Diuretic Agents

Clinical Physiology and Pharmacology

Edited by

Donald Seldin
Gerhard Giebisch

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The Dropsical Woman (La Femme Hydropique) by Gerard Dou (1613-1675) (Louvre, Paris, reprinted with permission).

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PREFACE

Robert Pitts pointed out many years ago the inadequacy of defining diuretic agents in terms of their capacity to increase the flow of urine. Such a definition poses at least two difficulties. First, it is possible to enhance urine flow, yet at the same time increase the amount of salt or water or both in the body: an infusion of saline, for example, may augment sodium and water excretion yet expand the extracellular volume. Second, water loads may stimulate urine flow yet increase body water. However, from a clinical point of view, the usual purpose of diuretic administration is to diminish extracellular volume, not merely augment water and sodium excretion. For this reason, it is useful to restrict the term "diuretic" to agents which not only increase the urinary excretion of sodium chloride and water, but at the same time reduce extracellular volume.

In recent years the most widely used diuretics have been agents which have the capacity to inhibit sodium transport systems along the renal tubule. At first, these agents, such as mercurial diuretics, were empirically discovered, and the transport systems which they inhibited were unknown. In more recent years, detailed knowledge of the transport systems along all parts of the nephron has become known, thereby providing detailed information concerning their mechanism of action and site of inhibition. This has allowed insights into how different urine patterns are produced by various diuretics. The outline of this preface reflects the chapter organization and order of this book.

THE DETERMINANTS OF DIURETIC-INDUCED NATRIURESIS

SALT INTAKE

Normal individuals usually consume fairly large amounts of salt. In consequence, the effective extracellular volume (ECF) is on the high side and the

renin–angiotensin–aldosterone system (RAA) tends to be suppressed. A diuretic-induced natriuresis may not stimulate an appreciable activation of the RAA system because the high sodium intake prevents a drastic reduction in ECF. A steady-state eventuates in which ECF is only modestly reduced and the RAA remains relatively quiescent. Potassium and hydrogen excretion may therefore not rise greatly. On a low-sodium diet (which results in shrinkage of ECF), however, a modest diuretic-induced natriuresis further reduces ECF, thereby eliciting marked activation of the RAA system. Under such circumstances persistently high distal tubule sodium delivery (caused by pharmacologic inhibition of sodium transport), in the presence of high levels of aldosterone, causes marked potassium and hydrogen losses. It is therefore of the greatest importance to appreciate the state of sodium intake so as to anticipate not only the magnitude of extracellular volume reduction but also the potential dangers of potassium and hydrogen loss.

Efficacy of Diuretic Inhibition of Sodium Transport

The efficacy of a diuretic depends on three factors: (1) potency, the magnitude of inhibition of the transport system; (2) the capacity of the transport system that is inhibited; and (3) the site of action along the nephron where the diuretic acts. At present, the most effective diuretics are inhibitors of sodium chloride transport in the thick ascending limb of Henle's loop. Loop diuretics mobilize large amounts of sodium chloride and water and produce a copious diuresis with a sharp reduction of the ECF. As the site of action of diuretics moves downstream, their effectiveness declines: thiazide diuretics, active in the distal convoluted tubule, and potassium-sparing diuretics, such as triamterne, amiloride, and spironolactones, increase sodium excretion only moderately because the transport systems they inhibit have low transport capacity.

Diuretics acting on the proximal tubule where the largest fraction of filtered sodium is reabsorbed would be expected to be the most powerful agents to promote loss of sodium and reduction of ECF. However, such agents may not result in greatly increased urinary excretion of sodium because avid reabsorption at uninhibited distal tubule sites can retrieve large increments of the delivered sodium. Moreover, increased fluid and salt delivery out of the proximal nephron may stimulate the secretion at more distal tubule sites of potassium and hydrogen ions. As a consequence, sodium excretion in the final urine may be minimal while excretion of potassium and hydrogen ions may be significantly augmented.

The Internal Regulatory Environment

Diuretic-induced shrinkage of the ECF will activate counterregulatory mechanisms: the RAA system will be stimulated, vasopressin (ADH) release augmented, the sympathetic nervous system and catecholamine secretion increased, and secretion of such natriuretic factors as atrial natriuretic peptides and ouabain-like humoral agents is suppressed. If, however, as in chronic heart failure, natriuresis improves cardiac performance, all of these counterregulatory systems may revert toward a normal state. It should be pointed out that the most potent of the internal regulatory factors, aldosterone, may be elevated prior to diuretic administration, as in chronic heart failure. Alternatively, it may be activated as a direct result of a successful diuretic response.

Chronic diuretic-induced natriuresis may result in a sequence of events that can significantly blunt the initial diuresis: Glomerular filtration rate may fall, proximal reabsorption of sodium and fluid may increase, and distal tubule transport systems may be activated as evidenced by cell hypertrophy and stimulation of the sodium, potassium, and hydrogen ion transport systems.

Nephron Mass and Nephron Function

Diuretics are sometimes administered in a setting of chronic renal disease. Even though diuretic inhibition of sodium transport per nephron may be potent, the increase in urine sodium excretion may be small because few nephrons remain functional. If clinical advantage is to be taken of the small increase in sodium excretion, dietary sodium must be dramatically restricted so as to facilitate a negative balance of sodium, thereby leading to a reduction in ECF.

THE USE OF DIURETICS TO EXPLOIT SECONDARY EFFECTS

The purpose of diuretic administration is not restricted to the inhibition of renal sodium transport so as to reduce ECF. The burgeoning knowledge of the location and mechanisms of renal transporters provides a basis for the use of diuretics to influence the renal excretion of such important ions as, for example, potassium and calcium. Diuretics can accelerate potassium excretion by increasing distal sodium delivery, even though urinary sodium excretion may not be greatly augmented. Thiazide diuretics are especially useful for reducing hypercalciuria, both by augmenting proximal reabsorption (secondary to reduced ECF) and by a direct effect, stimulating calcium reabsorption in distal

tubule cells. On the other side of the coin, hypercalcemic states may be treated with loop diuretics acting on the thick ascending limb where they effectively inhibit calcium reabsorption.

SPECIAL DIURETICS

These agents are designed to affect transport without any specific effects upon sodium chloride. Carbonic anhydrase inhibitors may be employed to inhibit sodium bicarbonate transport in metabolic alkalosis, vasopressin (ADH) inhibitors are useful in the treatment of hyponatremic states, and uricosuric agents may be helpful to alleviate hyperuricemia.

EXTRARENAL EFFECTS OF DIURETICS

It is increasingly apparent that transport systems similar to those in the kidney are present in other tissues and are susceptible to diuretic inhibition. Carbonic anhydrase inhibitors diminish formation of aqueous fluid in the eye when given either systemically or locally. Cochlear transport systems are vulnerable to the action of ethacrinic acid and furosemide at high doses. Furosemide produces venodilatation and may be useful in the treatment of pulmonary edema independent of its renal action.

DIURETIC COMPLICATIONS

These often reflect an exaggeration of physiologic goals. Excessive natriuresis may lead to salt depletion and vascular insufficiency, potassium depletion and alkalosis, and hyponatremia. Several metabolic derangements may also result from diuretic treatment. If the goal of diuretic therapy is to augment sodium excretion, then the consequences of successful natriuresis and of changes of other renal and extrarenal transport mechanisms must be fully appreciated to forestall complications. In addition, diuretics may produce toxic effects quite independent of their renal action.

CONCLUSION

The present volume attempts to analyze the action of diuretics along four lines: we describe, first, the localization and type of transport systems inhibited by diuretics. Second, we define the indications and consider the primary and

secondary effects of diuretics within the kidney. Third, we analyze the systemic consequences of diuretic action, including therapeutic and toxic effects. Finally, we explore the modulation of the renal action of diuretics by internal regulatory adjustments. By weaving together these various components we hope that a more comprehensive appreciation of diuretic action may be achieved. The ultimate goal of this approach is to deepen understanding of the net physiologic consequences of diuretic administration, thereby making therapy effective and safe.

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PART I

History of Diuretics

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CHAPTER I

A History of Diuretics

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Diuretics, as therapeutic agents that act on the kidney to increase salt and water excretion, have a relatively short history. On the other hand, the very reason for which diuretics were developed, i.e., mobilization of excess body fluids, has a long history which dates back to the beginnings of medicine. No history of diuretics would be complete without some consideration of this long prelude, which is particularly important for an appreciation of the wonders that diuretics have accomplished and the essential niche they now occupy in therapeutics.

The agonal picture of volume overloaded patients drowning in their dropsy, after prolonged suffering and invalidism, has been a matter of human sympathy and medical concern since the earliest days of recorded history. "Flooding of the heart," the ancient Egyptians termed it, and shrouded in the mist of antiquity are the first musings on its treatment [9]. Among the celestial cures recorded on the pillars of the Aesklepion at Epidaurus is that of a Spartan girl, Arete, who suffered from dropsy and asked the god for relief. Aesculapius cut off her head, turned her upside down until the fluid ran out, and then replaced her head [31]. A cure, the same records indicate, that could not be repeated! In reviewing the history of diuretics this chapter will center around measures to treat this very condition, i.e., dropsy, for that is the principal problem which mankind in general, and medicine in particular, have had to deal with.

Diuretic Agents: Clinical Physiology and Pharmacology

It is the recorded measures for treating dropsy that provide the beginnings of the history of diuretics, which, much like that used by Aesculapius, were not always strictly diuretic in nature. The use of drugs to induce an actual diuresis is also ancient, dating back to observations made from the effect of foods prepared for the sick, and preserved in folklore throughout the ages. Such knowledge became codified rather early. Egyptian concoctions for "causing one to urinate" and "to expel fluid accumulations from the body and heart" are recorded in the Hearst Medical Papyrus dating back to 1550 B.C.E. These complex mixtures of plants and minerals in beer and honey were administered with proper incantations that were typical of the religious overtones of Pharaonic medicine. Treatment became more pragmatic with the advent of the relatively more secular and definitely more rational Greek medicine [13, 16, 35]. This is illustrated in the section on the management of dropsical patients from *On Regimen in Acute Diseases* of the Hippocratic Corpus:

> Laborious exertion, fomentations and abstinence are to be enjoined. The patient should eat dry and acrid things, for thus will he pass the more water, and his strength be kept up. If he labours under difficulty of breathing, if it is the summer season, and if he is in the prime of life, and is strong, blood should be abstracted from the arm, and then he should eat hot pieces of bread, dipped in dark wine and oil, drink very little, and labour much, and live on well-fed pork, boiled with vinegar, so that he may be able to endure hard exercises.

The text goes on to give:

> A draught for a dropsical person. Take three cantharides, reving their head, feet, and wings, triturate their bodies in three cupfulls (cyathia) of water, and when the person who has drunk the draught complains of pain, let him have hot fomentations applied. The patient should be first anointed with oil, should take the draft fasting, and eat hot bread with oil.

While some relief must have been obtained by these modes of therapy, their effectiveness perhaps can be best gleaned from a recounting of the death of Heraclitus (540–480 B.C.E.) by Diogenes Laertius (3rd century C.E.) in his *Lives of Famous Philosophers* (Vitae philosophorum):

> He became so misanthropic that he withdrew and went off to live on herbs and plants in the mountains. But when this diet made him dropsical, he returned to the city and consulted the doctors, asking them about his condition in the form of a riddle: Could they change the wet weather into a drought? Since they did not understand, he shut himself up in a stable, hoping to cure himself and dry up the water by the heat of manure, with which he covered himself. To no avail—he ended up dead of it at age sixty.

The recommendations of Hippocrates (460–377 B.C.E.) were to remain a mainstay of the treatment of dropsy well into the 20th century (sweating, catharsis, bleeding) until the advent of clinically effective diuretics, while others remain in use to this day (dietary restriction). The popular perception of their

FIGURE 1. Aesculapius defending the tools of his trade against innovators (Honoré Daumier, 1859).

merits also remained unchanged from those of Heraclitus, as graphically expressed in a cartoon (Fig. 1) by Honoré Daumier (1808–1879), a contemporary of Claude Bernard (1813–1878).

The diuretic properties of various plants and minerals were also codified. Dioscorides (40–90 C.E.), whose *De Materia Medica* was to become the supreme authority on medicinal substances for over 1500 years, commented on the diuretic properties of several plants (juniper, radishes, cassia, cinnamon, dill, wormwood, periwinkle, squill). Arabic medicine expanded on this, monastic medicine nurtured it, and throughout the Renaissance information continued to accrue on the diuretic properties of medicinal plants. As a rule plants considered to have diuretic properties were introduced for the elimination of the spirits or humors that caused disease. Their utility in dropsy was a coincidental finding. A father figure of modern pharmacology is considered by some to be Aureolus Theophrastus Bombastus von Hohenheim (1493–1541), commonly known as Paracelsus. A man of many interests and a pioneer chemist, Paracelsus can be regarded as the originator of chemical pharmacology and

therapeutics that began the march away from herbals [25]. He is certainly a key figure in the history of diuretics as will be detailed in the section on mercurials.

The purgative, and to a lesser extent emetic, property of herbs or their extracts was the basis for their successful use in the treatment of dropsy. Hippocrates commented on the use of purgatives in one of his aphorisms (Section VI, No. 14): "In a case of dropsy, when the water runs by the veins into the belly, it removes the disease." As with diuretic plants, purgatives were an integral component of the general materia medica used to treat a multitude of diseases (other than dropsy) to restore altered humoral balances that were considered the cause of illnesses. Over time, mixtures of plants, with varying properties, were developed specifically for the treatment of dropsy. One example of these from the *Materia Medica for the Use of Students,* published in Philadelphia in 1880, lists the following for the management of dropsy under the name "cider mixture":

> A compound infusion is used in dropsy, of which the following formula: Juniper berries, mustard seeds, and ginger, each half an ounce; horseradish, parsley root, each an ounce; cider, two pints—dose, a wineglassful two or three times a day.

Mechanical means of removing blood (leeches, bloodletting, cupping, lancing), also came to be used in the therapy of dropsical patients (Fig. 2). Once again, their use stemmed from the notion that diseases resulted from humors generated by inflammation in the system and that blood removed from the proximity of the site that was painful or the organ considered to cause the disease would remove the noxious humors and provide cure. Neither Hippocrates nor Caelius Aurelianus (c. 400 C.E.) mention leeches, although Galen (129–200 C.E.) and Pliny (23–79 C.E.) discussed them. Of interest is the recommendation of Areteus (30–90 C.E.) to use leeches in angina accompanied by dyspnea. Avicenna (980–1037) commented on their advantage over cupping. Leeches were especially in vogue during the latter part of the 18th and early 19th centuries [1, 7, 13]. The most sanguinary physician in history is said to have been F. J. V. Broussais (1772–1838), a pupil of Bichat (1771–1802), surgeon of the armies of France, and from 1831 Professor of General Pathology at Paris [16]. He believed that the physician should dominate nature and not merely try to assist it as Hippocrates had maintained. He was in the custom of ordering hundreds of leeches daily. The last of the great bloodletters was J. B. Bouillaud (1796–1881), who considered Broussais the "Messiah of Medicine." Bouillaud was a skillful and learned physician who played an important role in establishing the connection between rheumatic fever and heart disease and in 1835 came to recognize the merits of digitalis as the "opium of the heart" [8]. To appreciate how much blood could be removed one needs to consider the number of leeches applied (usually 10–30) and that when fully gorged each leech could contain about one-half to one ounce of blood. To increase the quantity of blood removed the tail was snipped or salt and vinegar sprinkled on the

FIGURE 2. Seventeenth century woodcut showing scarification by lancing (Wellcome Institute Library, London).

leech. Leeches were considered particularly useful in children or the physically weak, who could not stand the harsher bloodletting [18].

The injudicious use of bloodletting, which had been extensively used as a general therapeutic measure, was condemned by Hippocrates. By far the most extensive account of bloodletting in antiquity is that of Galen (129–199), who devoted three lengthy works to venesection in which he criticized Hippocrates for not including it in his Aphorisms and for not having laid down with sufficient precision the rules of venesection for dropsy. In the Middle Ages, the directions for phlebotomy and its techniques were minutely detailed and often determined by astrological considerations, being permitted only on favorable days and at propitious hours. Discussion on whether bleeding should be practiced at the start of the disease or later in its course and at a site close to or distant from the disease dominated Arabic therapeutics and extended well into the Renaissance. Leonardo Botallo (b. 1530), physician to the French kings Charles IX and Henry III, was a fervent advocate of frequent and copious bloodletting. Lorenzo Bellini (1643–1704), known for his contributions to renal anatomy, studied phlebotomy and wrote on its utility in clinical medicine. Throughout history bloodletting had its advocates and opponents. By the beginning of the 18th century the detrimental effects of phlebotomy led to increased criticism of its use. Bernardino Ramazzini (1633–1717), professor at Padua, who in a period when phlebotomy was much in favor, wrote "it seems as if the phlebotomist grasped the Delphic sword in his hand to exterminate the innocent victims rather than destroy the disease." By the first half of the 19th century, as experimental medicine began to assert itself, bloodletting fell in gradual disfavor but remained in use in the treatment of pulmonary edema well into the first half of the 20th century [1, 7–9].

Measures to combat dropsy continued to include considerable superstition and ritual best illustrated in the description of one Athanasius Kircher in 1646 of a wooden cup sent him by the Jesuits in Mexico which would color water poured into it a deep fluorescent blue. This was the celebrated *lignum nephriticum*, first noted in 1545 by Nicolas Monardes and Francisco Hernandes as a remarkable diuretic for renal and dropsical troubles. In the 17th century these cups became esteemed gifts fit for royalty [16]. Their mechanism of action remains a mystery. Their disappearance from the materia medica best speaks to their merit as a diuretic or lack thereof.

A sense of how information accrued through the centuries came to be used in the therapy of dropsy during the pre-Richard Bright era can be gleaned from the writings of the period. Thomas Sydenham (1624–1689), the great reformer of clinical medicine in England, writes in his *Treatise on Gout and the Dropsy* (1675):

> With respect to the evacuation of the water it is well worth observing, that weak purgatives do more mischief than good in dropsical cases . . . of all diseases the dropsy requires the roughest and quickest purgatives . . . With respect to purging for

> the cure of dropsy, great care must be had to carry off the water as speedily as the strength will permit; it being proper to purge every day, unless great weakness, or the too violent operation of the purgative, should require a day or two to be interposed. For if purging be used only at distant intervals (though the last purge brought away plenty of water) we shall allow time for the fresh collection of water and by such a delay instead of accomplishing the cure, leave it unfinished. . . . There are other cases, likewise where the waters are not to be discharged by vomiting or purging; for instance in weak constitutions and hysteric subjects, they cannot be evacuated by purgatives, and much less by vomitives, but are to be carried off by diuretics. Several of this kind are extolled in the writings of physicians, but the most, if not the only efficacious ones, in my opinion, are those prepared from lixivial salts . . . in two quarts of Rhemish wine, with one to two pugils of common wormwood, and prescribe four ounces of filtered liquor to be taken constantly every morning and at five in the afternoon, and at night until the swelling disappears.

He then gives a list of mixtures of mustard seed, seneca, juniper berries, winter's bark, and horseradish, which alongside with other herbal medicines (celery, parsley, asparagus, and cucumber seeds) were exalted as diuretics beginning with the Hippocratic Materia Medica. Relevant to the changes that were occurring is an added annotation on digitalis by George Wallis, editor of the 1863 edition of Sydenham's text:

> I was convinced of the superior efficacy of this medicine over any other in the present practice, in a dropsical case at Hampstead; a lady had long laboured under visceral obstruction, which at last brought on a dropsy, an anasarca united with ascites, and tympany; squills, pariera brava, alkaline salts, etc. were tried in vain; at last the digitalis purpurea was given two grains twice a day, for 3 days she passed considerably more water than she had done for 10 or 14 days before, notwithstanding the different diuretics which had been tried to produce this effect, and I am persuaded that the digitalis purpurea is amongst the first and most certain of the class of diuretics.

