16] which evaluates the renal and extrarenal processes acting to re-establish and maintain water balance in man describes these nicely (Fig. 1).

Factors in Fluid Transfer

1.7. *Tonicity and Osmotic Pressure.* A red blood cell suspended in a salt solution of such concentration that no net flow of fluid crosses the cell membrane, that is, so that the cellular volume remains unchanged, is said to be in an isotonic solution.* This solution may or may not

* An isotonic (isoplethechontic) solution for rabbit erythrocyte is one containing 1.12 per cent sodium chloride[869].