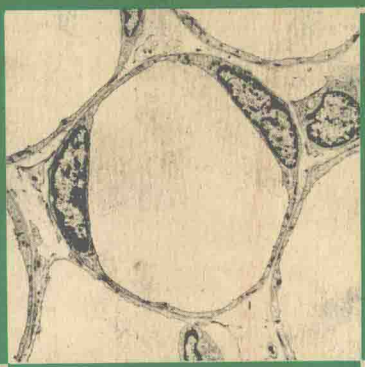
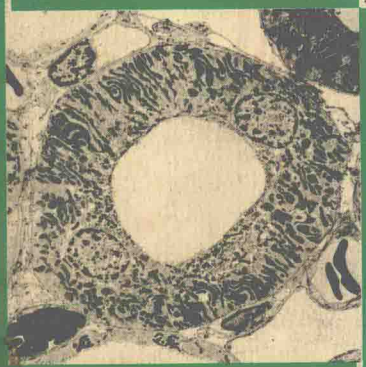
urinary concentrating mechanism

Structure and Function





Rex L. Jamison

Wilhelm Kriz

Urinary Concentrating Mechanism:

STRUCTURE AND FUNCTION

REX L. JAMISON, M.D.

Associate Professor of Medicine,
Stanford University School of Medicine
Head, Division of Nephrology,
Stanford University Hospital

WILHELM KRIZ, DR. MED.

Professor of Anatomy and Chairman, Anatomical Institute,
University of Heidelberg

New York Oxford
OXFORD UNIVERSITY PRESS
1982

Library of Congress Cataloging in Publication Data

Jamison, Rex L
Urinary concentrating mechanism.

Bibliography: p.
Includes index.
1. Kidneys. 2. Renal tubular transport.
I. Kriz, Wilhelm, 1936– joint author.
II. Title. [DNLM: 1. Kidney concentrating ability. 2. Kidney medulla. WJ303 J32u]
QP249.J35 599.01'49 80-18260
ISBN 0-19-502801-5

Printing (last digit): 9 8 7 6 5 4 3 2 1

Printed in the United States of America

Urinary Concentrating Mechanism

To Dede and Heidrun

Preface

> There are ancient cathedrals which, apart from their consecrated purpose, inspire solemnity and awe. Even the curious visitor speaks of serious things, with hushed voice, and as each whisper reverberates through the vaulted nave, the returning echo seems to bear a message of mystery. The labor of generations of architects and artisans has been forgotten, the scaffolding erected for their toil has long since been removed, their mistakes have been erased, or have become hidden by the dust of centuries. Seeing only the perfection of the completed whole, we are impressed as by some superhuman agency. But sometimes we enter such an edifice that is still partly under construction; then the sound of hammers, the reek of tobacco, the trivial jests bandied from workman to workman, enable us to realize that these great structures are but the result of giving to ordinary human effort a direction and a purpose.
>
> (Gilbert Lewis and Merle Randall in their Preface to *Thermodynamics*, published by McGraw-Hill in 1923)

The subject of this book may be likened to a cathedral in two ways. The extraordinary structure of the mammalian renal medulla is surely one of nature's architectural masterpieces, inspiring in the observer the same feelings of wonder and admiration that one experiences when viewing a great cathedral like the one at Reims, for example. On the other hand, the construction of an hypothesis which explains how the kidney concentrates urine is still in progress and, like the masons or carpenters working on one portion of the nave, we cannot visualize the final edifice. Nevertheless, there is reward for those involved in or watching its construction, as scaffolding is finally removed to reveal a newly finished section.

The purpose of this book is to describe clearly the structure and function of the mammalian renal medulla with regard to the mechanism of urinary concentration and dilution. The last book on the same subject, by Dicker, was published eleven years ago (146). Beautifully written, its main theme was that the countercurrent

multiplication mechanism by the loop of Henle had been firmly established. In the final chapter, Dicker discussed some important unsolved problems, among them the failure to take into account the peculiar anatomy of nephrons (particularly in the medulla), the paucity of information concerning the microcirculation of the medulla, and the fact that the then current views of the concentrating mechanism rested heavily on micropuncture experiments in anesthetized animals.