Following Richard Bright's report on dropsy (1827), the disease came to be classified as renal or cardiac in origin. Insight into how limited the options remained can be gleaned from the treatment of "acute renal dropsy" in the 1859 edition of *Clinical Lectures* by Robert Bentley Todd of London [34]:

> The great thing is to promote free sweating, and this may be best done by the hot-air bath; or if you fear its debilitating effects (which are to be taken into account in weakly subjects), you may substitute the warm bath.
>
> You should next, endeavour to obtain relief to the congestion of the kidneys. This is in part effected by restoring the function of the skin. Local bleeding by leeches and cupping will do much in some cases, but little in others. Now and then when your patient is plethoric and robust, you may save time and trouble, take some blood from the arm, but these, you must remember, are exceptional cases. As a rule, general bleeding is better avoided.
>
> Purgatives, as indirect means of relieving the congestion of the kidneys are of great value; they eliminate water and the various morbid matters. Sudorifics may also be employed, and of this the best is the liquor ammoniae acetatis . . .
>
> When the congestion of the kidney has been relieved diuretics may be given with advantage. Of all this large class, the best I can think, is the common cream

> of tartar . . . benzoate of ammonia is often very efficacious. Digitalis, with due precaution, is also very useful.
>
> Irritative diuretics (as cantharides, squills) must be avoided, for obvious reasons, although they are very serviceable in other forms of dropsy. Broom tea is also useful; and the latter derives some advantage from the taraxacum which it contains.
>
> I must caution you against the use of mercury. This mineral, so valuable in some diseases, is in these cases useless and even mischievous; at any rate, I have failed to observe any benefit from it.

For the treatment of "cardiac dropsy" Todd describes his treatment of one patient:

> For the relief of the dropsy, a great deal can be done by attention to the position of the patient, and by the administration of diuretics. With the view of supporting his powers we gave our patient tonics and iron; and finding his kidneys acting imperfectly, we gave him digitalis. But in such cases it is desirable to be careful in administering this medicine, and it is good to combine it with some tonic. I frequently combine it with ammonia, or give the tincture of digitalis with the tincture of sesquichloride of iron.
>
> There was much difficulty in getting the kidneys to act, and the greatest benefit was from the bicarbonate of potassium, either alone or in combination with the powder of jalap.
>
> The dropsy has been kept down best by means of acupuncture: the quantity of water that has oozed away from him, and the relief that he has obtained is surprising. There is another method of relieving anasarcous legs, lately revived on the continent, incision instead of pricking the leg at various points . . . Each is apt to become the center of an erysipelatous inflammation.

Drainage of subcutaneous edema fluid by incision (Fig. 2), and later by the insertion of Southey's tubes (Fig. 3), were terminal drastic measures fraught with danger. Hippocrates had warned of the problem in one of his aphorisms (Section VI, No. 8): "In dropsical persons, ulcers forming on the body are not easily healed." With the advent of lancing time proved him right. Many an unfortunate patient succumbed to the complications of incisions to relieve edema, none so famous as Samuel Johnson (1709–1784). Johnson, who had been incapacitated for months by his terminal dropsy, had been lanced for the removal of edema. On the morning of December 13, 1784, he lanced himself and cutting very deep bled to death that night. His autopsy revealed an enlarged heart, an atrophic left kidney, and an enlarged right kidney. The latter was secondary to nephrolithiasis and the former to an aortic valve defect [32].

Looking back over this prelude to the history of diuretics, a history as ancient as the earliest civilizations, it is remarkable that hardly any of the diuretics used today are older than the First World War (Fig. 4). By the time that World War II started, only four drugs were accepted as effective agents to increase urine flow: caffeine, a mild diuretic at best; digitalis, a powerful agent but effective only in heart failure; mercury, which despite its improvement as an organomercurial, remained potentially a toxic one; and acidifying agents, whose utility was questioned by most.

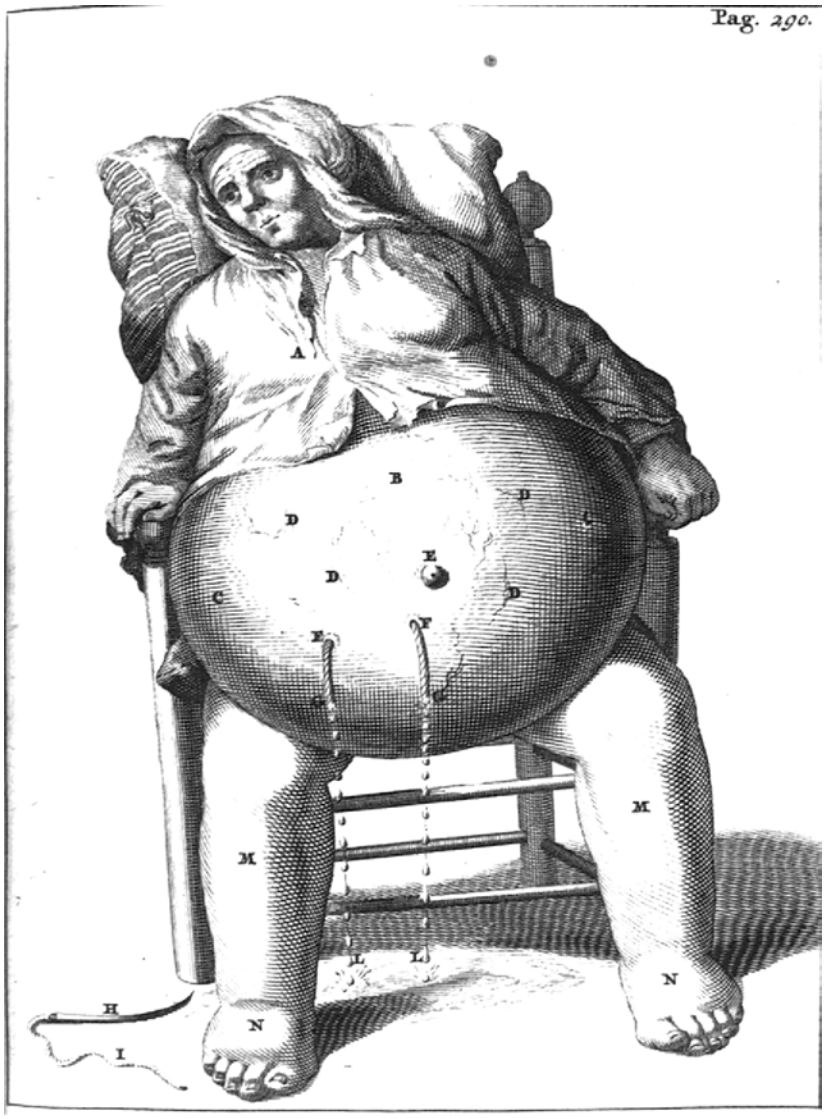

FIGURE 3. A woman with dropsy treated by paracentesis from Frederik Dekker's *Exercitationes Practicae Circa Mendendi Methodum* (Practical Exercises in Methods of Treatment) (Leyden, 1694) (courtesy of the Blocker History of Medicine Collections, Moody Medical Library, The University of Texas Medical Branch at Galveston).

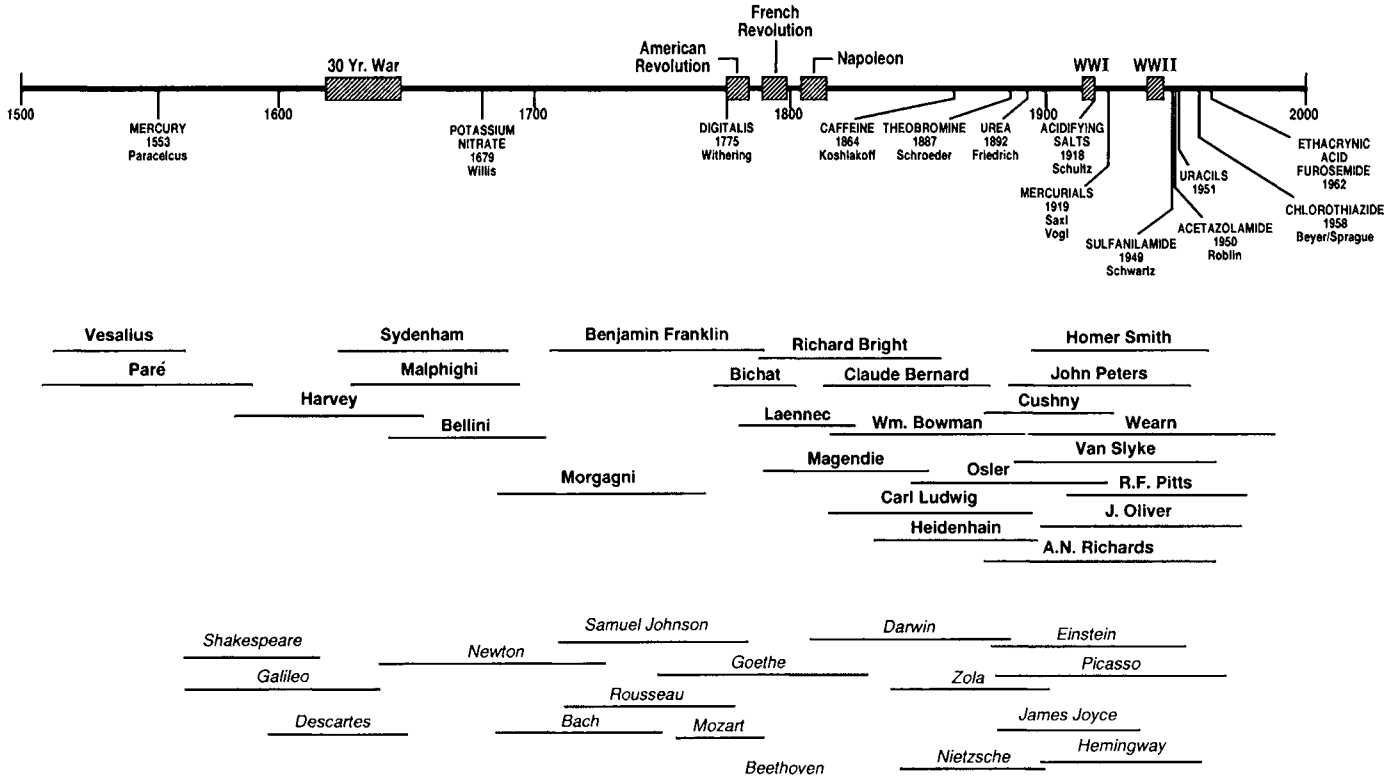

FIGURE 4. Time-line of the discovery of diuretics presented alongside that of contemporary figures in medicine, nephrology, and the liberal arts.

The history of diuretics in earnest had to await an understanding of the functions of the kidney and its role in the regulation of urine volume. A decrease in urine output had been observed in dropsical patients but was considered a subordinate phenomenon. The painting of a physician examining the urine of a dropsical woman in the Louvre notwithstanding (Fig. 5), the role of the kidney

FIGURE 5. The Dropsical Woman (La Femme Hydropique) by Gerard Dou (1613–1675) (Louvre, Paris).

in edema formation was not appreciated. What the physician in the painting is performing is uroscopy (visual examination of the urine), long an integral component of the practice of medicine that was to be condemned in the 17th century. The earliest dissenting opinion that the kidney does play a role has been attributed to the French physician, P. Merklen, who in 1903 reported that edema preceded the onset of oliguria [23, 35]. He was led to this view because of the belief that tissues bound water, thereby causing secondary oliguria, and that the diuresis attributed to herbs and chemicals was due to direct interruption of the water binding properties of the tissues [17]. The appreciation of the relation between edema and oliguria was to await subsequent studies that were to elucidate renal function.

In his *Body Water*, published in 1935, John Peters (1887–1956) characterized knowledge of diuretic drugs as being in a "hopelessly chaotic state" [26]. This condition was soon changed drastically by the work of Peters, Alfred N. Richards (1876–1966), Homer Smith (1895–1962), and their associates. The subsequent understanding of the mechanisms underlying diuretic therapy paralleled the development of renal physiology and the role of the kidney in the accumulation of excess volume. By then, almost a century and a half had elapsed between the introduction of the first two effective diuretic agents to treat edema: digitalis in 1775 and the organic mercurials in 1919. Another 30 years elapsed before the introduction of sulfanilamide in 1949 (Fig. 4).

All three were discovered by serendipity. Another force that was to herald the beginning of the modern era of diuretics was increased understanding of organic and molecular chemistry that now allowed for involvement of the pharmaceutical industry directly in the development of new and more potent agents. It was the relationship between organic chemists and the new breed of renal physiologists that was to provide the basis for the development of new and effective diuretics. Diuretics, in turn, were to provide, initially renal physiologists and subsequently renal biochemists, powerful probes with which to explore renal function.

DIGITALIS

The most important contribution of herbal medicine to the materia medica of the 18th century was foxglove. The purple foxglove, a rather common plant growing throughout the greater part of Europe, is not mentioned by the founding father of herbal medicine, Dioscorides, or in any of the ancient herbals. In the Middle Ages, Welsh physicians employed the foxglove for the preparation of external remedies. It was then known as "foxes-glew" or "foxes-music," because of its resemblance to an ancient musical instrument consisting of bells hanging on an arch support. During the Renaissance, Leonhard Fuchs (1501–

1566), Professor of Medicine at Tubingen, in his *De Historia Stirpium* (Basel, 1542), written to teach botany, termed the plant digitalis, after the popular German name for "Fingerhut." In the 17th century, John Parkinson (1567–1650), an apothecary and Director of the Royal Courts at Hampton Court, described it in his *Theatrum Botanicum* (London, 1640) [12]. Used principally as a purgative, digitalis made its first appearance in the London Pharmacopaeia of 1677, but it was in 1785 that digitalis received its scientific baptism at the hands of William Withering (1741–1799) in his classic *An Account of the Foxglove and Some of Its Medical Uses* (London, 1785).

Withering began his career as a botanist, obtained his medical degree from Edinburgh, and settled to practice medicine at Edgbaston, near Birmingham. It is there that he discovered the diuretic properties of digitalis [1, 16]. His own description of the discovery provides a good sense of the contributions of herbal medicine and of clinical research of the period:

> In the year 1775, my opinion was asked concerning a family receipt for the cure of dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove.
>
> My worthy predecessor in this place, the very humane and ingenious Dr. Small, had made it a practice to give his advice to the poor during one hour in the day. This practice, which I continued until we had an Hospital opened for the reception of the sick poor, gave me the opportunity of putting my ideas into execution in a variety of cases; for the number of poor who thus applied for advice, amounted to between two and three thousand annually. I soon found the Foxglove to be a very powerful diuretic.

At the time dropsy was considered a primary disease, the distinction between cardiac and renal dropsy had to await the analysis in 1813 by John Blackall (1771–1860) of the nature and cure of his dropsical cases and in 1827 the report of Richard Bright (1789–1858) of his own medical cases. It is not surprising then to read of Withering's own disappointment when this new diuretic drug failed to induce a diuresis in all cases of dropsy. Withering was quite cognizant of the toxic properties of digitalis and warned that the drug was to be discontinued if disturbances of the kidneys, stomach, or pulse were observed. Its failure to induce a diuresis in all cases and the fatal results of its negligent use led to attacks on Withering by several of his contemporaries, most notably by John C. Lettson (1744–1815), one of the founders of the Medical Society of London [1, 6, 35].

It was not until the middle of the 19th century that the action of digitalis as a cardiac stimulant was appreciated, following the physiologic studies of its cardiac effects in animals by Carl Ludwig (1816–1895) and Hermann F. Stannius

(1808–1883). That digitalis remains as effective today as it was in the 18th century is due to its unique cardiac actions. As such its diuretic properties were limited to patients with congestive heart failure, and even then it was not always effective. The discovery of its direct and indirect actions on the kidney had to await advances in renal physiology and the elucidation of the central role of the kidney in edema formation.

SALT AND DIET

The role of dietary manipulation to treat dropsy had been practiced for centuries. It had been used, with varying degrees of success, by nature healers, herbalists, and medical practitioners [1, 8, 35]. The favorable results of these dietary regimens had been attributed to its various constituents (asparagus, celery, berries), its limited fluid content (dry diets), or high potassium content (potato diet). Mention of an association between salt intake and fluid retention was made by Caelius Aurelianus in the 5th century C.E., who noted that drinking large quantities of water, particularly salt fluid, could cause dropsy. Stephen Hales (1677–1761), famous for being the first to estimate blood pressure in a horse, produced dropsy by injecting water into the vein of his experimental animals [20]. These observations notwithstanding, the role of dietary manipulation in the management of dropsy remained equivocal and poorly defined.

Philip Karrell (1806–1886), personal physician to Tsar Alexander III of Russia, was the first to advocate a simple dietary regimen (200 ml of milk four times a day) for the treatment of dropsy, which he presented to the Medical Society of St. Petersburg in 1866. He credited his observations to a Doctor Inosemtzoff, who in 1857 had published a book titled *De la Cure de Lait,* which is also the title Karrell gave his paper. Karrell reported not only on the improvement of dropsy with his regime but also that of asthma, neuralgias, and liver disease. He attributed the curative powers of milk to its "diaphoretic, diuretic, resolvent or tonic" effects. Charles Richer (1850–1931), Professor of Physiology in Paris, famous for introducing the term "anaphylaxis" in medicine, reported in 1881 on the diuretic action of milk as well as that of different sugars. The use of a milk diet continued for over 40 years before the mechanism of its effectiveness was elucidated [16, 35].

Credit for the role of salt in edema formation belongs to two French physicians, Charles C. Achard (1860–1944) and M. Loeper, who in 1901 demonstrated that salt fed to patients in congestive heart failure could not be recovered as chloride in the urine and was not accompanied by an increase in plasma chloride. This finding was duplicated in the following 2 years by Fernand Widal (1862–1929) and his group in France and independently by Hermann Strauss (1868–1944) in Germany. Subsequently, Louis Henri Vaquez (1860–1936)

and Léon Ambard (b. 1876) demonstrated that congestive symptoms and pulmonary edema could be induced by the liberal feeding of salt and that patients on restricted salt diets could tolerate large amounts of water without an increase in edema. Shortly thereafter, in 1905, it was shown that the main feature of the milk diet of Karrell was its low salt content which led to the development of other forms of salt poor diets for the treatment of edema. However, as electrolyte measurements then were limited to that of chloride, the effect of salt restriction was attributed to its chloride content, hence the appellation, *cure de déchloruration*, allowed for the continued use of diets containing other salts of sodium [3, 16, 28, 35].

Unfortunately, these important observations went unnoticed, and dietary treatment remained empirical, centered primarily on caloric and water restriction, with little, if any, emphasis on salt content. While there was sporadic advocacy for salt restriction, particularly in the treatment of hypertension, the central role of sodium restriction was to await metabolic studies, conducted during and after the Second World War, that led to an understanding of the role of the kidney in salt retention. Subsequent studies confirmed the primacy of sodium in the production of edema as summarized eloquently by J. P. Peters in 1948 [27].

