# THE DIURETIC MANUAL

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# Foreword

The mid-to-late twentieth century has been marked by dramatic advances in pharmacotherapeutics. The development of drugs such as antibiotics, chemotherapeutic agents, anticoagulants, anesthetics, hypnotics, sedatives, receptor antagonists, analgesics, anti-inflammatory agents, and psychotropic agents, and the purification and synthesis of hormones have changed the practice of medicine and led to the effective treatment and cure of a host of diseases. Progress in the area of diuretic therapy has been equally dramatic and therapeutically successful. A perusal of the history of diuretic therapy serves as a window by which to observe the accretion of knowledge of renal physiology as each new class of diuretics has exerted effects at specific yet different sites in the nephron. For several decades, the mercurial diuretics that acted on the proximal and distal nephron to decrease reabsorption were paramount in the treatment of edematous states. Side effects, including mercury intoxication, agranulocytosis, and sudden death after intravenous injection, limited their use. Carbonic anhydrase inhibitors such as acetazolamide ultimately proved to be weak diuretics but provided great insights into tubular function. These agents, by virtue of their ability to inhibit carbonic anhydrase in the tubular cell, resulted in impaired $H^+$ secretion and induced urinary sodium, bicarbonate, potassium, and water excretion. Of greatest importance, however, structure-activity studies of carbonic anhydrase inhibitors gave rise most unexpectedly to the class of diuretics known as benzothiadiazides, of which chlorothiazide was the first to be clinically utilized to any significant degree. These agents produce a chloride diuresis and clearly demonstrate the independence of their action on sodium, chloride, and water excretion from the inhibitors of carbonic anhydrase. The property of inducing sodium excretion has also served to establish the benzothiadiazides as the

linchpin around which virtually all antihypertensive therapy is based and they have become the prototype of step 1 drugs for the treatment of millions of patients with hypertension. Most recently the "loop" diuretics, including furosemide, ethacrynic acid, and bumetanide, have achieved a prominent place in diuretic therapy. The primary effect of these drugs is to decrease chloride and sodium reabsorption in the ascending limb of the loop of Henle.

The diuretic manual developed by Dr. Puschett and his colleagues provides an indepth discussion of the many uses of modern diuretics including therapy of edematous states found in a variety of clinical disorders, management of hypertension, and adjunctive therapy of patients with absorptive hypercalciurias and renal stones. Extensive discussion is provided regarding the modern concepts of renal physiology in order for the reader to understand the action of specific types of diuretics. The section on diuretic site and mechanism of action serves to highlight the sophisticated technologies presently utilized in the study of renal physiology and mechanism of diuretic action which are providing fundamental insights into the molecular biology of renal tubular cells.

Based on the data presented in this manual, it seems clear that the next decade will most likely witness the development of additional diuretic agents specifically tailored to intervene in the basic biochemical reactions that are responsible for the characteristic and complex transport systems for water and solute in the various parts of the human nephron. The rapid evolution of diuretic therapy over the past quarter century and the excitement of the present state-of-the-art justifiably lead to considerable anticipation for the advances of the future.

Gerald S. Levey, M.D.

*Pittsburgh, Pennsylvania*

# Preface

Diuretics are among the most heavily utilized therapeutic agents in clinical medicine. Despite this fact, there is no single source to which the clinician can refer which provides, in one volume, suggestions for their employment in various disease entities, as well as the physiologic and pharmacologic bases for their administration. This book represents an attempt by my colleagues and me to provide this sort of information. In Part I, chapters 1–13, we have detailed specific suggestions for therapy in eleven types of disorders and/or special patient populations. In each chapter, these recommendations follow concise introductory material with regard to the establishment of a diagnosis and a review of what is currently known about pathogenesis. Furthermore, potential complications and important drug interactions of the diuretics are presented. Some repetition of salient points will be noted, as we recognize that our readers may not have time to peruse every chapter. It is hoped that Part I will be of use to practicing physicians of all kinds, but especially to general practitioners, general internists, nephrologists, and cardiologists. House officers may also find the practical aspects of these chapters helpful in their day-to-day management of patients.

Chapter 14 outlines the renal physiologic principles upon which sound therapeutic decisions are based. Accordingly, this portion of the book should prove to be of interest to medical students as well as to those physicians who have a more compelling interest in understanding how and why diuretics work. Part II appendixes consisting of several special topics. The commercially available diuretics are listed, classified as to their relative potencies, their major and minor sites of action within the nephron and the indications for their use.

It is appropriate, at this juncture, to thank my colleagues who have so unselfishly given of their time, which I recognize included many evenings and weekends of work. I also thank their wives, husbands, and children, who had less time with them because of their contributions to this book. We are all grateful to the secretarial staff of the Renal-Electrolyte Division of the University of Pittsburgh School of Medicine who have toiled so diligently to produce the manuscript. My special thanks to my Associate Editor, Dr. Arthur Greenberg, who has not only contributed importantly to these pages, but has collated and reviewed all of the material contained herein.