Those familiar with the subject will realize the wealth of new experimental evidence and the several new hypotheses which have been published since Dicker's book was written and appreciate the availability of a new account which incorporates, indeed emphasizes, the accomplishments of the past decade. In the stout belief that structure underlies function and that nowhere is this more dramatically evident than in the renal medulla, we have threaded chapters and sections about anatomy and ultrastructure among those concerning nephron and tubule into a closely knit fabric, hoping that the pattern will be more easily discerned.

We have limited the scope of the book. Among the subjects not covered at all, or not extensively, are the molecular mechanism of action of antidiuretic hormone, neonatal development, comparative physiology, and clinical disorders of the concentrating mechanism. We have tried to achieve a balance between what is well established and familiar on the one hand and what is controversial, exciting, and novel on the other, being careful to distinguish between the two.

This book is intended for those who wish to understand how the mammalian kidney forms a urine of widely varying total solute concentration. We hope it will be found useful by those embarking on an investigative career, or contemplating such an embarkation; and by established researchers and teachers interested in the kidney. To our peers and colleagues whose work helped shape the present account, we hope we have described their work accurately and that they will consider the views presented as fair. References are usually cited in chronological, rather than numerical, order.

We wish to acknowledge the technical assistance of Saliha Sabanović, Bruni Koura, and Ingrid Hartmann; Ingrid Ertel, photographer; Richard Neckenauer, artist; and the staff of Medical Illustration at Stanford. Dr. Brigitte Kaissling contributed much of the work on ultrastructure. Prof. Dr. Roland Taugner and Dr. August Schiller (Physiological Institute, Heidelberg) collaborated on all freeze-fracture electron micrographs. Dr. Lise Bankir (Necker Hospital, Paris) prepared or helped prepare all vascular casts. Drs. Jose Arrascue, Michael Barrett, Carlos Battilana, John Buerkert, Dennis Dobyan, David Gelbart, Gene Gussis, Gunther von Hagens, Paul Johnston, Kevin Lemley, Phillip Pennell, Veeraf Sanjana, Klaus Tiedemann, Herbert Weber, Fred Weisser, and especially Frank Lacy collaborated on some of the work cited from our laboratories. Our colleagues, Alan Michaels, Bryan Myers, Ralph Rabkin, Robert Swenson, Michael Weiner, and especially Dennis Hall, Roy Maffly, and Channing Robertson contributed hours of discussion, criticism, and comments.

The research performed in our laboratories would not have been possible without generous support from Deutsche ForschungsGemeinschaft, the National Institutes of Health, the American Heart Association, the California Heart Association, the National Kidney Foundation, the Kidney Foundation of Northern California, the John and Mary Markle Foundation, the John Simon Guggenheim Foundation, Hoechst Pharmaceutical, Merck, Sharpe and Dohme, Stanford Satellite Dialysis Center, Inc., Mr. and Mrs. Rachford Harris, and Mr. and Mrs. George Kwong.

We owe a special debt of gratitude to Maria Goos and Darlene Vian who did all the typing and to Brenda Jones and Jeffrey House of Oxford University Press for their careful editing, unlimited patience, and constant encouragement.

To each one we offer our deepest thanks.

Stanford R.L.J.
Heidelberg W.K.
April 1980

Contents

I

Introduction to Function

1

General Description of Water Diuresis and Antidiuresis

It is the purpose of this chapter to describe the changes in urinary flow and composition that maintain a normal state of body hydration. The rest of the chapters are devoted to explaining the mechanism by which those changes are produced.

When a large volume of water is swallowed, there is usually a delay of 10 min until urinary flow begins to rise, 50 min until the response reaches its maximum intensity, and about 90 min until flow returns to its original level (Fig. 1-1) (333). This time course of events is almost universal in man and other mammals, but it is useful to focus on the rodent, for over the past 20 years much of the progress in understanding urinary concentration and dilution, from both a structural and a functional point of view, has been based on experiments in various rodents (and the rabbit as well).