Henry A. Schroeder (b. 1906) was the first to point out the importance of salt as compared to water in the management of congestive heart failure. In a series of 23 edematous patients reported in 1941, he showed that weight loss invariably resulted when salt ingestion was limited to 1 g per day without any restriction of water intake. With the elucidation of the role of salt in the formation of edema, the administration of water "to the limit of water balance," to help the elimination of sodium by the kidneys and avoid cellular dehydration, emerged as another component of the dietary management of edema. The advice to "drink plentifully to clear dropsy" had been voiced as early as 1772 by William Withering and was revived at the turn of the century by Austin Flint (1836–1915) and in 1896 by William Osler (1849–1919) [1, 35].

Shortly after the end of World War II, the drive to restrict salt led to the introduction of cation-exchange resins in the management of edema. It was first shown that the acid forms of these resins ("hydrogen exchangers"), in doses of 40–150 g per day, were capable of mobilizing significant amounts of sodium into the stool. Their undesirable side-effects on the gastrointestinal tract and associated electrolyte disturbances (hypokalemia, acidosis), led to the development of exchange resins that were weak organic acids. Their usefulness was limited by the large amounts of the resins that had to be ingested daily, the variable amount of sodium removed, the gradual tolerance that developed, the continued need to restrict sodium, and their constipating effect [15, 28, 35]. All of this led to their limited use in the treatment of edema but the emergence of their use in treatment of hyperkalemia.

MERCURIALS

Mercury has an ancient medical history. Depending on the compound prescribed, it had been used as a cathartic (mercurous chloride), as an antiseptic (bichloride of mercury), and as an anti-syphilitic (first as a mercuric compound, and then as organic mercurials such as was introduced by Paul Ehrlich (1854–1915) in the form of the magic bullets, arsphenamine and neoarsphenamine). The diuretic properties of mercury were recognized by Paracelsus, in his quest for "specific" remedies derived from chemicals [25]. His report in 1553 of the diuretic action of mercury and its curative effect in dropsy is quite revealing:

> Mercury is the specific remedy in dropsy. This is due to a morbid extraction of salt from the flesh, a chemical process of solution and coagulation. As such this process does not depend at all upon quality and complexion, but is a "celestial virtue" endowed with its own "monarchy" to which quality and complexion are subservient. Mercury will drive out the dissolved salt, which has a harmful corrosive action on the organs, and preserve the solid—coagulated—state of the salt in the flesh, where it is needed to prevent putrefaction. Mercury will effect the cure specifically in everybody, although it causes vomiting in one and sweating in another. Neither vomiting nor sweating—the universal cures of the ancients—are therefore the curative factors. Hence he errs who says the patient must be cured with sweating or vomiting, for he fails to consider the manifold variety of man and that any effect of such remedies is merely the expression of the different reaction of individuals to the same remedy, not the cure itself.

Paracelsus used mercurous chloride, or calomel, an inorganic form of mercury, which was advocated for the mobilization of edema as late as the end of the 19th century. Various mixtures of calomel with foxglove and squill continued to be used through the first decade of the 20th century [11]. The most widely used of these contained metallic mercury with equal parts of digitalis and squill, and were labeled after prominent physicians or institutions: Niemeyer Pills, Guy's Hospital Pills, Baillie's Pills, and Addison's Pills. The specific merits of the latter in the treatment of diseases of the heart is extolled in an article that appeared in Guy's Hospital Reports in 1866:

> A very favorite combination of my late senior colleague Doctor Addison (Thomas Addison, 1793–1860) consisted of a grain of calomel, a grain of powdered digitalis, and a grain of powdered squill, given night and morning for several days. These remedies act powerfully upon the whole of the abdominal glands; free bilious evacuation takes place, a larger quantity of urine is excreted, and the venous distension is greatly lessened, and secondarily the right side of the heart is relieved of its excessive fullness.

The mechanism of action of calomel was unknown, although in 1866 it was demonstrated by Ernst Jendrássik (1858–1921) of Budapest that the urine of calomel-induced diuresis contained a significant amount of chloride. Because of the deleterious and occasional fatal effects of absorbed mercury, this form of

treatment gradually fell into disfavor, except as a last resort. In the meantime organic mercurials had come into use in the treatment of syphilis. While there is no fundamental difference between the diuretic action of organic and inorganic mercury, the inorganic form ionizes quite freely, binds to protein and is slow to reach the kidney, while the organic form ionizes poorly, is less protein bound, and reaches the kidney rapidly [10, 14]. Hence the greater diuretic property of organic mercurials first observed by Alfred Vogl (1895–1973), then a third-year medical student working in the Wenckebach Clinic in Vienna. The story told by Vogl was eloquently summarized by Julius Comroe [9] from whom the following quote is paraphrased, with some modifications:

> On October 7, 1919, in postwar Vienna, Johanna M., a young girl debilitated by congenital syphilis, was admitted to the First Medical University Clinic in Vienna under the care of Doctor Paul Saxl for treatment. It was not an "interesting case," the diagnosis was evident, and treatment was impossible. During rounds Doctor Saxl asked Vogl, a third-year medical student, to inject salicylate of mercury into the patient every other day; he thought it too late for it to be of any good, but at least it was active treatment and would do no harm. The drug was not available on the ward. Vogl ordered it in a water solution. When the drug did not appear for several days he phoned the pharmacy, only to learn to his embarrassment that salicylate of mercury was insoluble in water and would require another prescription for an oil solution. While still on the phone to the pharmacy, Vogl was approached by an elderly former army surgeon, named Raszowsky, who had been discharged when the Austro-Hungarian army disintegrated at the end of World War I. Producing a small box from his pocket, the surgeon said, "I received this sample in the mail this morning; it's a new mercurial antisyphilitic, Novasurol. Maybe you can use it instead." And with a sad smile he added, "I have no patients, anyway."
>
> At that time a new generation of hospital nurses was evolving, well educated and well trained. Making precise and beautiful charts was their pride, with everything recorded in various colors. They collected urine from each patient and measured its volume daily. Blue columns of varying height indicated the 24-hour urine production. On the day of the first injection, a tall, blue column on Johanna's chart indicated that her urine output had markedly increased. This appeared again after the second and third injections. Vogl excitedly mentioned it at rounds, his report was greeted with a benevolent smile and a lengthy discussion of biological rhythms.
>
> When after a lapse of 4 days he started the injections again, the tall blue columns promptly reappeared. Vogl then injected Novasurol into a patient with syphilitic heart disease in advanced congestive failure, in whom other diuretics had failed. Vogl was convinced that they had just witnessed "the greatest man-made diuresis in history." Now everyone became genuinely excited. Under a rather transparent blanket of secrecy, the search for more patients on whom to test the discovery continued. They were repeatedly able to reproduce these miraculous results, causing deluges at will, to the mutual delight of the patients and themselves. It was evident to Vogl now that the new antisyphilic drug was also a powerful diuretic, to be added to those already in use then: infusions of sarsaparilla, urea and theobromine. In January 1920, Vogl moved on to Berlin to continue his studies. Saxl and Robert Heilig, Vogl's student successor on the ward, continued to work with Novasurol. The name of Vogl does not appear in Saxl's original report or in Saxl and Heilig's subsequent article, both published in 1920.

Novasurol, a double-salt of sodium mercurichlorophenol acetate and diethylbarbituric acid, had been developed by the Bayer Company as a new antisyphilitic organomercurial and marketed as Merbaphen in the United States, where the first report of its success appeared in 1924 in a little-known publication, *Therapeutic Gazette,* under the title of "Novasurol in Cardionephritis with Edema"! Within a decade the direct effect of organomercurials on the kidney was established when it was shown that mercurials injected into one renal artery resulted in a prompt ipsilateral marked diuresis with only a delayed and insignificant diuresis from the contralateral kidney. Moreover, a strong diuresis persisted when the kidney of a dog injected with a mercurial was transplanted into the neck of a control dog [2]. The localization of their site of action within the nephron had to await another 40 years for the advent of clearance and micropuncture studies.

Soon after the introduction of Novasurol as a diuretic, its unrestricted use led to a number of cases of severe mercurialism. Nevertheless, for the next four decades organomercurials became a mainstay of the treatment of edema, and a succession of organomercurials of increasing diuretic efficacy and diminishing toxicity were introduced. Clearly, they were superior to what had been available previously: digitalis, which was effective only in patients with heart failure, and caffeine, a relatively mild diuretic. However, their lack of oral activity, their toxicity, and their tendency toward tachyphylaxis limited their utility in the regular treatment of edema. The search for less toxic organomercurials led to the introduction of mersalyl in 1924, developed at the Hoechst Laboratories and marketed by Winthrop as Salyrgan; it remained in vogue well into the 1950s [14, 17].

XANTHINES

For nearly four decades, beginning with the latter part of the 19th century and until the introduction of organomercurials, xanthines were the mainstay of diuretic therapy [3, 4, 22, 35]. The first xanthine to be used for its diuretic effect was caffeine in 1864. A resident physician in St. Petersburg, Russia, by the name of Koshlakoff, described a patient in severe congestive heart failure given citrated caffeine to improve cardiac function. One-quarter of a gram of citrated caffeine was given every 2 hr for 16 days. The urinary output increased, edema subsided, and the patient improved. Gradually, however, the patient appeared to become habituated to the drug, the urine output fell and the edema recurred [35].

Shrubs and berries containing caffeine and its analogs were described as diuretics in several herbals of the past. What prompted Koshlakoff to use caffeine is uncertain. In the early 1920s, Alfred N. Richards (1876–1966), then professor of pharmacology at the University of Pennsylvania, was frustrated by his

inability to explain to medical students the mechanism for the diuretic action of caffeine. He had used caffeine to study the renal microcirculation [29]. It was an effort to explain diuresis that led Richards and Joseph T. Wearn (1893–1984) to seek samples of tubular fluid at different points along the tubule that was to herald the era of micropuncture. Caffeine was one of the agents used in these studies [30, 36].

Caffeine held its undisputed position as a diuretic until 1887 when W. von Schroeder investigated the diuretic properties of theobromine, the alkaloid of cocoa bean and an analog of caffeine. Theobromine exceeded caffeine in both diuretic capacity and duration of action. The clinical demonstration of its efficacy led to the introduction of a combination of theobromine and sodium salicylate as a diuretic agent, which was successfully marketed by Knoll Company under the trade name of Diuretin in 1888. The third xanthine diuretic, theophylline, was extracted from tea leaves in 1888 but not introduced into therapeutic use until 1902, when it was synthesized and marketed by Bayer Company under the trade name of Theocin. In 1908, a new synthetic agent, aminophylline (theophylline ethylene diamine) was introduced by G. D. Searle and Company under the trade name of Emphyllin. The quest for orally effective xanthines with fewer side-effects led to the introduction of aminouracils, of which aminometradine (Rolicton) was marketed in 1953, too late for it to find a niche, as the sulfonamyl revolution in diuretic therapy was in full swing (Fig. 4).

The newer xanthine derivatives were considered especially valuable in patients with elevated blood urea in whom the use of organomercurials and acidifying agents were contraindicated. They remained in vogue well into the 1950s and were recommended as a diuretic by such luminaries as Paul Dudley White and Paul Wood. The solubility of the newer agents proved to be particularly suitable for the experimental investigation of their action. It allowed for the identification of a tubular effect of these agents in addition to their stimulation of cardiac output and renal vasodilation. It is not unexpected then that when a drop in glomerular filtration rate was observed once a diuresis was initiated by mercurials the xanthines were observed to sustain diuresis. This was to provide the basis of their clinical administration in succession—intramuscular mercurial followed 2 hr later by intravenous theophylline or aminophylline. The successful combination was marketed as Novurit, Mercurophylline, and Mercuzanthine [4, 10, 14, 28, 31, 35].

ACIDIFYING SALTS AND POTASSIUM SALTS

The diuretic effect of acidifying salts was described at the end of World War I. The two principal agents used were calcium chloride and ammonium chloride. Calcium chloride was the weaker of the two; when it was shown that its intravenous use resulted in calcification of the heart and soft tissues it quickly fell

out of favor, while oral ammonium chloride remained in use. However, when it became evident that the large doses (600 g) of ammonium chloride necessary for effective diuresis were toxic, ammonium chloride was used only infrequently. Furthermore, the severe metabolic acidosis that followed the large doses of ammonium chloride came to be termed "chloride acidosis" and gradually resulted in the limitation of its use. As a relatively mild diuretic of inconstant effectiveness its use was on the decline until the introduction of organomercurials, when once again it gained popularity as an adjunct to mercurial therapy. Other acidifying agents used, albeit less commonly, were ammonium bromide, ammonium nitrate, and magnesium sulfate [14, 28, 35].

Potassium salts were also used [19]. Potassium nitrate, or "salt of niter," had been recommended for the treatment of dropsy by Thomas Willis (1621–1675) in the 17th century (Fig. 4). With time other salts of potassium came into use. The remarks of Thomas Watson (1792–1882), a leading clinician of his day and author of one of the most widely read books in English on clinical medicine, *Lectures on the Principle and Practice of Physics* (1843), are illuminating in this respect:

> Diuretics are notoriously of most uncertain operations; sometimes completely answering our wishes, oftener perhaps disappointing them altogether. When the urine is strongly acid, and deposits, on cooling a sediment like brick dust, it may be well to try, at first, the alkaline diuretics, and particularly the salts of potass. Nitre, added to the common saline draught; or a combination of the acetate and bicarbonate of potass; or the bitartrate in small doses; or the iodide of potassium; or the liquor potasse.

Potassium salts remained in use well into the 20th century. The order of their diuretic efficacy was purported to be that of nitrate, chloride, bicarbonate, acetate, and citrate. As the toxic effects of potassium salts came to be appreciated their use was restricted. Interest in potassium salts was revived in 1932 when the use of potassium chloride to induce mercurial diuresis was introduced as a substitute for that of ammonium chloride.

OSMOTIC AGENTS

As early as 1892, W. Friedrich (b. 1864) had recommended urea in relatively small doses (2–14 g/day) for use in cardiac edema and cirrhotic ascites. In 1896, Georg Klemperer (1865–1946) used it successfully in cases of hepatic ascites, using larger doses (16–20 g/day). In the same year, and again in 1921, Hermann Strauss emphasized the merits of urea as a diuretic when given in large doses. Franz Volhard (1872–1905) used doses of 40–60 g per day in the treatment of patients with renal disease and reported a patient who had received 12 kg of urea over a period of 6 months [24, 28, 35]. The diuretic response to urea was considered equivalent to that of the available xanthines. By the 1940s

the prolonged use of urea was an accepted form of diuretic therapy because of its lack of toxicity and undiminished potency. The presence of renal insufficiency was not considered a contraindication; in fact, it was indicated because it lacked the nephrotoxicity of mercurials.

The use of a variety of other osmotic agents, including glucose, sucrose, xylose, mannitol, sorbitol, and creatinine were subsequently explored [3, 14, 28, 35]. Solutions of acacia or Gum Arabic, with a molecular weight of 240,000 and the potential to increase oncotic pressure, were recommended for nephrotic patients well into the 1940s. Unlike urea, all of these agents had to be administered intravenously, further limiting their usefulness. All resulted in only a modest sodium diuresis and caused an undesirable, at times symptomatic, volume overload. The only one to achieve some degree of continued clinical success was mannitol. Presently, its use is limited principally to forestall acute tubule necrosis and to diminish cerebral edema.

CARBONIC ANHYDRASE INHIBITORS

The last of the diuretic agents to be discovered by serendipity were the carbonic anhydrase inhibitors. Their subsequent development was to mark the entry of organic chemists into a new era characterized by diuretic design rather than fortuitous discovery.

The observation in 1937 that patients receiving one of the new antimicrobials, sulfanilamide, developed metabolic acidosis was to pave the way for the recognition of its diuretic property. Carbonic anhydrase had been discovered in 1932. In 1940, D. Keilin and T. Mann, two biochemists in Cambridge, had reported the carbonic anhydrase inhibitory properties of sulfanilamide. In 1942, Rudolph Höber had shown that the metabolic acidosis of frogs given sulfanilamide resulted from the increased excretion of bicarbonate. The presence of carbonic anhydrase in the kidney had been shown by Horace Davenport in 1941. These individual observations were essential links in establishing the role of carbonic anhydrase in urine acidification proposed earlier by Robert Pitts (1908–1977). Using sulfanilamide, Pitts and his associates showed that the reabsorption of bicarbonate was dependent on the secretion of hydrogen in the urine of dogs, a process requiring renal carbonic anhydrase that could be inhibited by sulfanilamide. That carbonic anhydrase is only a facilitator of this process was evident from the outset when the administration of massive doses of sulfanilamide, which inhibited over 99% of enzymatic activity, resulted in the excretion of less than 20% of the filtered bicarbonate [5, 21, 22, 28].

The connection of hydrogen ion secretion to sodium reabsorption was shown by William Schwartz, then a fellow at Peter Bent Brigham Hospital, in a study of the diuresis induced with sulfanilamide in three patients in congestive

heart failure who were refractory to mercurial diuretics [33]. The results, reported in 1949, showed that the diuretic activity of sulfanilamide resulted from inhibition of hydrogen secretion, thereby augmenting the excretion of sodium bicarbonate. The doses necessary to accomplish diuresis with sulfanilamide were large and nearly toxic. This limited its clinical usefulness but was sufficient for Richard O. Roblin (1907–1985), a chemist at American Cyanamid Company (Lederle Laboratories), to embark on the synthesis of other carbonic anhydrase inhibitors. Shortly after experimenting with a number of sulfanilamide-like compounds, Roblin discovered acetazolamide, an agent that was 2–3 orders of magnitude more potent than sulfanilamide as an inhibitor of carbonic anhydrase, which at low doses could inhibit 99% of the carbonic anhydrase activity of the kidney.

Acetazolamide was marketed as Diamox in 1954. Its life as a diuretic was limited (1954–1958) by the introduction of chlorothiazide in 1957. In addition, it quickly became evident that acetazolamide did not work after repeated administration because its diuretic effect was curtailed by the development of metabolic acidosis. The concurrent discovery of carbonic anhydrase in the eye led to its use in the treatment of wide-angle glaucoma. Thus, by the time acetazolamide was released in 1954, it had a new indication that was to become its principal utility in clinical medicine. The effective use of carbonic anhydrase inhibitors in glaucoma led to the development of a number of new agents, initially at Lederle Laboratories and, more recently, in the Merck, Sharp and Dohme Research Laboratories [10].

CHLOROTHIAZIDE

In 1943 Sharp & Dohme Inc. (merged with Merck and Company in 1952 to become Merck, Sharp and Dohme (MSD)) had set up what came to be known as the Renal Program headed by Karl H. Beyer, a pharmacologist, and James M. Sprague, an organic chemist (Fig. 6). Prompted by the work of Roblin on heterocyclic sulfonamides, the renal team embarked on an exploration of other sulfonamide derivatives that could mobilize edema by the elimination of sodium with chloride, rather than bicarbonate. Starting with sulfanilamide and modifying its structure, a series of compounds were developed and studied for their natriuretic and chloruretic properties. The first drug, dirnate, while a diuretic in animals, had limited success clinically. In 1955, 6½ years after the report by Schwartz, Frederick C. Novello, an organic chemist recruited to the Renal Program, synthesized chlorothiazide, and another pharmacologist who had joined the Renal Program, John E. Baer, showed that the new compound increased the excretion of sodium and chloride in almost equal amounts with minimal loss of bicarbonate. This was a landmark discovery that was to revo-

FIGURE 6. The Renal Team at Merck, Sharp & Dohme Research Laboratories responsible for the discovery and development of chlorothiazide, which was recognized by the Lasker Award in 1975. From left to right: John E. Baer, Ph.D.; Karl H. Beyer, Jr., M.D., Ph.D.; Frederick C. Novello, Ph.D.; and James M. Sprague, Ph.D. (c. 1966).

lutionize the treatment of edema. Fourteen months of clinical tests established chlorothiazide as a safe orally effective diuretic that began to be marketed in 1957 [4, 5]. Initially, chlorothiazides were thought to act in the ascending loop of Henle. Subsequent studies, however, identified its principal site of action on the distal tubule, with a small acetazolamide-like effect in the proximal nephron.