*Pittsburgh, Pennsylvania*

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PART

# I

# DIURETIC THERAPY PHYSIOLOGIC BASIS AND CLINICAL ASPECTS

# Contents

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chapter

# 1

# Edema Formation and the Physiologic Basis for Diuretic Usage

## An Introduction

Jules B. Puschett, M.D.

With the exception of those edema states which represent local phenomena (for example, related to venous stasis), the final common pathway by which edema occurs is the perception by the kidney of some signal or series of stimuli, that cause(s) the retention of salt and water. This may be appropriate and salutary in the patient with hemorrhagic shock. On the other hand, this response of the kidney to enhance sodium reabsorption may be inimical to the patient's best interests, as in the patient with congestive heart failure, who often already has an expanded extracellular fluid volume. Therefore, what the congestive heart failure and hemorrhagic shock patient have in common with the patients suffering from ascites and/or edema due to hepatic disease or the nephrotic syndrome, is an apparent hypoperfusion of the renal vascular bed. While not entirely understood, the pathogenesis of these disorders probably includes alterations in the physical forces which regulate transport across the glomerular capillaries ("glomerular factors"), and those involved in the post-glomerular circulation, which regulate tubular reabsorption ("tubular factors"). In addition, one or more humoral mechanisms may be involved. Diuretics are substances which act to impair sodium transport within the tubular system, leading to an increased excretion of sodium ions with an attendant anion, which carry with them filtered water. In certain special circumstances, diuretics may act, in part, not by altering tubular ionic reabsorption, but by raising filtered sodium load through the mechanism of increasing renal blood flow and glomerular filtration rate (GFR). An example of this type of diuretic agent is the xanthine class of drugs e.g., theophylline. Table 1.1 presents a list of drugs which can act as diuretic agents. It will be noted that some of them, such as digitalis glycosides, can have both glomerular and tubular effects.

**TABLE 1-1.** Mechanisms of Action of Drugs Capable of Diuretic Effects

| Drug | Presumed Mechanism of Effect |
|---|---|
| 1. Drugs Which Enhance the Filtered Load of Sodium | |
| a. Xanthine derivatives (theophylline, etc.) | a. ↑ Renal blood flow due to afferent arteriolar vasodilatation |
| b. Dopamine | b. ↓ Renal vascular resistance, ↑ renal blood flow |
| c. Dobutamine | c. ↑ Cardiac contractility and ↑ cardiac output |
| d. Digitalis glycosides | d. Augment renal perfusion by improving cardiac output |
| 2. Drugs Which Impair Tubular Reabsorption[a] | |
| a. Acetazolamide | a. Carbonic anhydrase inhibition |
| b. Thiazides | b. Unknown; additional proximal effect, if any, thought to be due to carbonic anhydrase inhibition |
| c. Metolazone | c. Unknown; proximal effect (seen only with loop blockade) not due to carbonic anhydrase inhibition |
| d. Furosemide | d. Unknown |
| e. Ethacrynic acid | e. Unknown |
| f. Bumetanide | f. Unknown |
| g. Mercurials | g. Intrarenal release of mercuric ions by rupture of C-Hg bonds with capture of thiol groups |
| h. Spironolactone | h. Competitive inhibition of tubular effects of aldosterone |
| i. Triamterene | i. Unknown (direct inhibitory effect on potassium secretion) |
| j. Amiloride | j. Unknown |
| k. Digitalis glycosides | k. Inhibition of $Na^+$-$K^+$ ATPase |

[a]See also Part II (Appendix 2).

## Physiologic Principles

An understanding of the formation of edema and the potential utility of diuretics in the management of this abnormality is based upon certain physiologic principles regarding glomerular and tubular function. In order for edema formation to occur, the patient must excrete less sodium than he is taking in. In other words, positive sodium and water balance must occur. The excretion of sodium can decline leading to positive sodium balance, either because the filtered load of sodium is reduced or because tubular reabsorption is increased, or both. Theoretically, therapy should be aimed

at raising filtered load or reducing tubular reabsorption, or both. As a practical matter, it is usually difficult or impossible to increase the filtered load of sodium which has been abnormally lowered by a disease process. Thus, for the most part, treatment is directed toward inhibiting the tubular transport of sodium. In some cases, therapy can also be aimed at a reversal of the underlying pathophysiologic process. Examples of the latter include: an improvement in cardiac output in the patient with congestive heart failure, thus re-establishing normal or near-normal renal perfusion and glomerular filtration rate; or, therapy of glomerular disease in patients with nephrotic syndrome, leading to the correction of abnormal physical forces across the glomerular capillaries.