Water diuresis may be induced in an awake, restrained rat by the continuous intravenous infusion of hypotonic dextrose solution until a water load equivalent to 4% of the body weight has been given over a period of 2 hr (18). Thereafter, a positive water balance is sustained by infusing hypotonic dextrose at a rate equal to the volume of urine voided in the preceding collecting period. The urine remains free of glucose; the plasma osmolality and sodium concentration decline slightly; and the concentration of urea in the plasma does not change measurably. As illustrated in Figure 1-2, urinary flow rises progressively for 3 hr and then reaches a plateau, whereas urinary osmolality drops more rapidly, reaching a minimum value of 70 mOsm/kg H_2O within 2 hr. The latter time course also characterizes the fall in urinary urea and sodium concentrations.

During the transition from antidiuresis to water diuresis, the rate of total solute excretion rises slightly, owing to an increased excretion of urea. For a few hours urea excretion is twice that of control animals, a phenomenon known as urea *exhaltation* (571), but it eventually returns to prediuretic levels despite a persistently high urinary flow rate. The transient increase in urea excretion parallels a loss of urea which normally accumulates in the inner medulla, but comes from the total body pool of urea, since the actual quantity of urea sequestered in the tiny medulla is very small.

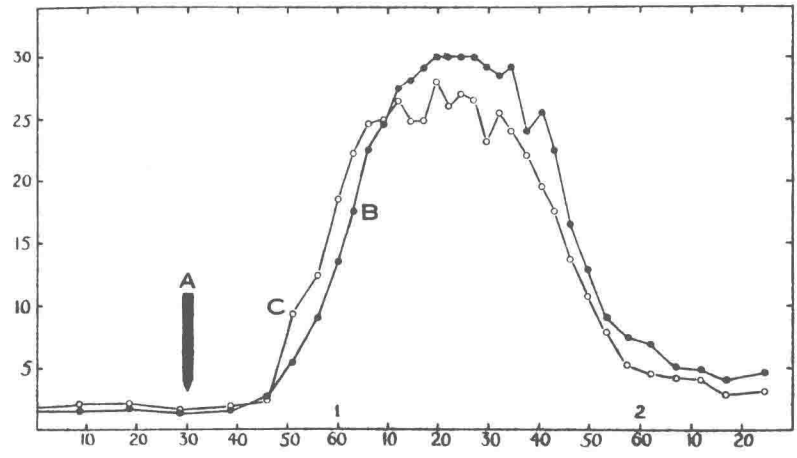
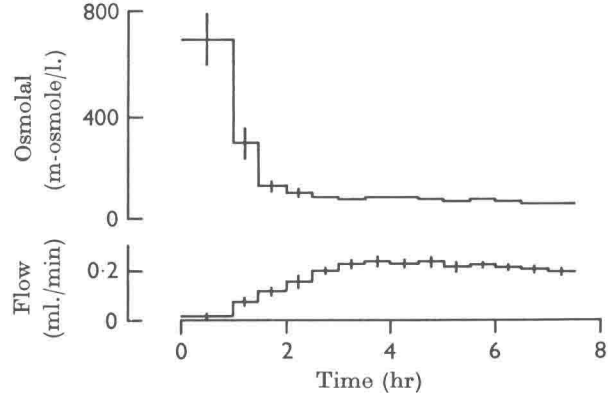


Fig. 1-1 Response of right and left kidneys to the introduction of water into the stomach. At point A, 250 ml tap water at a temperature of 30°C was given by stomach-tube. B and C are urine flow from the right and left kidney, respectively. Ordinate = urine flow, ml per 15 min. Abscissa = time in min (below) and hr (above). From A. Klisiecki et al., *Proc. Roy. Soc. Lond. B.* (333) by permission.

Fig. 1-2 Mean solute concentration and urinary flow during water diuresis. Vertical bars represent ± S.E. of mean. From J. C. Atherton et al., *J. Physiol.* (18) by permission.