Two of the first clinical reports on chlorothiazide, published in 1957, were on its use in the treatment of hypertension. Edward Freis and Ilse Wilson in Washington and William Hollander and Robert Wilkins in Boston independently reported the effectiveness of chlorothiazide in the treatment of hypertension [9]. While a role for salt restriction in the treatment of hypertension had been used and the Kempner Diet, then in style, had its strong advocates, the use of a diuretic agent in the management of hypertension had not been entertained seriously.

Because of their safety and effectiveness as oral agents in the management of edema and hypertension, as well as their usefulness in the exploration of renal function in the laboratory, the sulfonamyl diuretics can easily be ranked among the most important pharmacological discoveries and, alongside the antibiotics, one of the noteworthy drugs of post-World War II medicine.

LOOP DIURETICS

The increased understanding of the renal handling of sodium led to the quest for more potent diuretics that could act at a more proximal site of the nephron than that of thiazides, where larger quantities of sodium are absorbed. This was important for in cases of pulmonary edema where fluid had to be removed quickly from the body mersalyl (Salyrgan) continued to be used well after chlorothiazide became available, since the latter induced an excretion of only 5% of filtered sodium whereas the maximum effect of salyrgan was about 20% of the filtered load of sodium.

The search began in two laboratories. At the MSD Laboratories in West Point, Pennsylvania, an agent based on the structure of chlorothiazide was sought; at Hoechst Laboratories in Frankfurt, Germany, the structure of the sulfonamyl derivatives was the starting point [5, 22]. The MSD Laboratories eventually synthesized ethacrynic acid, a potent inhibitor of sodium in the thick ascending limb of Henle. At Hoechst, chemists synthesized furosemide in 1959 and released it in 1964. Its principal site of action was also the thick ascending limb of Henle, with a minor additional inhibitory effect on sodium reabsorption in the proximal tubule attributable to its sulfonamide structure. Since furosemide was active orally and had little toxicity, it soon became the loop diuretic of choice.

POTASSIUM-SPARING DIURETICS

One of the side-effects of diuretics is the excessive excretion of potassium caused by the increased delivery of sodium to the distal tubule, in a setting of increased levels of aldosteronism associated with the underlying disease state or induced by volume depletion secondary to successful diuresis.

While potassium losses could be clinically managed by potassium supplementation, it prompted the quest for agents that could block the distal secretion of potassium by interfering with the reabsorption of sodium at this site [10, 14]. The first agent to be used for this purpose was spironolactone, a competitive inhibitor of aldosterone, introduced in 1961 by G. D. Searle. A second agent, triamterene, was developed by Smith, Kline, and French. It was quickly recognized as a distal noncompetitive inhibitor of sodium reabsorption, resulting secondarily in diminished potassium secretion. Moreover, it could block the potassium losses caused by other diuretics while potentiating their effect to the extent that it was capable of blocking sodium reabsorption in the cortical collecting tubule. Another potassium-sparing agent, amiloride, was introduced by the MSD Research Laboratories.

All three "potassium-sparing" diuretics are characterized by a primary inhibition of sodium reabsorption in the distal nephron—spironolactone by a competitive inhibition of aldosterone, triamterene and amiloride by a blockade of sodium channels. Secondarily, all three agents diminish potassium and hydrogen secretion. Spironolactone differs from the other two diuretic agents only in its dependence on the presence of aldosterone for the expression of its inhibitory action.

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PART II

Renal Electrolyte Transport and Its Regulation

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CHAPTER II

Renal Electrolyte Transport and Its Regulation

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In this chapter we review how the kidney transports electrolytes and water, and how these processes are regulated. The chapter will then form the basis for an understanding of the multiplicity of diuretic effects, many potentially therapeutic, some responsible for unwanted side effects. The nephron is divided into a number of functional segments, shown in Fig. 1. We begin by discussing the mechanisms of renal Na^+, Cl^-, H^+, HCO_3^-, and K^+ transport. Sections addressing the transport of NH_4^+, Ca^{2+}, Mg^{2+}, and phosphate follow. We conclude with a discussion of water transport, urinary concentration and dilution, and transport of diuretics.

SODIUM, CHLORIDE, HYDROGEN, BICARBONATE, AND POTASSIUM TRANSPORT

PROXIMAL TUBULE

Approximately 50% of filtered NaCl and 70–90% of filtered $NaHCO_3$ are reabsorbed in the proximal tubule. The proximal tubule is subdivided into three segments, the most proximal S_1, the middle S_2, and the terminal S_3 segment. In

Diuretic Agents: Clinical Physiology and Pharmacology

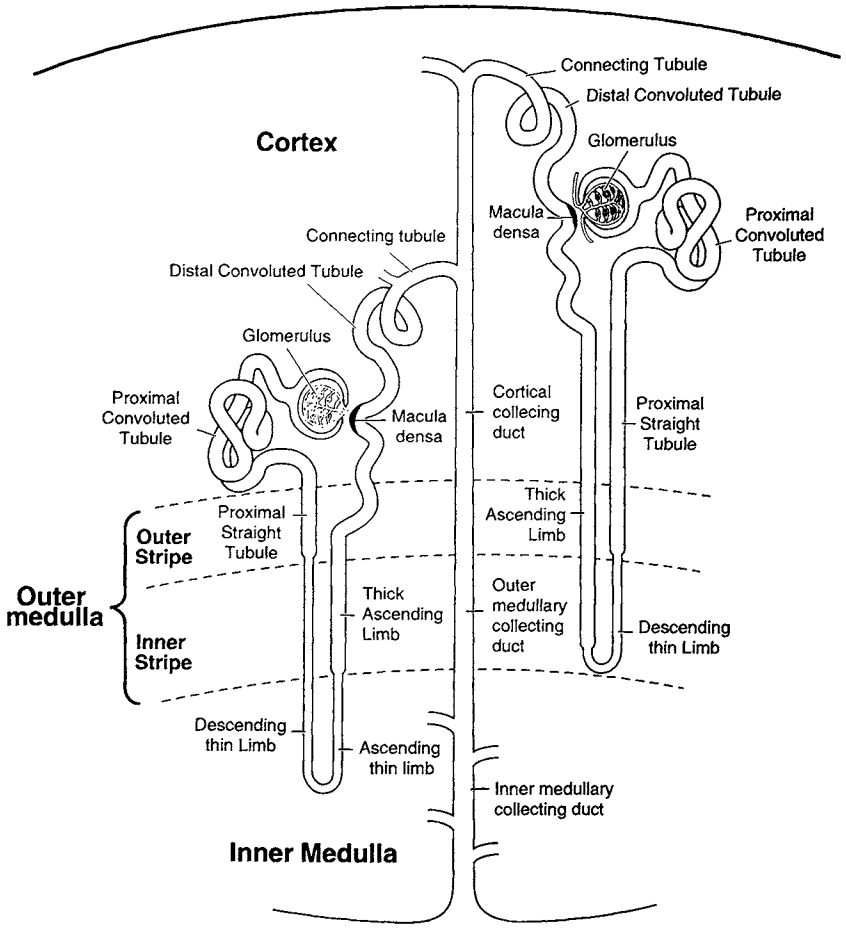

FIGURE 1. Segments of the nephron.

general, Na^+ transport mechanisms are qualitatively similar in these segments, but differ quantitatively. Transport rates in S_1 are most rapid, slower in S_2, and slowest in S_3. The proximal tubule can also be divided into an early proximal convoluted tubule which includes S_1 and part of S_2 and is convoluted and a proximal straight tubule which includes the remainder of S_2 and S_3 and is straight (Fig. 1).

Figure 2 shows a general model of a proximal tubule cell containing the most important transporters that are key to NaCl and $NaHCO_3$ reabsorption. A number of these transport proteins have been purified and/or cloned. The

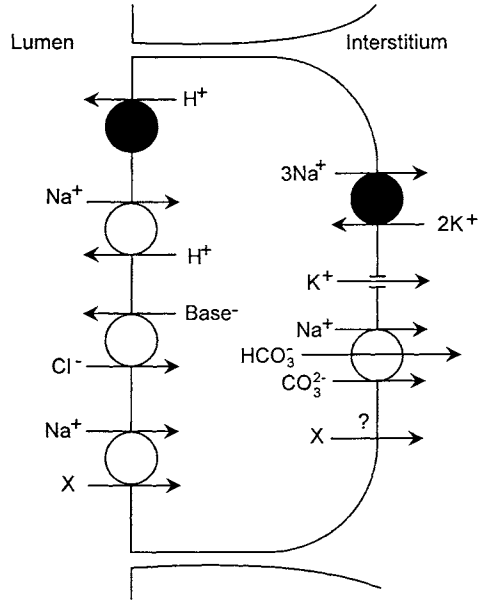

FIGURE 2. Proximal tubule Na^+ and H^+ transporters. ●, Active transport mechanism; ○, passive transporter; =, channel.

Na/K ATPase includes two subunits, α and β. All of the transport functions are mediated by the α subunit. The β subunit is heavily glycosylated and may play a role in trafficking of the Na/K ATPase to the basolateral membrane. Three isoforms of the α subunit and two isoforms of the β subunit have been identified. The predominant isoforms expressed in the kidney are $\alpha 1$ and $\beta 1$, but this varies between nephron segments and among species.

Five Na/H antiporter isoforms have been cloned. These all have a similar structure with an amino terminal domain containing 10–12 membrane spanning regions and a large carboxyterminal cytoplasmic regulatory domain. The predominant isoform encoding the proximal tubule *apical* membrane Na/H antiporter is NHE-3. In some segments of the proximal tubule, there is also a basolateral membrane Na/H antiporter, which is encoded by NHE-1. This is not shown in Fig. 2 because basolateral Na/H exchange does not contribute to transepithelial Na^+ or H^+ transport, but rather contributes to cellular housekeeping functions. The Na/H antiporter is inhibited by the diuretic *amiloride*. However, the concentrations of amiloride achieved clinically are too low to inhibit this transporter. Thus, *clinically amiloride is without effect on the proximal tubule.*

Acidification

Reabsorption of filtered $NaHCO_3$ from the proximal tubule luminal fluid is mediated by H^+ secretion, as shown in Fig. 3. H^+ secreted into the luminal fluid neutralizes OH^- ions causing luminal acidification. Luminal carbonic anhydrase then catalyzes the conversion of $HCO_3^- \rightarrow CO_2$ and OH^-; the CO_2 then diffuses out of the lumen. CO_2 inside the cell, now catalyzed by intracellular carbonic anhydrase, combines with OH^- and forms HCO_3^-. OH^- and H^+ are formed from H_2O within the cell. The H^+ is secreted into the lumen while the HCO_3^- exits across the basolateral membrane. As can be seen, both luminal and cellular carbonic anhydrase play key roles in this scheme. *Luminal* carbonic anhydrase activity is encoded by the membrane-bound isoform, type IV carbonic anhydrase. Cytoplasmic activity may be encoded by the membrane bound type IV or by cytosolic type II carbonic anhydrase.

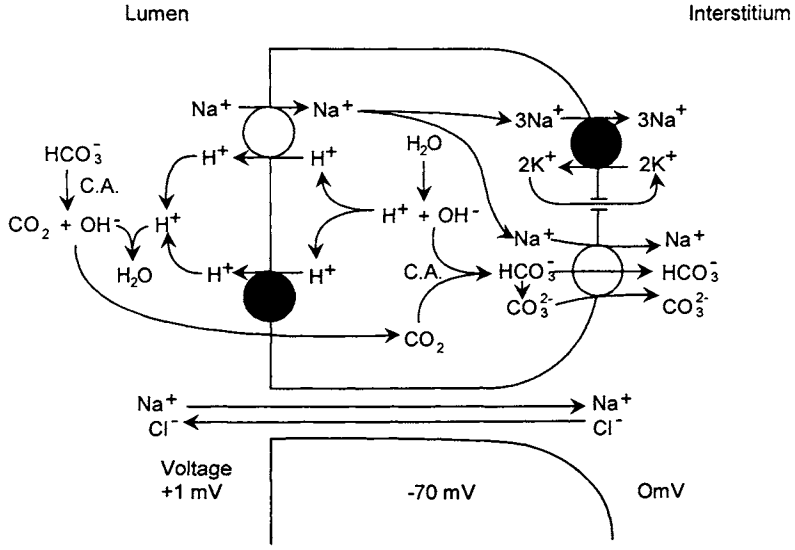

FIGURE 3. Proximal tubule $NaHCO_3$ reabsorption. H^+ is secreted into the proximal tubule lumen by an Na/H antiporter and an H ATPase. OH^- generated within the cell by apical membrane H^+ secretion reacts with CO_2 to form HCO_3^- and CO_3^{2-}, which exit with a Na^+ on the basolateral membrane $Na^+/HCO_3/CO_3$ cotransporter. Na^+ absorbed by the Na/H antiporter exits the cell on the basolateral membrane NaK ATPase and the $Na/HCO_3/CO_3$ cotransporter. K^+ which enters the cell on the NaK ATPase exits on a basolateral membrane K^+ channel. Carbonic anhydrase catalyzes the conversion of HCO_3^- to CO_2 and OH^- in the lumen and the reverse reaction in the cell. Electrogenic H^+ secretion generates a small lumen positive voltage which generates a current flow across the paracellular pathway. This comprises mostly Na^+ efflux and Cl^- influx into the lumen. ●, Active transport mechanism; ○, passive transporter; =, channel. C.A., carbonic anhydrase.

As will be discussed later, *carbonic anhydrase inhibitors* block proximal tubule HCO_3^- absorption because they prevent the formation of CO_2 and OH^- from HCO_3^- in the luminal fluid and the conversion of CO_2 and OH^- to HCO_3^- within the cell. In the absence of carbonic anhydrase, secreted H^+ would react with luminal HCO_3^- to form H_2CO_3, which could then slowly dehydrate to form CO_2 and H_2O. The CO_2 would then diffuse into the cell where it could form H_2CO_3 and then slowly dissociate to H^+ and HCO_3^-. However, rates of proximal tubule HCO_3^- absorption observed in the presence of carbonic anhydrase inhibitors are greater than would be predicted from the uncatalyzed rates of H_2CO_3 dehydration and CO_2 hydration. The explanation for the high rate of carbonic anhydrase independent HCO_3^- absorption likely resides in H_2CO_3 recycling. Following inhibition of carbonic anhydrase, luminal H_2CO_3 concentration rises and cytoplasmic H_2CO_3 concentration falls. This generates an increased gradient for nonionic diffusion of H_2CO_3 which, together with a high apical membrane H_2CO_3 permeability, allows H_2CO_3 recycling to support a limited but significant rate of luminal acidification. Thus in the presence of carbonic anhydrase inhibitors, rates of $NaHCO_3$ absorption are significantly slowed, but are not as slow as would be predicted from uncatalyzed rates of H_2CO_3 dehydration and CO_2 hydration.

In general, apical membrane H^+ secretion in the proximal tubule occurs by two distinct mechanisms, electroneutral transcellular $NaHCO_3$ absorption, and electrogenic HCO_3^- absorption. Approximately two-thirds of HCO_3^- absorption is mediated by a transcellular electroneutral mechanism, while one-third is mediated by an electrogenic mechanism. These mechanisms will now be discussed.

1. *Electroneutral Transcellular $NaHCO_3$ Absorption (Fig. 3).*

In this mode, the basolateral membrane Na/K ATPase utilizes the energy of ATP hydrolysis to transport Na^+ out of the cell and K^+ into the cell. K^+ then diffuses out across the basolateral K^+ conductance, generating a cell-negative voltage. The low cell $[Na^+]$ provides a driving force for the apical membrane Na/H antiporter and allows Na^+ to enter passively while actively extruding H^+. The transporter functions with a 1:1 $Na^+:H^+$ stoichiometry. Base generated within the cell exits either as HCO_3^- per se, or as CO_3^{2-} on the $Na/HCO_3/CO_3$ cotransporter. CO_3^{2-} is formed from HCO_3^- according to the reaction: $2HCO_3^- \rightarrow CO_2 + CO_3^{2-} + H_2O$. The $Na/HCO_3/CO_3$ cotransporter carries two negative charges. The electrochemical driving force for Na^+ is in the direction of cell entry. However, because of the high cell-negative voltage there is a large favorable electrochemical gradient for efflux of HCO_3^- and CO_3^{2-}, which drives the transporter.

If one considers three turnovers of the Na/H antiporter, three H^+ enter the

luminal fluid leading to the generation of three HCO_3^- in the cell. This is accompanied by the movement of three Na^+ from the lumen into the cell. The $Na/HCO_3/CO_3$ cotransporter mediates the exit of one HCO_3^- and one CO_3^{2-}, equivalent to three HCO_3^-, with one Na^+. The Na/K ATPase would then have to turn over 2/3 times to effect absorption of two Na^+ and entry of 4/3 K^+, the latter exiting via the basolateral membrane K^+ conductance. In sum, these processes lead to no net charge transfer (the number of cations and anions crossing each membrane are equal), such that there is no requirement for paracellular transport. Net transport across the apical membrane involves movement of three Na^+ into the cell and three H^+ into the lumen, resulting in zero net charge transfer. Transport across the basolateral membrane results in absorption of three Na^+, one HCO_3^-, and one CO_3^{2-}, with recycling of K^+, once again resulting in no net charge transfer.

2. Electrogenic H^+ Secretion (Fig. 3).

A second mechanism of transport involves apical membrane electrogenic H^+ secretion. Here, H^+ is actively secreted into the luminal fluid driven by metabolism of ATP. HCO_3^- and CO_3^{2-} formed in the cell then exit across the basolateral membrane on the $Na/HCO_3/CO_3$ cotransporter, once again as described above. This must be accompanied by Na^+ efflux on the basolateral membrane cotransporter and thus requires entry of an Na^+ across the apical membrane, likely by Na^+-coupled transport of solutes such as glucose, amino acids, phosphate, and mono- and dicarboxylic acids. This mode of transport is electrogenic in that for every three H^+ secreted into the lumen and three negatively charged base equivalents exiting to the interstitium, only one Na^+ is absorbed. Thus, this mechanism will generate a lumen positive voltage (approximately +1 mV) which will drive a passive paracellular current that could be outward cation diffusion or inward anion diffusion. Based on the measured properties of the proximal tubule tight junction, it will likely involve some combination of Na^+ diffusion out of the lumen (equivalent to net $NaHCO_3$ absorption) and Cl^- diffusion into the lumen (equivalent to net HCl secretion or Cl^-/HCO_3^- exchange).

NaCl Absorption

There are three general mechanisms of NaCl absorption in the proximal tubule, electroneutral transcellular NaCl absorption, electrogenic Na^+ absorption, and passive paracellular NaCl absorption (Fig. 4).