*Glomerular Factors*

Filtered load essentially depends upon GFR alone as this ion is not protein bound and since plasma sodium concentration varies very little except in unusual circumstances. The ability of the kidney to filter solute is a function of the hydrostatic pressure in the glomerular capillaries which, in turn, is a function of the blood pressure (Figure 1-1). The glomerular hydrostatic pressure favors filtration; this force is opposed by the plasma oncotic pressure as well as by the intratubular pressure. This relationship can be quantified and has been measured in the experimental animal.

If we define SNGFR as the filtration rate of a single filtering unit of the kidney or nephron, and $K_f$ as the ultrafiltration coefficient, and $\bar{P}_{uf}$ as the net force for ultrafiltration, then

$$SNGFR = K_f \times \bar{P}_{uf}.$$

Since $\bar{P}_{uf}$, is in turn the difference ($\overline{\Delta P}$) between the mean hydrostatic pressure drop across the glomerular capillary and the difference ($\Delta \bar{\pi}$) between glomerular capillary and Bowman's space colloid oncotic pressure (1), it is clear that

$$SNGFR = K_f (\overline{\Delta P} - \Delta \bar{\pi}).$$

Since $K_f$ is the product of the hydraulic permeability of the capillary wall (K) and the total surface available for filtration (S)

$$SNGFR = K \times S \times \bar{P}_{uf}.$$

It has been determined that in addition to the major role that $K_f$, $\overline{\Delta P}$ and $\overline{\Delta \pi}$ play in the determination of SNGFR, glomerular plasma flow rate ($Q_A$) also exerts a considerable influence. SNGFR is directly related to $Q_A$ by an expression which includes the single nephron filtration fraction (SNFF) as follows:

$$SNFF = SNGFR/Q_A.$$

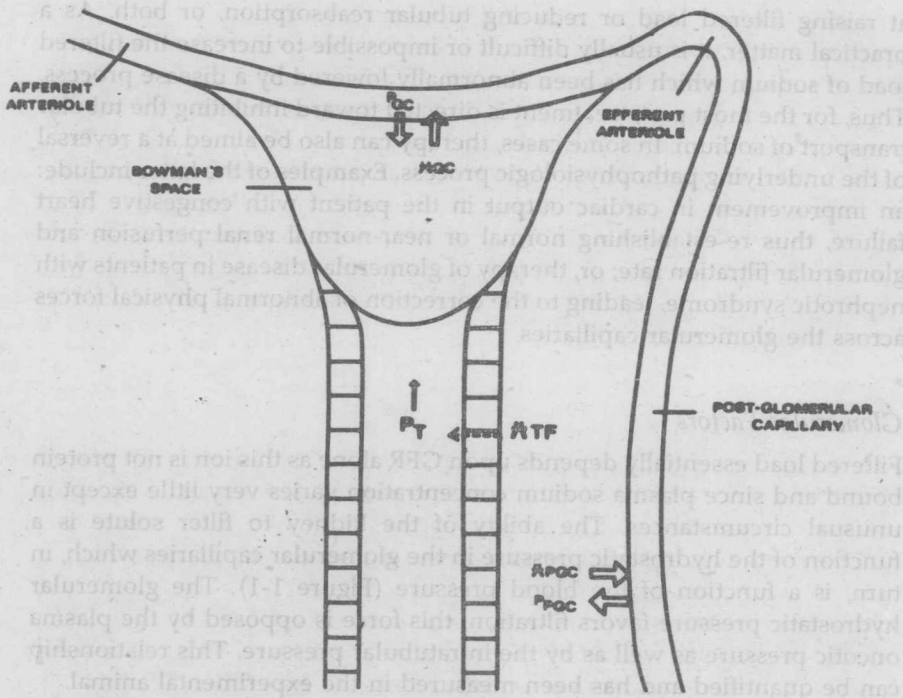


**Figure 1-1.** The physical forces which regulate glomerular filtration include $P_{GC}$, the glomerular capillary hydrostatic pressure, the main force for ultrafiltration, and the glomerular capillary oncotic pressure ($\pi$ GC), which is the major force opposing filtration. Pressure in Bowman's space and in the tubular system ($P_T$) also opposes filtration but, except in the circumstance of tubular obstruction, is usually so small as to be negligible. Proximal tubular reabsorption depends in a major way on the interplay of physical forces across the post-glomerular circulation. Here, the post-glomerular capillary oncotic pressure ($\pi$PGC) is an important factor favoring reabsorption, and is opposed by hydrostatic pressure in the post-glomerular capillary ($P_{PGC}$), which is usually small. Any oncotic force due to protein in the tubular lumen ($\pi$TF) would also retard reabsorption, but this force probably only becomes of any significance in advanced disease states. Active transport of sodium forms the major force moving proximal tubular fluid and electrolytes from tubular lumen to capillary blood.

The SNFF represents that portion of the blood coursing through the glomerulus ($Q_A$) that becomes glomerular ultrafiltrate (SNGFR). Rearrangement of the equation yields:

$$SNGFR = SNFF \times Q_A,$$