The time course of changes in urinary flow rate and composition associated with the reverse transition from water diuresis to antidiuresis in an unanesthetized animal has not been studied in exactly the same fashion, that is, by continuously measuring urinary flow and clearances in an animal after removing its water supply. Such an experiment would be lengthy and difficult to interpret because of several variables that might influence the outcome. For example, the period of dehydration required to achieve a maximum urinary osomolality in normal human subjects not previously in a state of positive water balance is 16 to 18 hr (415). To shorten the observation period, antidiuretic hormone (ADH) is typically administered to an animal under circumstances in which hydration is controlled. The studies of Atherton, Hai, and Thomas (20) illustrate many aspects of the events associated with the transition from water diuresis to antidiuresis in the rat. Water diuresis was induced exactly as described above. The rats were encouraged to void every 15 to 30 min. After a high urinary flow lasting an hour (usually 3 hr after the experiment had begun), lysine-vasopressin was administered through an indwelling tail vein catheter. Figure 1-3 illustrates the changes in urinary osmolality and flow after the onset of ADH infusion at rates ranging from 2.5 to 30 μU min^{-1} (100 g body wt)$^{-1}$. There was no perceptible response to the lowest infusion rate, and infusion rates exceeding 30 μU min^{-1} (100 g body wt $^{-1}$) did not further accelerate the antidiuretic response. Within these limits, both the rate of increase in urinary osmolality and the maximum osmolality achieved were functions of the dose of ADH. The maximum response took 2 hr, and was considerably less than the maximum osmolality of urine specimens obtained from dehydrated rats (approximately 3000 mOsm/kg H_2O).

Dehydration following water deprivation augments urinary concentrating ability more than the administration of ADH to the normally hydrated or water-loaded subject (169,292,316). The increase in concentrating ability results at least in part from accumulation of more urea in the inner medulla and papilla. Coincident with the urea accumulation and during the initial decline of urinary flow, urinary excretion of urea is temporarily reduced, a phenomenon called *abatement* (550). A modest increase in urinary sodium excretion follows the administration of ADH under certain circumstances (536,550,620). However, the transience and variability of the response at physiological doses of ADH make it probable that vasopressin has no physiological role in regulating sodium excretion (20).

Osmolar and Free Water Clearance

The osmolality of the glomerular ultrafiltrate is the same as that of plasma regardless of the final urinary concentration. Whether osmolality of urine is higher or lower than that of plasma depends on both active and passive transport processes in the renal tubule.

When urine is maximally dilute, the urinary flow rate is approximately 15% of the filtered load of water (GFR) (580). Except under abnormal circumstances, at least 85% of the filtered load of water is therefore always reabsorbed [designated by

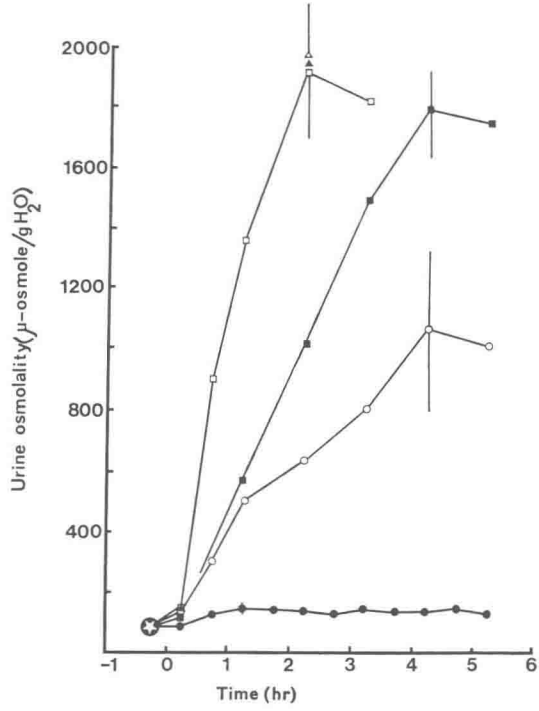
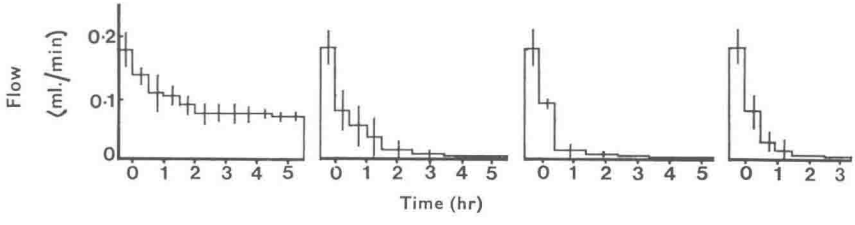