1. Electroneutral Transcellular NaCl Absorption (Fig. 4).

Transcellular Na^+ absorption may result, as described above, from the coordinated activities of the basolateral membrane Na/K ATPase and K^+ channel,

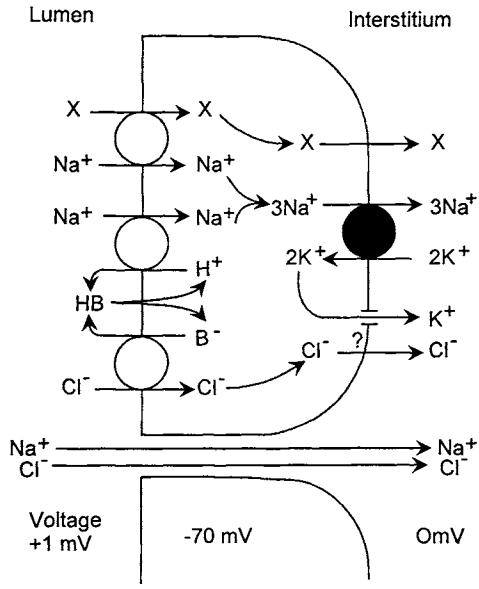

FIGURE 4. Proximal tubule NaCl absorption. Three modes of NaCl absorption are shown. Electroneutral transcellular NaCl absorption is mediated by parallel apical membrane Na/H and Cl/base exchangers, with the protonated base recycling across the apical membrane. Electrogenic Na^+ absorption is mediated by a Na^+-coupled cotransporter which carries a number of different solutes (designated X). Na^+ which enters the cell across an apical membrane transporter, exits the cell on the basolateral membrane Na/K ATPase. K^+ which enters the cell on the Na/K ATPase exits on a basolateral membrane K^+ channel. The mechanism of basolateral membrane Cl^- efflux is not fully understood but may involve a Cl^- conductance, a KCl cotransporter, or a $Na(HCO_3)_2/Cl$ exchanger. Electrogenic Na^+ absorption establishes a lumen negative voltage which drives a paracellular current. In addition, active transport of $NaHCO_3$ and organic solutes generates a high luminal Cl^- concentration which drives paracellular Cl^- absorption and generates a lumen + voltage that drives paracellular Na^+ absorption (passive paracellular NaCl absorption). •, Active transport mechanism; ○, passive transporter; =, channel; B^-, base; HB, protonated base.

and the apical membrane Na/H antiporter. However, if in addition, an apical membrane Cl/base exchanger operates at a rate equal to that of the apical membrane Na/H antiporter the net result is NaCl absorption. Secretion of H^+ and a negatively charged base (B^-) at equal rates leads to generation of the neutral acid, HB, which is lipophilic and is thought to recycle across the apical membrane. It is also possible that a specific HB transporter exists. Thus, with this mode of transport there is no net H^+ secretion and thus no luminal acidification or bicarbonate absorption. Na^+ and Cl^- enter the cell across the apical membrane at equal rates.

The nature of the base exchanged with Cl^- is not totally settled but appears to include OH^-, formate$^-$, and oxalate$^-$. Na^+ which enters the cell on the Na/H antiporter exits on the basolateral membrane Na/K ATPase. Possible mecha-

nisms of basolateral membrane Cl^- efflux include: (i) a Cl^- conductance; (ii) an electroneutral KCl transporter where K^+ exits with Cl^- rather than across the K^+ conductance; and (iii) a $Na(HCO_3)_2/Cl$ exchanger where Na^+ and $2HCO_3^-$ enter the cell in exchange for Cl^-. The Na^+ and HCO_3^- can then leave the cell on the $Na/HCO_3/CO_3$ cotransporter. With all of these mechanisms, the net result is efflux of equal amounts of Na^+ and Cl^- with recycling of various ions. Thus, transcellular NaCl absorption is electroneutral, requiring no paracellular transport.

2. *Electrogenic Na^+ Cotransport (Fig. 4).*

Na^+ can also cross the apical membrane on a cotransporter which carries Na^+ and another solute such as sugars, amino acids, phosphate, sulfate, or organic anions such as citrate. Na^+ then exits across the basolateral membrane on the Na/K ATPase. The other solute exits the basolateral membrane by a variety of mechanisms including facilitated diffusion. If the number of Na^+ ions exceeds the number of negative charges on the cotransported solute, transport is electrogenic and will generate a lumen-negative voltage. This will then serve to drive either paracellular Cl^- absorption (resulting in net NaCl absorption) or paracellular Na^+ secretion (resulting in Na^+ recycling). Once again, the relative magnitudes of these passive processes are determined by the ratio of Na^+ and Cl^- permeabilities of the tight junction.

3. *Passive Paracellular NaCl Absorption (Figs. 4 and 5).*

The last mechanism of NaCl absorption is passive paracellular NaCl absorption. Because the proximal tubule is highly permeable to water (see below), the total concentration of solutes in the luminal fluid remains relatively constant along the length of the tubule. Thus, the active reabsorption of organic solutes

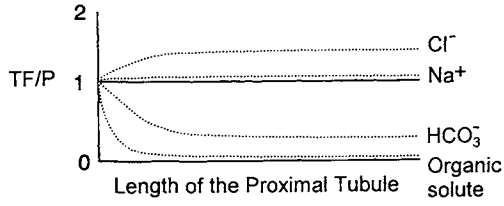

FIGURE 5. Profile of solute concentrations along the length of the proximal tubule. The ratio of tubular fluid to plasma solute concentration (TF/P) is plotted as a function of length along the proximal tubule. Active reabsorption of organic solutes with secondary water reabsorption leads to decreases in luminal organic solute concentrations and small increases in the luminal concentrations of Na^+ and Cl^-. Active reabsorption of $NaHCO_3$ with secondary water reabsorption leads to a decline in luminal HCO_3^- concentration and a further increase in luminal Cl^- concentration.

from the luminal fluid leads to water reabsorption which results in a modest increase in the concentration of Na^+ and Cl^- in the lumen (Fig. 5). In addition, the rapid rate of $NaHCO_3$ absorption in the early proximal tubule causes water reabsorption, resulting in a decrease in luminal HCO_3^- concentration and an increase in luminal Cl^- concentration (Fig. 5). The net result is a small concentration gradient for passive Na^+ absorption and large concentration gradients for passive Cl^- absorption, HCO_3^-, and organic solute secretion. Because proximal tubule paracellular permeability for Cl^- greatly exceeds that for HCO_3^- and organic solutes, passive Cl^- absorption predominates. This leads to a lumen-positive voltage which drives passive Na^+ absorption. The net result is passive *paracellular* NaCl absorption.

Regulation of NaCl and $NaHCO_3$ Absorption (Table 1)

The majority of filtered NaCl and $NaHCO_3$ reabsorption takes place in the proximal tubule, and this nephron segment is also an important site of regulation, by modulation of both transcellular and paracellular ion fluxes. Because of the *key* role of the apical membrane Na/H antiporter in proximal salt retrieval from the filtrate, this transporter is a key site of regulation. As pointed out above, the Na/H antiporter mediates 2/3 of transcellular $NaHCO_3$ absorption and all of transcellular NaCl absorption. In addition, by mediating $NaHCO_3$ absorption, it also contributes to the high luminal Cl^- concentration which provides the driving force for passive paracellular NaCl absorption (Fig. 5). In many conditions, the activity of the $Na/HCO_3/CO_3$ cotransporter is regulated in parallel with that of the Na/H antiporter. This allows significant changes in the rates of $NaHCO_3$ and NaCl transport, while cell pH remains close to normal.

TABLE 1 Regulation of Proximal Tubular NaCl and $NaHCO_3$ Absorption

Glomerulotubular balance
Luminal pH and HCO_3 concentration
Direct effect of luminal flow rate on the Na/H antiporter
Chronic adaptation in the Na/H antiporter and the $Na/HCO_3/CO_3$ cotransporter
Decreases in intracellular pH (metabolic acidosis, K^+ deficiency)
Effective arterial volume
Physical factors
Angiotensin II
Endothelin
Renal nerves ($\alpha 2$ adrenergic, dopamine)
Miscellaneous
PTH

In general there are three physiologically important regulatory determinants of proximal tubule NaCl and $NaHCO_3$ absorption. First, increases in glomerular filtration rate (GFR) cause proportional increases in NaCl and $NaHCO_3$ absorption. Because augmentation of GFR increases the filtered loads of these solutes, parallel stimulation in reabsorption is required to prevent massive bicarbonaturia and salt wasting. This phenomenon is referred to as *glomerulotubular balance.* Three mechanisms have been identified to explain this phenomenon. First, increases in GFR and thus luminal flow rate lead to increases in luminal pH and HCO_3^- concentration. In the presence of higher luminal flow rates, a given rate of H^+ secretion will lower the luminal HCO_3^- concentration and thus pH to a lesser degree. The net result is a higher luminal pH and HCO_3^- which causes the rate of cellular H^+ secretion to increase. Second, acute increases in luminal flow rate cause a rapid activation of Na/H antiporter activity. The mechanism responsible for this effect is not yet elucidated but may involve flow dependent mixing of an unstirred layer in the lumen, or may involve activation of a signaling pathway by cell stretch. Last, chronic elevations of GFR lead to adaptive increases in the activities of the Na/H antiporter and the Na/HCO_3/CO_3 cotransporter.

A second major regulator is cell pH. Decreases in cell pH, which occur in metabolic acidosis and K^+ deficiency, increase the activities of the Na/H antiporter and the Na/HCO_3/CO_3 cotransporter, leading to increased rates of $NaHCO_3$ reabsorption. However, in metabolic acidosis there is significant inhibition of passive paracellular NaCl absorption. This occurs because the concentration of $NaHCO_3$ in the filtrate is low, and thus the ability of $NaHCO_3$ absorption to decrease luminal HCO_3^- concentration and increase luminal Cl^- concentration is limited. The net result is inhibition of passive NaCl absorption.

One of the most important regulators of proximal tubule transport is effective arterial volume. Decreases in effective arterial volume increase net $NaHCO_3$ and NaCl absorption. This is of prime importance in the regulation of the effective arterial volume and blood pressure, and is likely important in mediating the effect of volume contraction to maintain metabolic alkalosis. Contraction of effective arterial volume has been shown to lower tight junction and paracellular permeability which can decrease the backleak of HCO_3^- into the lumen and thus increases net HCO_3^- absorption. However, given that some NaCl is absorbed across the paracellular pathway, a decrease in permeability cannot explain the observed increase in NaCl absorption. Thus, decreased effective arterial volume also directly stimulates transcellular NaCl and $NaHCO_3$ absorption.

Stimulation of transcellular NaCl absorption in response to decreased effective arterial volume is related in part to coordinated effects of increased peritubular capillary protein concentration and decreased peritubular capillary hy-

drostatic pressure (so-called physical factors). Decreases in effective arterial volume lead to efferent arteriolar vasoconstriction which results in a decrease in peritubular capillary hydrostatic pressure and an increase in filtration fraction, which secondarily results in higher peritubular capillary oncotic pressures. Both of these physical factors would be expected to increase the rate of fluid movement into the peritubular capillary, but it is not clear how this leads to an increase in tubular NaCl transport. The above changes in glomerular hemodynamics are likely related to changes in the levels of hormones such as angiotensin II, autocrine/paracrine factors such as endothelin-1 and endothelin-3, or increased renal nerve activity.

In addition, these factors have been demonstrated to regulate directly proximal tubule transport, independent of changes in hemodynamics. Angiotensin II, endothelins, and α_2 adrenergic catecholamines increase apical membrane Na/H antiporter activity, whereas dopamine inhibits Na/H exchange. In addition, dopamine lowers Na^+ reabsorption by inhibiting basolateral Na/K ATPase activity. PTH (parathyroid hormone) is also a potent inhibitor of the proximal tubular Na/H antiporter, but the physiologic significance of this is unclear.

Potassium Transport

The proximal tubule reabsorbs 50–70% of filtered K^+. The magnitude of K^+ absorption parallels the magnitudes of Na^+ and volume absorption. This relationship is due to the fact that the majority of K^+ absorption occurs passively and is indirectly coupled to volume absorption. Volume absorption causes an increase in luminal K^+ concentration which provides a driving force for K^+ diffusion across the paracellular pathway. There may also be some convective K^+ absorption (solvent drag) which would be more directly coupled to volume absorption.

The proximal tubule cell has K^+ conductances on its apical and basolateral membranes. The *basolateral* K^+ conductance, mediated by ATP-inhibitable K^+ channels, is physiologically important because it plays a key role in the generation of the cell-negative potential. The latter is a major driving force for passive movement of positively charged solutes across the apical brush border membranes. Under certain experimental conditions small active transcellular K^+ fluxes can be demonstrated, but these fluxes are physiologically insignificant. Thus, the majority of proximal tubule K^+ absorption is passive and coupled directly and indirectly to volume absorption.

In the S_3 proximal tubule some passive K^+ secretion into the luminal fluid has been reported. This flux is driven by high medullary interstitial K^+ concentrations. Such passive secretion, which continues in the thin descending limb, is a component of potassium recycling and is discussed below.

Thin Limbs of the Loop of Henle (Fig. 6)

The thin descending limb of the loop of Henle begins in the outer medulla as a gradual transition from the pars recta and ends with a hairpin turn at the tip of the loop of Henle. In general, thin limbs from juxtamedullary nephrons descend deeply into the medulla, while thin limbs from more superficial nephrons descend only superficially into the medulla. After the hairpin turn, the ascending limb begins. While *juxtamedullary* nephrons have well developed thin ascending limbs that end at the junction of the inner and outer medulla, more superficial nephrons lack thin ascending limbs.

Transport in the thin limbs is mostly passive. As fluid descends in the thin descending limb, it is exposed to an increasingly hypertonic interstitium. Because the water permeability of descending segments is relatively high, and solute permeabilities are relatively low, most of the osmotic equilibration occurs by water absorption. This leads to a fluid that arrives at the tip of the loop of Henle that is almost isosmotic with the interstitium, but is very different in com-

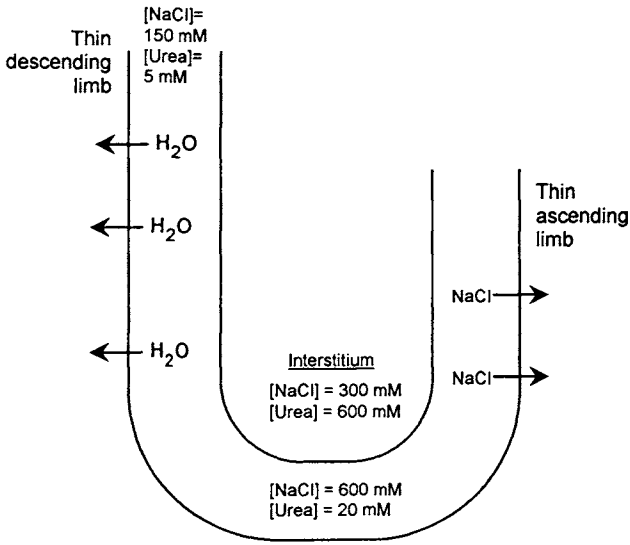

FIGURE 6. Passive H_2O and NaCl absorption in the inner medulla. The thin descending limb is highly permeable to water and relatively impermeable to solutes. As tubule fluid travels down the thin descending limb, luminal NaCl and urea are concentrated by water abstraction. The thin ascending limb has a high NaCl permeability and low permeabilities to urea and water. As the tubular fluid travels along the thin ascending limb, there is passive NaCl absorption. Although there is a large gradient for urea secretion, permeability is low.

position. Such luminal fluid has significantly less urea, but significantly higher concentrations of NaCl than are present in the medullary interstitium (Fig. 6).

The thin ascending limb has a very low water permeability and very high permeabilities to Na^+ and Cl^-. Cl^- permeability is two to four times that of Na^+ permeability. While there is some permeability to urea, it is significantly lower than NaCl permeability. As fluid passes along the thin ascending limb, the transepithelial NaCl concentration gradient (lumen greater than interstitium) leads to significant passive NaCl absorption. While there is also a passive gradient for urea to enter the lumen, the lower urea permeability limits this flux. Because the Cl^- permeability is significantly larger than the Na^+ permeability, passive NaCl absorption leads to a lumen-positive voltage. This lumen-positive voltage serves as a passive driving force for absorption of all cations, including K^+, Ca^{2+}, and Mg^{2+}. While in theory, Na^+ and Cl^- absorption could occur across the paracellular pathway, significant evidence suggests that at least part of Cl^- reabsorption is transcellular and takes place across apical and basolateral membrane Cl^- conductances.

It should be noted that all of the driving forces for passive transport are established by passive H_2O absorption in the thin descending limb. Thus, any condition which alters medullary interstitial osmolality will also affect passive H_2O absorption in the thin descending limb and secondarily regulate passive solute fluxes in the thin ascending limb. This effect is most pronounced with *loop diuretics* which almost completely inhibit the generation of a hypertonic medullary interstitium.

Water abstraction in the thin descending limb causes a significant increase in the concentration of HCO_3^- and pH in the luminal fluid. Under most conditions, there is no significant transepithelial flux of $NaHCO_3$ in the thin limbs. One exception is in the presence of *carbonic anhydrase inhibitors*. Here, decreased rates of proximal tubule HCO_3^- absorption and normal rates of water abstraction in the thin descending limb combine to generate very high luminal concentrations of HCO_3^- and H_2CO_3, which provides a driving force for significant passive absorption. While the specific ion species transported have not been established, the low ionic permeability of the thin descending limb and the limited ability to form CO_2 in the absence of carbonic anhydrase suggest that the transported species is H_2CO_3.

Driven by the high medullary interstitial K^+ concentration, K^+ diffuses passively into the thin *descending* limb. Most of this K^+ is reabsorbed in the thin and thick ascending limbs and the medullary collecting duct. The physiologic purpose of this "K^+ recycling" is presently not clear. Possibly, the accumulation and high concentration of K^+ in the medullary interstitium may limit the passive loss of K^+ from the collecting ducts. In the thin *ascending* limb, K^+ absorption is passive, driven by the lumen positive voltage.

THICK ASCENDING LIMB

The thick ascending limb (TAL) begins at the junction between the inner and the outer medulla for deep nephrons and at the tip of the loop of Henle for more superficial nephrons. The thick ascending limb includes medullary and cortical segments and ends at the juxtaglomerular apparatus, where the nephron abuts against its own glomerulus.

Figure 7 shows a cell model that includes mechanisms for NaCl and $NaHCO_3$ absorption in the thick ascending limb. The mechanism of NaCl absorption begins, once again, with an NaK ATPase in the basolateral membrane. K^+ which enters the cell on the Na/K ATPase exits on a basolateral membrane K^+ channel. The resulting decrease in cell Na^+ concentration provides the driving force for the apical membrane electroneutral Na/K/2Cl cotransporter. When considered on the basis of electrochemical gradients, there is a large passive electrochemical gradient for Na^+ entry on this transporter, including a significant chemical concentration gradient as well as the cell negative voltage. This provides the driving force for the transport of K^+ and Cl^- against their passive electrochemical gradients. Potassium which enters the cell across the apical membrane mostly recycles back into the lumen across the apical membrane K^+ channel. Some K^+ may exit across a basolateral membrane K^+ channel, leading to K^+ absorption. As noted above, the Na^+ which enters the cell exits on the Na/K ATPase. Cl^- which enters the cell from the lumen exits through a basolateral membrane Cl^- channel. There may also be some contribution from basolateral membrane KCl cotransport.

The Na/K/2Cl cotransporter has been well characterized. Na^+ first binds to the transporter, promoting the binding of K^+ and Cl^-. Binding of K^+ then promotes the binding of a second Cl^-. This second Cl^- binding site appears to also be the binding site for *loop diuretics*. Competition with Cl^- for binding at this site provides the mechanism by which loop diuretics inhibit NaCl absorption in the thick ascending limb. The affinity of this transporter for Na^+ is very high, with half maximal transport rates achieved at concentrations less than 10 m*M* Na^+. Similarly, K^+ affinity is very high. Given that the transporter has two Cl^- binding sites, it likely has two separate Cl^- affinities. One of these affinities, probably that related to binding of the second Cl^- ion is lower, allowing changes in luminal Cl^- concentration to affect transporter rates. Once the transporter is fully occupied with substrates, the complex translocates to the internal surface of the cell membrane where substrates are released.

The cDNA encoding the thick ascending limb Na/K/2Cl cotransporter has recently been cloned by two groups of investigators, based on its homology to the flounder Na/Cl cotransporter and the ubiquitous Na/K/2Cl cotransporter. The clone has been referred to as NKCC2 (referring to the second Na/K/2Cl

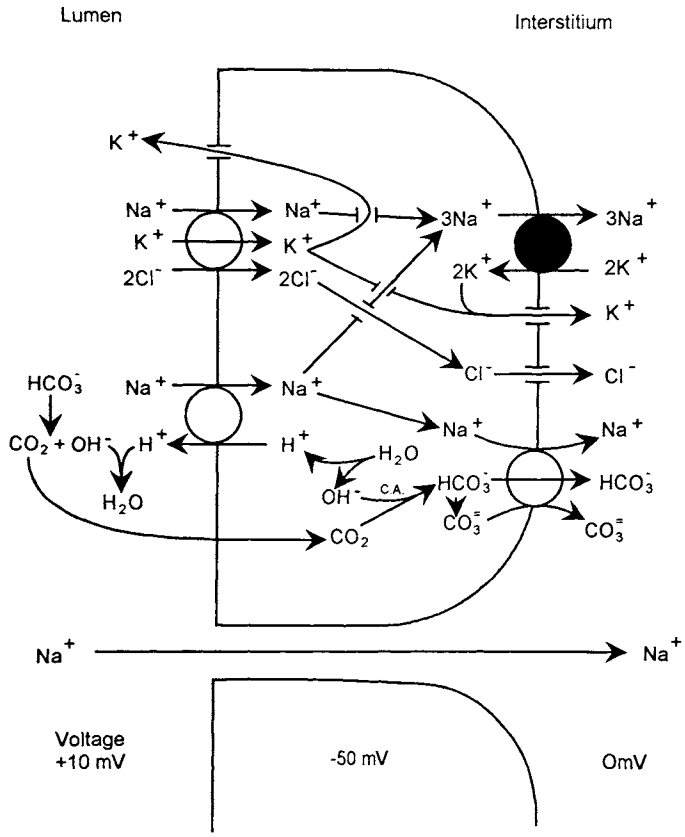

FIGURE 7. Thick ascending limb NaCl and $NaHCO_3$ absorption. Na^+ enters the cell across the apical membrane on the Na/K/2Cl cotransporter, driven by the low cell Na^+ concentration. A significant fraction of K^+ which enters on the cotransporter recycles across an apical membrane K^+ conductance. Cl^- which enters on the cotransporter exits the cell on a basolateral membrane Cl^- channel. H^+ is secreted into the lumen by an Na/H antiporter. OH^- generated by apical membrane H^+ secretion reacts with CO_2 to form HCO_3^- and CO_3^{2-}, which exit with a Na^+ on the $Na/HCO_3/CO_3$ cotransporter. Na^+ which enters the cell across apical membrane transporters exits the cell on the basolateral membrane Na/K ATPase and the $Na/HCO_3/CO_3$ cotransporter. K^+ which enters the cell on the Na/K ATPase exits across a basolateral membrane K^+ channel. Because transcellular NaCl absorption is electrogenic, a lumen + voltage is generated which drives a paracellular current. ●, Active transport mechanism; ○, passive transporter; =, channel.

cotransporter isoform cloned) or as BSC1 (referring to the first bumetanide sensitive cotransporter cloned). In both cases, the cDNAs are similar and encode a protein of predicted size of 120 kDa, with 12 transmembrane domains, a large extracellular domain, and large cytoplasmic aminoterminal and carboxy-

terminal domains. It is likely that this isoform is expressed in the kidney only on apical membranes. A second isoform, referred to as BSC2 or NKCC1 encodes a more ubiquitously expressed Na/K/2Cl cotransporter, which may mediate such functions as cell volume regulation.

Patch clamp studies have extensively characterized K^+ and Cl^- channels in this epithelia. The apical membrane of the thick ascending limb has been found to contain a number of K^+ channels. A "maxi-K^+" channel has been found in cultured cells of the TAL. This channel is Ca^{2+}-activated, has a single channel conductance of 140–150 pS, and is inhibited by barium and stimulated by depolarization of the apical cell membrane. At physiologic apical membrane voltage and cell Ca^{2+} concentration, its open probability is too low to account for the observed K^+ conductance of the apical membrane. It has been suggested that this maxi-K^+ channel may play a role in cell volume regulation.

Two additional K^+ channels with lower single channel conductances, of ~30 or 70 pS, respectively, have also been defined. Their open channel probability is much higher; they are highly K^+ selective (high $P_K:P_{Na}$) and slightly inwardly rectifying. The open probability of these channels is regulated by the cytoplasmic ATP:ADP ratio, with increases in the ratio inhibiting the K^+ channel. These K^+ channels are voltage insensitive and inhibited by low cytosolic pH and barium. The 30 pS K^+ channel is similar to the secretory K^+ channel in the apical membrane of cortical collecting duct (CCD) cells and will be described in more depth later. The 30 pS K^+ channel in the TAL and the CCD are encoded by similar genes, ROMK1 and ROMK2 (rat outer medullary K channel), and their function has been explored in heterologous expression systems such as the oocyte membrane.

Basolateral membrane Cl^- channels have also been characterized by application of the patch clamp technique. Two groups of investigators have found 40 pS channels which are highly Cl^- selective. The open probability of the Cl^- channel is regulated by the concentrations of Cl^- both inside and outside the cell. However, regulation by intracellular Cl^- concentration occurs at lower concentrations (0–50 m*M*), while regulation by extracellular Cl^- concentration occurs at higher concentrations (50–300 m*M*). Regulation by intracellular Cl^- concentration is key in that increases in Cl^- entry across the apical membrane on the Na/K/2Cl cotransporter will raise intracellular Cl^- concentration and increase the open probability of the basolateral membrane Cl^- channel.

To understand the net result of the activity of the individual transporters in the cell model shown in Fig. 7, let us consider one turnover of the Na/K ATPase molecule. Three Na^+ enter the cell with three turnovers of the Na/K/2Cl cotransporter, and exit with one turnover of the NaK ATPase. K^+ transported into the cell on the apical and basolateral membrane both recycle across their respective membranes on K^+ channels. The six Cl^- which enter the cell exit through the basolateral membrane Cl^- conductance. The net result is the trans-

epithelial absorption of six Cl^- ions and only three Na^+ ions. Thus, NaCl transport is electrogenic and generates a lumen-positive voltage. This lumen-positive voltage can then drive a paracellular current which could involve either passive absorption of three Na^+ or passive secretion of three Cl^- to complete the circuit. Because the tight junction of the thick ascending limb is highly Na^+ selective ($P_{Na}/P_{Cl} = 2-6$), most of the paracellular current involves passive Na^+ absorption. Furthermore, the thick ascending limb is impermeable to water so that active NaCl absorption lowers luminal [NaCl] to values below those of plasma and interstitial fluid. This concentration gradient generates an additional lumen positive diffusion voltage because the tight junction is Na^+ selective. As will be discussed below, lumen positive voltage in the thick ascending limb provides a pathway for passive paracellular absorption of other cations including K^+, Ca^{2+}, Mg^{2+}, and NH_4^+. Thus, loop diuretics which inhibit NaCl absorption and the lumen positive voltage, inhibit absorption of these cations.

The thick ascending limb also absorbs 5–10% of the filtered load of $NaHCO_3$. The mechanism for this appears to be similar to that in the proximal tubule (Fig. 7). Apical membrane H^+ secretion is mediated by an Na/H antiporter that is encoded by NHE-3. HCO_3^- generated in the cell exits on an Na/HCO_3/CO_3 cotransporter. This allows some Na^+ efflux, but the majority of basolateral membrane Na^+ efflux occurs on the NaK ATPase. The possibility of other basolateral membrane transport mechanisms, including a K/HCO_3 cotransporter, has been raised.

NaCl absorption is regulated in this segment (Table 2). Thick ascending limb NaCl absorption is an important component of urinary concentration, and thus it is not surprising that regulators of urinary concentration regulate NaCl absorption in this segment. Arginine vasopressin stimulates NaCl absorption in the medullary thick ascending limb, and hypertonicity inhibits NaCl absorption. PGE-2, also known to inhibit urinary concentration, inhibits NaCl transport. Increases in delivery of NaCl to the thick ascending limb increase the rate of NaCl absorption (glomerulotubular balance). NaCl absorption is also regu-

TABLE 2 Regulation of Thick Ascending Limb NaCl Absorption

Factors which regulate urinary concentration
Arginine vasopressin
Hypertonicity
PGE-2
Glomerulotubular balance
Effective arterial volume
Renal nerves (beta catecholamines)
Mineralocorticoids
PGE-2

lated by effective arterial volume, such that volume contraction enhances NaCl absorption and volume expansion inhibits NaCl absorption in the thick ascending limb. These effects are mediated by a number of factors. Beta adrenergic catecholamines increase NaCl absorption, providing a possible mechanism for similar effects of renal nerves. In addition, mineralocorticoids increase NaCl absorption in the thick ascending limb. Last, as noted above, PGE-2, whose levels increase in volume expansion, inhibits NaCl absorption.

$NaHCO_3$ absorption in the thick ascending limb is also regulated. AVP, glucagon, and hyperosmolality inhibit $NaHCO_3$ absorption in this segment. The physiologic significance of these effects is unclear. Last, chronic metabolic acidosis increases the rate of $NaHCO_3$ absorption in the medullary thick ascending limb.

Distal Convoluted Tubule and Connecting Tubule

The distal tubule consists of several short nephron segments. The first of these is the distal convoluted tubule. While early micropuncture studies used this term to apply to the entire surface distal nephron beginning with the macula densa and ending with the confluence of multiple nephrons into the cortical collecting duct, more recent nomenclature defines this segment more narrowly. The distal convoluted tubule is a segment of approximately 0.5 mm in length that contains one cell type, begins at the macula densa, and ends with the beginning of the connecting tubule. The connecting tubule links the distal convoluted tubule with the initial cortical collecting tubule, and contains two cell types, connecting tubule cells and intercalated cells. The intercalated cells appear to be similar to intercalated cells in more distal nephron segments that mediate H^+/HCO_3^- transport. The connecting tubule cell is responsible for NaCl transport, and shares some of the properties of the distal convoluted tubule cell described below.

The mechanism of NaCl transport in the distal convoluted tubule cell is shown in Fig. 8. As in other tubule cells, the basolateral membrane Na/K ATPase is responsible for basolateral membrane Na^+ efflux and for maintaining a low cell Na^+ concentration. Na^+ enters the cell across the apical membrane by three mechanisms. The first of these is an apical membrane Na^+ conductance. This Na^+ channel allows electrogenic transcellular Na^+ transport which generates a lumen-negative voltage that provides a key driving force for paracellular Cl^- absorption. This mechanism of NaCl transport is similar to that occurring in the cortical collecting duct and will be described in that section. The apical membrane Na^+ channel is exquisitely sensitive to *amiloride* and is inhibited by low concentrations of *amiloride,* as well as *triamterene.*

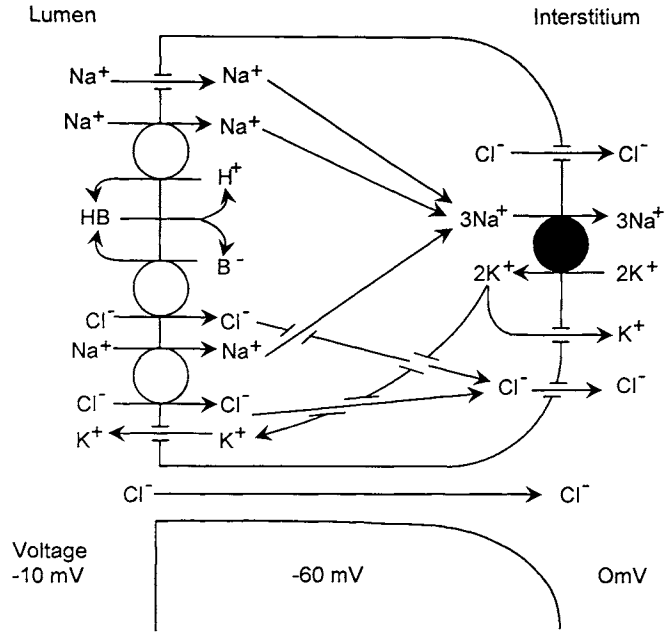

FIGURE 8. NaCl absorption in the distal convoluted tubule. Three modes of NaCl absorption are shown. Electroneutral transcellular NaCl absorption is mediated by parallel apical membrane Na/H and Cl/base exchangers, with the protonated base recycling across the apical membrane, and by an electroneutral Na/Cl cotransporter. Electrogenic Na^+ absorption is mediated by a Na^+ channel. Na^+ which enters the cell across an apical membrane transporter, exits the cell on the basolateral membrane Na/K ATPase. K^+ which enters the cell on the Na/K ATPase exits on a basolateral membrane K^+ channel but some K^+ may also be secreted by an apical K^+ channel. Cl^- exits the basolateral membrane across a Cl^- conductance. Electrogenic Na^+ absorption establishes a lumen negative voltage which drives a paracellular current. ●, Active transport mechanism; ○, passive transporter; =, channel.

The second mechanism of NaCl absorption in this segment involves parallel Na/H antiport and Cl/base exchange on the apical membrane, as described above for the proximal tubule. The H^+ and base recycle, Na^+ exits the basolateral membrane on the Na/K ATPase, and Cl^- exits the basolateral membrane through a Cl^- channel.

The last mechanism of NaCl absorption involves coupled NaCl cotransport. Here, the inward Na^+ gradient provides the driving force for active uptake of Cl^- into the cell. Na^+ exits the basolateral membrane on the Na/K ATPase, while Cl^- exits the basolateral membrane via a Cl^- channel. The net result is electroneutral NaCl absorption. The apical membrane NaCl cotransporter is inhibited by *thiazide diuretics*. The cDNA encoding the apical membrane elec-

troneutral Na/Cl cotransporter was recently cloned from a flounder urinary bladder library using expression in *Xenopus* oocytes. Then, by homology cloning a rat cDNA was derived which has been named rTSC1, referring to rat thiazide sensitive cotransporter 1. Although the protein encoded by this cDNA does not transport K^+, the predicted amino acid sequence is 60% identical to that of BSC1, the cDNA encoding the Na/K/2Cl cotransporter. The general organization of the protein structure is also similar. The mechanisms of NaCl absorption in the connecting tubule cell appear to be similar to those in the distal convoluted tubule.

These segments also mediate luminal acidification and HCO_3^- absorption. In the rat distal convoluted tubule, this process is largely mediated by an apical membrane Na/H antiporter. The mechanism for basolateral membrane base efflux has not been defined. In the connecting tubule, H^+ or HCO_3^- secretion are mediated by the intercalated cell. These intercalated cells appear to be similar, if not identical to, those present in the cortical collecting duct, and are discussed below. There are modest rates of K^+ secretion in these segments. Because more distal segments are quantitatively more important, the mechanisms of K^+ secretion and its regulation have not yet been extensively defined in these segments, but may involve an apical membrane K^+ channel.

Collecting Duct

NaCl Absorption

The collecting duct consists of a series of subsegments. Following the connecting tubule, there is the initial cortical collecting tubule (segment prior to the confluence of multiple tubules), followed by the cortical collecting duct, the outer medullary collecting duct (divided into outer stripe and inner stripe segments), and the inner medullary or papillary collecting duct. In general, these segments are similar, but significant differences exist. Below we describe some of the general mechanisms responsible for transport of NaCl, and H^+/HCO_3^-. Where relevant we note differences between segments.

As shown in Fig. 9, NaCl absorption is mediated by electrogenic transcellular Na^+ absorption with passive paracellular Cl^- diffusion. The basolateral membrane Na/K ATPase maintains low cell Na^+ concentrations which, along with the negative cell voltage, provides a favorable driving force for Na^+ to enter the cell through apical Na^+ channels. K^+, which enters the cell on the Na/K ATPase recycles across the basolateral membrane. In the cortical collecting duct, a significant fraction of the K^+ which enters the cell on the Na/K ATPase may also exit through an apical membrane K^+ channel (K^+ secretion; see below). Electrogenic Na^+ absorption generates a lumen-negative voltage which provides an important and essential driving force for passive paracellular

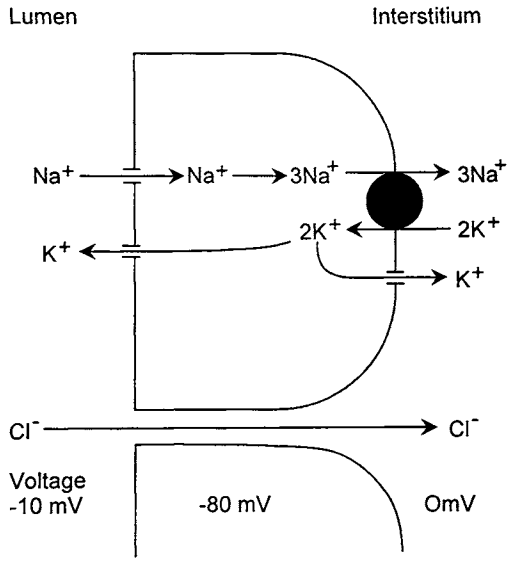

FIGURE 9. Na^+ transport in the principal cell of the cortical collecting duct. Electrogenic Na^+ absorption is mediated by an apical membrane Na^+ channel. Na^+ which enters the cell across the apical membrane channel exits the cell on the basolateral membrane Na/K ATPase. K^+ which enters the cell on the Na/K ATPase, exits on a basolateral or apical membrane K^+ channel. Electrogenic Na^+ absorption establishes a lumen negative voltage which drives a paracellular Cl^- absorptive current. ●, Active transport mechanism; ○, passive transporter; =, channel.

Cl^- absorption. In the cortical collecting duct and outer stripe of the outer medullary collecting duct, such electrogenic NaCl reabsorption is mediated by the principal cell. In the inner stripe of the outer medullary collecting duct, transcellular Na^+ transport rates are very low but increase again in the inner medullary collecting duct. In all of the above segments, the apical Na^+ channel is inhibited by low, micromolar concentrations of *amiloride*.

The nature of the apical membrane epithelial Na^+ channel has been studied using patch clamp techniques. Three types of epithelial Na^+ channels have been found in the apical membrane of collecting duct cells. The first of these, found most frequently in patches from the cortical collecting duct apical membrane, has a single channel conductance of 4–5 pS, an open probability of 0.4, is highly Na^+ selective with a $P_{Na}:P_K > 10$, has slow voltage-independent kinetics (long open and closed times), and is inhibited by *amiloride*. This highly Na^+ selective channel is the likely candidate for the major collecting duct Na^+ channel. The open probability of the channel is increased by cell hyperpolarization and by cell alkalinization.