Fig. 1-3a Mean urine osmolality (vertical bars = ± S.D. of maximal value at each dose) during continuous intravenous infusion of ADH at 2.5 (●), 5 (○), 15 (■), 30 (□, ▲), and 60 (△) μU min^{-1} (100 g body weight)$^{-1}$. The pre-ADH value represents the mean of all groups.

Fig. 1-3b Mean (±S.D.) urinary flow during continuous intravenous infusion of ADH at 2.5 (first graph), 5 (second), 15 (third), and 30 (fourth) μU (100 g body wt)$^{-1}$. The pre-ADH value represents the mean of all groups. From J. C. Atherton et al. *Pflügers Arch.* (20) by permission.



Smith as "obligatory reabsorption" (579)] and considered a "passive process." The remainder is variably reabsorbed ["facultative reabsorption" (579)] depending on water balance, and was at one time considered an "active" process. It has been unequivocally established that obligatory reabsorption of glomerular filtrate involves the transepithelial transfer of solute primarily in the form of NaCl and $NaHCO_3$, and that the latter processes require expenditure of energy. However "passive" can still be used to describe obligatory water reabsorption but only in a narrow sense in that water is not moved against an osmotic gradient. When urine is isosmotic to plasma, urinary flow is reduced from 15% to 1–3% of the GFR, depending on the excretory load of solute. One moiety of facultative reabsorption, amounting to approximately 12–14% of the GFR, can therefore also be considered passive since no evidence has been forthcoming to indicate that movement of this moiety of water is against an osmotic gradient.

What was meant by "active" water reabsorption was the absorptive process required to elevate urinary osmolality above that of plasma. By exclusion, this referred to the remainder of facultative reabsorption, equivalent to 1–3% of the glomerular filtrate. Theoretically this could occur by the reabsorption of a hypotonic solution (removal of water in excess of solute), by the secretion of a hypertonic solution (addition of solute in excess of water), or by a combination of the two processes. Under most circumstances it is thought that this osmotic work involves exclusively hypotonic reabsorption.

To describe these processes quantitatively, Wesson and Anslow (688) introduced the concepts "osmolar clearance" (C_{osm}), "free water clearance" (C_{H_2O}), and "negative free water clearance" ($T^C_{H_2O}$). These terms were quickly adopted by Smith and colleagues (579,580) and subsequently enjoyed widespread use in efforts to characterize the processes of urinary concentration and dilution.

Osmolar clearance C_{osm} is defined as:

$$C_{osm} = \frac{U_{osm} V}{P_{osm}} \tag{1-1}$$

where U_{osm} and P_{osm} are urine and plasma osmolality, respectively, and V is the urinary flow rate, usually expressed as ml/min. For a 70-kg man with a GFR of 125 ml/min, C_{osm} averages 2–4 ml/min (579). Osmolar clearance normally is independent of GFR and V. It describes the rate at which osmotically active solute is removed from the plasma along with a volume of water sufficient to contain the solute in an isosmotic solution. Any surplus of water exceeding this volume in the urine is therefore considered solute-free water (580,688). During water diuresis, urine thus consists of two virtual volumes—one containing all the solute in an isosmotic solution (C_{osm}) and the other consisting of solute-free water or, commonly, "free" water, C_{H_2O}, i.e.

$$V = C_{osm} + C_{H_2O} \tag{1-2}$$