Utilizing expression cloning in *Xenopus* oocytes, cDNAs encoding three sub-

units of this Na^+ channel have been identified. The first clone, referred to as αrENaC (α subunit of rat epithelial Na^+ channel) generates a small Na^+ current when expressed in *Xenopus* oocytes. The characteristics of this current are identical to those described above for the epithelial Na^+ channel, with a conductance of 4.9 pS, long open and closed times, and high Na^+ selectivity (P_{Na}:$P_K > 20$). Subsequently identified cDNAs, βrENaC and γrENaC, generate only minimal Na^+ currents when expressed alone or in combination. However, expression of β or γ subunits with the α subunit increases the magnitude of the Na^+ current. Finally, expression of α, β, and γ subunits together leads to expression of much larger Na^+ currents. α, β, and γrENaC are encoded by related genes which share approximately 35% amino acid identity. They also share a common structure with two membrane spanning domains and a large central extracellular domain that is heavily glycosylated and contains a cysteine rich sequence. Liddle's syndrome, a familial disease due to increased activity of the epithelial Na^+ channel, has been shown to be associated with an activating mutation in βrENaC or γrENaC. In addition, changes in dietary NaCl regulate the number of open rENaC channels.

In addition to the above channel, an 8-pS channel has been found with a P_{Na}:P_K of 5 (moderately Na^+ selective) and a 28-pS channel with a P_{Na}:P_K of 1 (nonselective). This latter channel has been identified in patches from the apical membrane of inner medullary collecting duct cells. This 28-pS channel is inhibited by cyclic GMP and likely represents the ANP inhibitable channel of the inner medullary collecting duct. All three of the above channels are inhibited by amiloride.

In addition to electrogenic Na^+ transport, some investigators have found *thiazide*-sensitive electroneutral NaCl absorption in the cortical collecting duct. The mechanisms responsible appear to be similar to those described above for the distal convoluted tubule and connecting tubule.

The cortical collecting duct is an important site for regulation of Na^+ transport (Table 3). Mineralocorticoid hormones *increase* the rate of Na^+ transport significantly. This effect is mediated by several effects including stimulation of apical membrane Na^+ channels, stimulation of the NaK ATPase, and stimulation of metabolic enzymes such as citrate synthase. It has been noted that increased activity of the apical membrane Na^+ conductance precedes the rise in Na/K ATPase activity. *Spironolactone* is a diuretic that inhibits Na^+ transport in

TABLE 3 Regulation of Collecting Duct Na^+ Absorption

Mineralocorticoid
Vasopressin
PGE-2
Bradykinin

this segment by blocking mineralocorticoid receptors. Vasopressin has also been demonstrated to increase Na^+ transport and to activate apical membrane Na^+ conductance, whereas both PGE-2 and bradykinin inhibit Na^+ transport. Atrial natriuretic peptide inhibits Na^+ transport in the inner medullary collecting duct and in the rat cortical collecting duct. As described above, this effect is likely mediated by inhibition of the cyclic GMP regulated Na^+ channel. *Amiloride* and *triamterene* inhibit Na^+ absorption by blocking the apical membrane Na^+ channel.

Acidification

In addition to NaCl absorption, the collecting duct is also an important site of urinary acidification. H^+/HCO_3^- transport in the initial cortical collecting tubule and cortical collecting duct is mediated by intercalated cells. These cells consist of two types. The type A intercalated cell, shown in Fig. 10, mediates H^+ secretion into the tubular fluid.

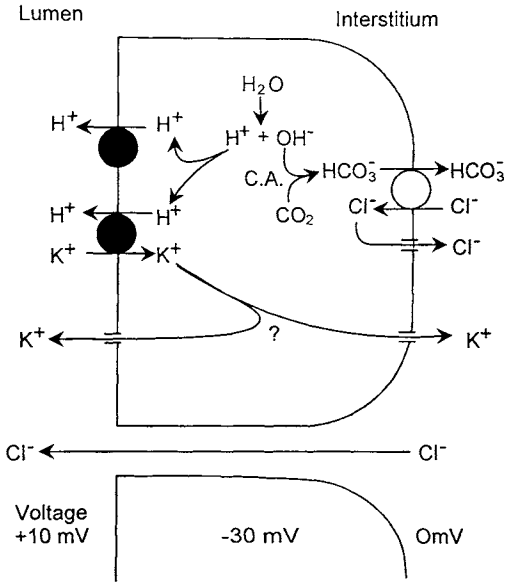

FIGURE 10. H^+ secretion in the type A intercalated cell. H^+ is secreted into the lumen by an H ATPase and an H/K ATPase. OH^- generated within the cell by apical membrane H^+ secretion reacts with CO_2 to form HCO_3^-, which exits across the basolateral membrane on a Cl/HCO_3 exchanger. Cl^- which enters the cell on the exchanger recycles across a basolateral membrane Cl^- channel. The fate of K^+ which enters the cell on the H/K ATPase, is not clear. Carbonic anhydrase catalyzes the conversion of CO_2 and OH^- to HCO_3^- in the cell. Electrogenic H^+ secretion generates a lumen positive voltage which generates a current flow (Cl^-) across the paracellular pathway. •, Active transport mechanism; ○, passive transporter; =, channel.

H^+ is secreted by one of two pumps, a vacuolar H ATPase or an H/K ATPase. The vacuolar H^+ ATPase is so named because it resembles the H^+ pump present within many intracellular compartments such as lysosomes, Golgi apparatus, and endosomes. It is a multisubunit complex that shares similarities with the mitochondrial F_0F_1 H^+ pump. Its source of energy is the metabolism of ATP to ADP which drives H^+ secretion across a special H^+-selective pore in the apical membrane.

The H/K ATPase is a member of a family of P-type ATPases which includes the Na/K ATPase and the Ca ATPase. These ATPases generally transport cations, have phosphorylated intermediates, and are inhibited by vanadate. They typically consist of two subunits, an alpha subunit responsible for all transport and catalytic functions and a beta subunit that is required for proper membrane targeting and thus necessary for transport function. The H/K ATPase was first identified as the major H^+ transporter in the stomach, and several isoforms have subsequently been found in the colon and in the toad bladder. The H/K ATPase metabolizes ATP to ADP and phosphate and uses the energy derived from this process to transport H^+ actively out of the cell and K^+ into the cell. The activity of the H/K ATPase increases in K^+ depletion and thus provides a mechanism by which K^+ depletion enhances both collecting duct H^+ secretion and K^+ absorption. The mechanisms by which the K^+ exits the cell are presently unclear. Electrophysiological studies show that intercalated cells have only minimal *apical* membrane conductances, and the *basolateral* membrane contains mostly a Cl^- conductance with only a small K^+ conductance.

HCO_3^- generated within the cell exits the basolateral membrane on a Cl/HCO_3 exchanger. This anion exchanger is similar to the red blood cell Cl/HCO_3 exchanger (AE1), except that the N-terminal portion is truncated, a modification that results from use of an alternative promoter in the AE1 gene. This Cl/HCO_3 exchanger allows HCO_3^- to exit the cell in exchange for Cl^- which then recycles across the basolateral membrane Cl^- conductance. Acidification mediated by the vacuolar H^+ pump is electrogenic and generates a lumen positive voltage. Cl^- then diffuses across the paracellular pathway driven by the transepithelial voltage. Whether acidification mediated by the HK ATPase is electrogenic depends on the fate of K^+. If K^+ exits the basolateral membrane via a K^+ conductance (or on a K/Cl cotransporter) transport will be electroneutral; if K^+ exits the apical membrane through a K^+ conductance, acidification will be electrogenic, hyperpolarize the apical membrane and reduce the lumen-negative transepithelial potential difference.

Alkalinization

The initial cortical collecting tubule and cortical collecting duct, as well as the connecting tubule, are also capable of net HCO_3^- secretion into the lumi-

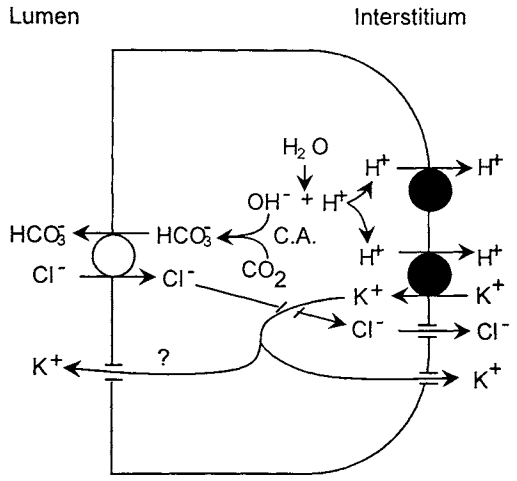

FIGURE 11. HCO_3^- secretion in the type B intercalated cell. H^+ is secreted into the interstitium by an H ATPase and an H/K ATPase. OH^- generated by basolateral membrane H^+ secretion reacts with CO_2 to form HCO_3^-, which exits across the apical membrane on a Cl/HCO_3 exchanger. Cl^- which enters the cell on the exchanger exits across a basolateral membrane Cl^- channel. The fate of K^+ which enters the cell on the H/K ATPase, is not clear. Carbonic anhydrase catalyzes the conversion of CO_2 and OH^- to HCO_3^- in the cell. ●, Active transport mechanism; ○, passive transporter; =, channel.

nal fluid. This transport is mediated by the type B intercalated cell (Fig. 11). The cell transports H^+ across the basolateral membrane using the same two transporters described for the apical membrane of the type A intercalated cell (Fig. 10). HCO_3^- which is generated in the cytoplasm exits across the apical membrane on a Cl/HCO_3 exchanger. This Cl/HCO_3 exchanger is molecularly distinct from that of the basolateral membrane of the type A intercalated cell and has apparently no relationship to the red cell Cl/HCO_3 exchanger. Although two other Cl/HCO_3 exchanger isoforms have been cloned, AE2 and AE3, it is not clear if these mediate apical membrane Cl/HCO_3 exchange. Cl^- which enters the cell then exits the basolateral membrane via a Cl^- conductance. This process is electroneutral and generates no transepithelial voltage if mediated by the vacuolar H ATPase. However, if mediated by the H/K ATPase it will be electroneutral if K^+ exits the basolateral membrane; if K^+ exits the apical membrane, the process will be electrogenic (see above).

A number of inhibitors exist which block H^+/HCO_3^- transport in the collecting duct. Bafilomycin A1 is a fairly specific inhibitor of the vacuolar H ATPase, and SCH28080 is a relatively specific inhibitor of the H/K ATPase. In addition, Omeprazole has also been identified as an inhibitor of the H/K ATPase, but can inhibit the vacuolar H ATPase. Disulfonic stilbenes such as SITS and DIDS in-

TABLE 4 Regulation of Collecting Duct Acidification

Acid/base status
Mineralocorticoids and distal Na^+ delivery
K^+ deficiency
β Catecholamines

hibit the above Cl/HCO_3 exchangers. These inhibitors have been helpful when applied to tubule membranes to define specific transport mechanisms, but they are not clinically useful because their systemic toxicity is too high when they are delivered at effective blood concentrations to their tubule site of action.

The collecting duct provides an important site for regulation of acidification (Table 4). As described above, the cortical collecting duct is capable of either net H^+ secretion or net HCO_3^- secretion. This function is performed by two cells, the type A and type B intercalated cells, respectively. Changes in dietary acid content regulate the activities of these two cells, secondarily regulating the direction of net acid transport. Thus, chronic feeding of an acid diet leads to an increase in type A intercalated cell activity and net H^+ secretion, while feeding an alkaline diet leads to an increase in the activity of the type B intercalated cell and net HCO_3^- secretion. The net effect of HCO_3^- secretion in type B intercalated cells is to oppose H^+ secretion by type A intercalated cells. It is the balance between these opposing transport processes that determines whether HCO_3^- is reabsorbed or secreted.

Another major regulator of distal H^+ secretion is the mineralocorticoid level. Mineralocorticoids work in concert with distal Na^+ delivery to enhance H^+ secretion in the connecting tubule and the cortical collecting duct. As described above, mineralocorticoids enhance Na^+ absorption by increasing the Na^+ conductance and Na/K ATPase activity. This creates a more favorable electrochemical gradient for H^+ secretion by increasing the lumen-negative potential. This effect is dependent on distal delivery of Na^+; if distal Na^+ delivery is inadequate, mineralocorticoids cannot enhance Na^+ transport. In addition to this Na^+-dependent effect, mineralocorticoids also stimulate H^+ secretion directly by their action on type A intercalated cells. This effect is independent of Na^+ transport. The relative importance of these two mechanisms has been determined in a number of clearance studies which consistently demonstrate that mineralocorticoids increase net acid excretion only in the presence of distal Na^+ delivery. Thus, although mineralocorticoids can directly stimulate H^+ secretion, the quantitatively more important effect depends on distal Na^+ delivery and is likely related to mineralocorticoid-induced stimulation of Na^+ transport. These results are similar to those seen with K^+ secretion in the cortical collecting duct. Thus, the generation of enhanced H^+ and K^+ secretion and

the development of hypokalemic alkalosis requires both high levels of mineralocorticoids *and* high rates of delivery of Na^+ to the distal nephron. Once again, *spironolactone* inhibits H^+ and K^+ secretion by blocking mineralocorticoid receptors.

A number of other forms of regulation have been found in the collecting duct. K^+ deficiency enhances H^+ secretion in the distal nephron, and one component of this effect may be related to activation of an apical membrane H/K ATPase. β-Adrenergic catecholamines have also been shown to stimulate HCO_3^- secretion in the cortical collecting duct. The physiological significance of this effect is not clear, but perhaps contributes a mechanism for protection against metabolic alkalosis. H^+ secretion is inhibited by Na^+-channel blockers such as *amiloride* and *triamterene*, both diuretics that lower the lumen-negative voltage.

K^+ Transport

The collecting duct is a major site for K^+ transport. Most of filtered K^+ is reabsorbed in the proximal tubule and thick ascending limb, such that the majority of K^+ that appears in the urine is secreted in the distal nephron. In general, the majority of this K^+ secretion occurs in the initial cortical collecting tubule and the cortical collecting duct. Some contributions to K^+ secretion may also be made by the distal convoluted tubule, the connecting tubule, and the outer stripe of the outer medullary collecting duct.

Figure 9 shows a cellular model of K^+ transport in the cortical collecting duct principal cell. As can be seen, Na^+ and K^+ transport are interrelated. The basolateral membrane Na/K ATPase actively transports K^+ from the interstitium into the cell, leading to high intracellular K^+ concentrations. K^+ can then exit across the apical or basolateral membranes across K^+ conductances. If K^+ were only to exit across the basolateral membrane conductance, there would be no net transport of K^+, whereas K^+ exiting across the apical membrane conductance leads to transepithelial K^+ transport. Apical membrane Na^+ transport provides not only substrate for the Na/K ATPase but also depolarizes the apical membrane potential and thus generates a transepithelial lumen-negative voltage which facilitates K^+ secretion.

The properties of apical membrane K^+ channels have been studied extensively by patch clamp techniques. Similar to the thick ascending limb described previously, there is a maxi-K^+ channel with a large conductance. It is activated by an increase in cytosolic Ca^{2+}, cell depolarization, and membrane stretching, but has a very low open probability and is unlikely to mediate a significant transepithelial K^+ flux. However, more important is a low-conductance K^+ channel, distinguished by a single channel conductance of approximately 30 pS, a high open probability, inward rectification, and a high K^+ selectivity.

This K^+ channel is relatively insensitive to changes in membrane voltage and cell Ca^{2+}. It is inhibited by high cytosolic ATP and a high ATP/ADP ratio and thus falls into the category of K_{ATP} channels. It is also stimulated by increases in cell pH and inhibited by decreases in cell pH, and is activated by protein kinase A and blocked by protein kinase C. As with most K^+ channels, this channel is sensitive to the inhibitory action of barium.

Using expression cloning in *Xenopus* oocytes, a cDNA encoding this ATP regulated inwardly rectifying channel has been identified from a rat outer medullary kidney library. The clone, named ROMK (rat outer medullary K^+ conductance), predicts a 45-kDa protein containing only two membrane spanning segments. This unusual topology for a K^+ channel is similar to that of a new family of K^+ channels which all have in common that they encode inwardly rectifying K^+ channels (the IRK channel family). When expressed in *Xenopus* oocytes, these channels display high K^+ selectivity, inward rectification, a single channel conductance of 35–45 pS, high open channel probability, pH sensitivity, and inhibition by mM [Mg^{2+}-ATP]. Thus, ROMK likely encodes the apical membrane K^+ channel of the cortical collecting duct. As described earlier, a similar channel also encodes the apical membrane K^+ conductance in the thick ascending limb of Henle's loop. Recent studies have identified three splice variants of ROMK. ROMK1 is expressed only in the collecting duct; ROMK3 is expressed only in the medullary and cortical thick ascending limb and distal convoluted tubule; and ROMK2b is expressed in distal nephron segments extending from the medullary thick ascending limb to the cortical collecting duct.

There is also evidence which suggests that a component of apical membrane K^+ secretion is mediated by a KCl cotransporter. This is based on experiments which have found that in the presence of luminal Ba^{2+}, a selective inhibitor of channel-mediated K^+ conductances, changes in luminal Cl^- concentration (below 15 mM) affect the rate of K^+ secretion without changing voltage. Low Cl^- concentrations in the lumen stimulate K^+ secretion.

In addition to K^+ secretion, the collecting duct can absorb K^+ in states of K^+ depletion. Most evidence supports the view that this process is mediated by the apical membrane H/K ATPase described above in type A intercalated cells (Fig. 10). Thus, in states of K^+ depletion, there is increased activity of the H/K ATPase in the apical membrane of intercalated cells of the connecting tubule and the collecting duct leading to enhanced H^+ secretion and K^+ absorption in states of K^+ depletion. It is not resolved how K^+ would leave the cell, but a small basolateral membrane K^+ conductance may mediate this second step of the reabsorption process. There is also some evidence that K^+ depletion can increase the paracellular permeability to K^+ in the outer medullary collecting duct, inner stripe. Because this segment possesses a lumen positive voltage, this would lead to enhanced passive K^+ reabsorption. Last, there is also evidence

for expression of an *apical* membrane Na/K ATPase in the medullary collecting duct in response to K^+ depletion, but its mode of operation has not been directly investigated.

Regulation of K^+ Secretion (Table 5)

In most cases, regulation of renal K^+ excretion is mediated by changes in K^+ secretion in the cortical collecting duct. The two main determinants of K^+ secretion in the cortical collecting duct are the *mineralocorticoid level* and the amount of *distal delivery of* Na^+ *and water* to the cortical collecting duct. Mineralocorticoid hormones enhance cortical collecting duct K^+ secretion in a number of ways. Initially, there is a rapid increase in apical membrane Na^+ conductance which: (1) depolarizes the cell, allowing enhanced K^+ efflux across the apical membrane K^+ channel; and (2) increases cell Na^+ concentration, causing increased Na/K ATPase turnover and increasing cell K^+ concentration. At later stages, there is an increase in the abundance of Na/K ATPase and an increase in the K^+ conductance of the apical membrane. Chronic increases in distal delivery of Na^+ and water lead to hypertrophy of principal cells with expansion of the basolateral membrane surface area and Na/K ATPase abundance.

In general, changes in effective arterial volume lead to alterations in distal delivery of Na^+, water, and aldosterone which result in opposing effects on K^+ transport. The net result is that physiologic changes in dietary NaCl and effective arterial volume have minimal effects on renal K^+ excretion. Thus, decreases in effective arterial volume lead to increases in aldosterone levels but lower distal delivery of Na^+ and water. Conversely, increases in effective arterial volume suppress aldosterone levels while enhancing distal delivery of Na^+ and water. Most causes of abnormal renal K^+ handling can be ascribed to clinical conditions in which the serum aldosterone and distal delivery of Na^+ and water do not change in opposite directions. The most common cause of this

TABLE 5 Regulation of Cortical Collecting Duct K^+ Excretion

Mineralocorticoids
Acid/base disorders
Distal Na^+ delivery
Vasopressin
K^+ balance
β Catecholamines

imbalance is related to diuretics. Diuretics which act at tubule sites proximal to the cortical collecting duct, such as *osmotic diuretics, carbonic anhydrase inhibitors, loop diuretics,* and *thiazides,* all enhance distal delivery of Na^+ and water. By inducing volume depletion they also increase mineralocorticoid levels. This combination enhances cortical collecting duct K^+ secretion and often induces hypokalemia.

In addition to these two major regulators, K^+ transport is also regulated by a number of other factors. K^+ loading or deprivation affects cortical collecting duct K^+ transport independent of changes in aldosterone and distal delivery. Chronic K^+ loading leads to increased principal cell basolateral membrane surface area, enhanced Na/K ATPase abundance, and increased density and activity of apical secretory K^+ channels. Conversely, chronic K^+ deprivation leads to increases in intercalated cell apical membrane surface area and H/K ATPase activity.

The effects of acid–base disorders on K^+ transport are complex. In general, the direct effect of changes in blood pH on the cortical collecting duct is for alkalosis to enhance K^+ secretion and for acidosis to inhibit K^+ secretion. A significant component of this effect is mediated by regulation of apical membrane K^+ channel activity by cell pH. Increases in cell pH increase the open probability and number of the apical membrane K^+ channels, while decreases in cell pH diminish open probability and channel density. pH-dependent modulation of K^+ secretion may also be mediated by changes in Na/K ATPase activity and in cell K^+ concentration, but these mechanisms are unlikely to play a major role.

Effects on whole kidney K^+ handling are more complicated, however. *Metabolic alkalosis* is also associated with enhanced distal delivery of a nonreabsorbable anion, namely HCO_3^-, further enhancing K^+ wasting and explaining the common association of hypokalemia with metabolic alkalosis. In *metabolic acidosis,* proximal tubule NaCl absorption is inhibited (see Proximal Tubule above), leading to *increased* distal delivery of NaCl and water and elevation in aldosterone levels. These latter effects increase cortical collecting duct K^+ secretion, opposing the direct inhibitory effect of acidosis to decrease K^+ secretion. The net result is that *chronic* metabolic acidosis is often associated with enhanced renal K^+ secretion, although the magnitude of this kaliuretic effect is far less than in metabolic alkalosis.

Last, vasopressin has been shown to increase cortical collecting duct K^+ secretion by stimulating apical K^+ (and Na^+) channel activity. The coincidence of high distal tubule flow rates with low vasopressin levels may explain why net K^+ transport remains fairly constant during water diuresis. Epinephrine has been shown to decrease K^+ secretion, but the physiologic significance of this effect is not clear.

It should also be noted that diuretics which act on the cortical collecting

duct lead to *decreased* cortical collecting duct K^+ secretion. Apical membrane Na^+ channel blockers such as *amiloride* and *triamterene* hyperpolarize the apical membrane and lower Na/K ATPase turnover rate, both of which will decrease K^+ secretion. *Spironolactone* blocks aldosterone receptors and thus decreases K^+ secretion.

AMMONIUM TRANSPORT

An important component of renal acidification is the excretion of NH_4^+ in the urine. While the kidneys excrete approximately 70 meq/day of acid, very little of this urine acid load is excreted in the form of unbuffered protons. Of the buffers in the urine NH_4^+ is quantitatively the most important and is the one that is most regulated. The majority of NH_4^+ synthesis occurs in the proximal tubule, where glutamine is metabolized to 2 NH_4^+ and 2 HCO_3^-. It is the *vectorial separation* of these two products in tubule cells that contributes importantly to acid/base regulation by NH_4^+. Thus, if both NH_4^+ and HCO_3^- were returned to the blood, the liver would convert them to urea and there would be no effect on acid/base balance. Similarly, if both moieties were excreted in the urine there would also be no effect on acid/base balance.

HCO_3^- formed from glutamine in the proximal tubule can exit the cell passive as HCO_3^- since HCO_3^- concentration is above electrochemical equilibrium in the cell. Because the only pathway for HCO_3^- exit is on the basolateral membrane ($Na/NCO_3/CO_3$ cotransporter), all of HCO_3^- exits across the basolateral membrane into the renal interstitium and the blood. NH_3 and NH_4^+, on the other hand, are excreted into the urine. This occurs by a number of steps. First, NH_3/NH_4^+ is preferentially transported from the proximal tubule cell into the luminal fluid by two mechanisms. The apical membrane Na/H antiporter carries NH_4^+ as a substrate in place of H^+ (*carrier-mediated ionic transport*). In addition, luminal acidification leads to trapping of NH_3 that diffuses across the apical membrane in the luminal fluid (*nonionic diffusion*).

Further downstream along the nephron, NH_3/NH_4^+ is transported out of the lumen in the thick ascending limb. Here the apical membrane has an unusually low permeability to NH_3. NH_4^+ is transported from lumen to peritubular fluid by three mechanisms. First, NH_4^+ is reabsorbed by the Na/K/2Cl cotransporter in place of K^+. Second, NH_4^+ can cross the luminal membrane through the K^+ channel. In both of these cases, NH_3 would then diffuse across the basolateral membrane. Third, NH_4^+ diffuses from lumen to peritubular fluid across the paracellular pathway driven by the lumen positive voltage.

As a result of such extensive reabsorption, NH_3/NH_4^+ is trapped in the medullary interstitium by countercurrent exchange. The final step in NH_4^+ excretion involves nonionic diffusion of NH_3 into the lumen of the medullary

collecting duct and trapping and conversion to NH_4^+ by low luminal pH. This explains the observation that for a given rate of NH_4^+ production, its excretion depends critically on formation of an acid urine.

Based on the above, diuretics can affect NH_4^+ excretion in many ways. First, any diuretic that affects tubular fluid acidification will alter the trapping of NH_3/NH_4^+ in the collecting duct. In addition, any diuretic that reduces proximal tubule acidification (*carbonic anhydrase inhibitors*) can diminish the trapping of NH_3/NH_4^+ in the proximal tubular lumen. In addition, *loop diuretics* can inhibit thick ascending limb NH_4^+ transport in two ways: by blocking the Na/K/2Cl cotransporter and by reducing the lumen positive voltage. Any diuretic that causes hyperkalemia will impair proximal tubule NH_3/NH_4^+ synthesis. In addition, reduced excretion of NH_4^+ in hyperkalemia has been postulated to be due, at lease in part, to displacement of NH_4^+ by K^+ on the Na/K/2Cl cotransporter in the TAL. As a consequence of this competition between K^+ and NH_4^+, NH_4^+ accumulation in the renal medulla is compromised.

CALCIUM TRANSPORT

Calcium homeostasis is maintained by the kidney excreting an amount of Ca^{2+} equal to that which is absorbed from the GI tract. Approximately 60% of plasma Ca^{2+} is ultrafilterable (that fraction not bound to albumin), including both ionized Ca^{2+} and Ca^{2+} complexed to anions such as phosphate, citrate, HCO_3^- and sulfate.

Once filtered, approximately 65% of Ca^{2+} is reabsorbed in the proximal tubule (Fig. 12). In the proximal tubule, Ca^{2+} reabsorption and Na^+ reabsorption are regulated in parallel, with tubule fluid to ultrafilterable Ca^{2+} concentrations ranging from 1.0 to 1.2. This observation suggests that the majority of Ca^{2+} absorption is passive. Consistent with this mode of transport, the proximal tubule has an extremely high passive paracellular permeability to Ca^{2+} that is equal to that of Na^+. While there may be an additional transcellular active component of proximal tubule Ca^{2+} absorption, it is at best small in magnitude and of poorly defined physiologic significance. Increases in proximal tubule Na^+ and volume absorption increase luminal Ca^{2+} concentration which leads to more Ca^{2+} being passively absorbed. In addition, some of the ultrafilterable Ca^{2+} may be reabsorbed by solvent drag. Both of these mechanisms explain the tight coupling between the rates of Na^+ and Ca^{2+} absorption in the proximal tubule.

Little Ca^{2+} absorption occurs in the thin limbs of the loop of Henle. Then, approximately 25% of filtered Ca^{2+} is reabsorbed in the thick ascending limb of the loop of Henle (Fig. 12). Once again, this appears to be mostly a passive

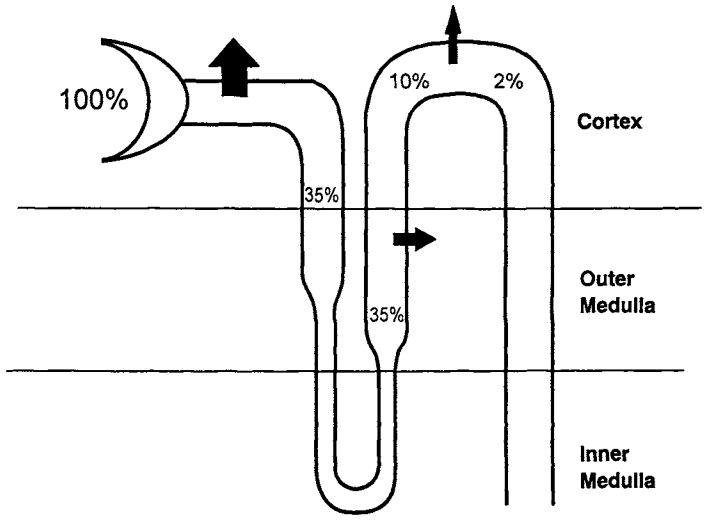

FIGURE 12. Ca^{2+} transport along the nephron. Numbers indicate percentage of filtered Ca^{2+} remaining in the luminal fluid. The majority of filtered Ca^{2+} is reabsorbed in the proximal tubule and the thick ascending limb. An important regulated fraction is reabsorbed in the distal convoluted tubule.

process, driven by the lumen-positive voltage. Thus, conditions which alter the rate of thick ascending limb NaCl absorption and the lumen-positive voltage will secondarily affect the rate of Ca^{2+} absorption. Thus, Na^+ and Ca^{2+} absorption are indirectly coupled. In addition to this passive Ca^{2+} flux, studies examining the regulation of Ca^{2+} absorption by PTH have demonstrated a small transcellular Ca^{2+} absorptive flux in the thick ascending limb.

An additional 8% of filtered Ca^{2+}, approximately 80% of the Ca^{2+} remaining after tubule fluid has passed the thick ascending limb, is reabsorbed in the "early" distal nephron, the distal convoluted tubule (Fig. 12). Although only a small fraction of filtered Ca^{2+} is reabsorbed in this segment, this segment is key to the tight regulation of renal Ca^{2+} excretion. It is also a tubule site where Ca^{2+} and Na^+ absorption can be dissociated. It is well established that the distal convoluted tubule mediates active Ca^{2+} absorption. At the beginning of the distal convoluted tubule, luminal Ca^{2+} concentration is approximately equal to 60% of ultrafilterable Ca^{2+} concentration, and this ratio falls to about 30% at the end of the distal tubule. Given the fact that this segment has a lumen negative voltage, the mechanism of Ca^{2+} absorption must be active.

The mechanism of distal convoluted tubule Ca^{2+} absorption is shown in Fig. 13. Ca^{2+} enters the cell from the luminal fluid most likely via a dihydropyridine-sensitive Ca^{2+} channel. Because cytoplasmic ionized Ca^{2+} concentra-

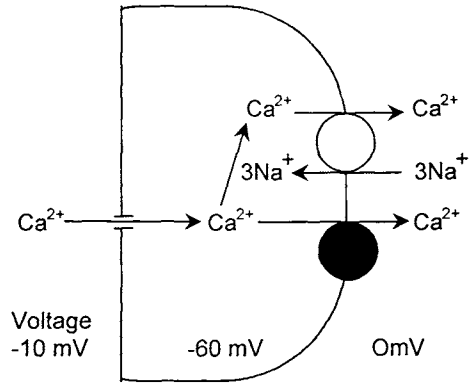

FIGURE 13. Ca^{2+} transport in the distal convoluted tubule. Ca^{2+} is reabsorbed from the luminal fluid across an apical membrane Ca^{2+} channel. Ca^{2+} then exits the basolateral membrane on either a Ca ATPase or a 3Na/Ca exchanger. ●, Active transport mechanism; ○, passive transporter; =, channel.

tion is 10^{-7} *M*, 4 orders of magnitude lower than that of extracellular fluid, and cell voltage negative compared to lumen, there is a large electrochemical gradient favoring passive Ca^{2+} entry. Within the distal convoluted tubule cell, low concentrations of free ionized Ca^{2+} must be maintained because high cell Ca^{2+} would complex ATP and other phosphorylated intermediates, events that would lead to cell death. To safeguard low cell [Ca^{2+}], apically reabsorbed Ca^{2+} in distal tubule cells is bound to Ca^{2+} binding proteins. One of these, calbindin-D28, has been localized in distal convoluted tubule cells. Ca^{2+} exits across the basolateral membrane by two mechanisms, a Ca ATPase, and a 3Na/Ca exchanger. The Ca ATPase has been well characterized and is of the P type ATPase type. The 3Na/Ca exchanger exchanges 3 Na^+ for 1 Ca^{2+} ion. Although not totally settled, it appears that the Ca ATPase mediates the majority of Ca^{2+} efflux in these cells. Paracellular permeability to Ca^{2+} is very low in this segment. Only small amounts of filtered Ca^{2+}, equivalent to 1–2%, are reabsorbed in the remaining downstream tubule segments (cortical and medullary collecting ducts).

Renal Ca^{2+} absorption is tightly regulated. Parathyroid hormone enhances Ca^{2+} absorption in the cortical thick ascending limb and in the distal convoluted tubule. These processes appear to be mediated by cellular increases in cAMP. PTH has been shown to lead to recruitment of dihydropyridine-sensitive Ca^{2+} channels to the apical membrane of the distal convoluted tubule cell. This process is associated with an increase in intracellular Ca^{2+} concentration.

Another important regulator of Ca^{2+} transport is effective arterial volume. In states of low effective arterial volume the kidney retains Ca^{2+}, while in states

of high effective arterial volume the kidney excretes Ca^{2+} at high rates. This effect is mostly attributable to changes of Ca^{2+} transport in the proximal tubule where decreases in effective arterial volume enhance Na^+ and water reabsorption and secondarily increase Ca^{2+} absorption. Changes in volume status may also modulate thick ascending limb Na^+ transport and voltage and secondarily affect Ca^{2+} absorption.

Last, changes in acid–base status regulate Ca^{2+} absorption. This effect is attributable to an effect of luminal pH on Ca^{2+} absorption in the distal convoluted tubule. Decreases in luminal pH inhibit apical membrane Ca^{2+} uptake leading to hypercalciuria, while increases in luminal pH have the opposite effect. Accordingly, metabolic acidosis often leads to hypercalciuria. Proximal renal tubule acidosis (RTA) is an exception in that distal nephron luminal pH is high as a consequence of diminished proximal HCO_3^- reabsorption. Alkalosis associated with high rates of distal delivery of HCO_3^- is often associated with Ca^{2+} retention.

Diuretics have diverse effects on Ca^{2+} absorption. *Carbonic anhydrase inhibitors* have a minimal effect on Ca^{2+} absorption. Because they inhibit proximal tubule salt and water reabsorption, they inhibit proximal tubule Ca^{2+} reabsorption. However, this is counterbalanced by enhanced distal convoluted tubule Ca^{2+} reabsorption in response to enhanced distal HCO_3^- delivery. *Loop diuretics* cause hypercalciuria by decreasing the lumen positive voltage in the thick ascending limb and secondarily inhibiting thick ascending limb Ca^{2+} absorption. However, if loop diuretics lead to decreased effective arterial volume, the expected hypercalciuria will be modest.

Thiazide diuretics cause renal Ca^{2+} retention and have been useful in the treatment of hypercalciuria. Part of this effect is related to a decreased effective arterial volume and increased proximal tubule Ca^{2+} reabsorption. However, there is also a direct effect of thiazide diuretics on the distal convoluted tubule. Two possible mechanisms have been proposed. By inhibiting apical membrane NaCl entry in the distal convoluted tubule there is a decrease in cell Na^+ concentration which would enhance basolateral membrane Na^+/Ca^{2+} exchange and lower intracellular Ca^{2+} concentration. As a consequence of a steeper transmembrane Ca^{2+} gradient, accelerated Ca^{2+} entry across the apical membrane would lead to enhancement of Ca^{2+} absorption. A second possible mechanism is that inhibition of apical membrane NaCl cotransport will also lower cell Cl^- concentration. Because the basolateral membrane of these cells has a large Cl^- conductance (Fig. 8), a decrease in cell Cl^- concentration will lead to cell hyperpolarization which again enhances passive Ca^{2+} entry across the apical membrane.

Amiloride also causes increased Ca^{2+} reabsorption. This effect occurs in the distal nephron and is likely due to cell hyperpolarization with secondary increases in apical Ca^{2+} entry.

MAGNESIUM TRANSPORT

Approximately 70–80% of plasma magnesium is ultrafilterable. Of this, 70–80% is in the ionic form, Mg^{2+}, while the remainder is complexed to phosphate, citrate, and oxalate (Fig. 14).

Approximately 20–30% of filtered Mg^{2+} is reabsorbed in the proximal tubule. Because this is less than the fraction of filtered water reabsorbed, luminal Mg^{2+} concentration rises to levels that exceed the ultrafilterable plasma Mg^{2+} concentration by a factor of about 1.5. Similar to Ca^{2+}, Mg^{2+} reabsorption in the proximal tubule parallels Na^+ and water reabsorption. Thus, Mg^{2+} reabsorption is enhanced in volume contraction and inhibited in volume expansion. Mg^{2+} absorption is absent in the descending thin limb of Henle's loop, and in fact there may be some Mg^{2+} secretion.

The major site of renal Mg^{2+} absorption is the thick ascending limb of the loop of Henle where 50–60% of filtered Mg^{2+} is reabsorbed (Fig. 14). Studies of single tubules suggest that the majority of this flux occurs in the cortical thick ascending limb. Similar to Ca^{2+}, there is some question as to the relative magnitudes of passive and active Mg^{2+} absorption. Studies examining the effect of voltage on Mg^{2+} absorption suggest that all or most of Mg^{2+} absorption is passive. However, studies examining the mechanism of hormonal regulation of Mg^{2+} absorption suggest that a transcellular component also exists in parallel. This cellular mechanism by which Mg^{2+} is absorbed is poorly defined. Pro-

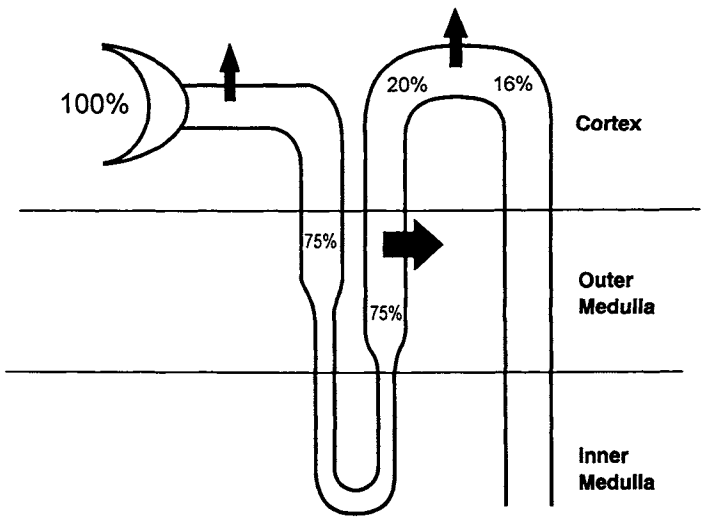

FIGURE 14. Mg^{2+} transport along the nephron. Numbers indicate percentage of filtered Mg^{2+} remaining in the luminal fluid. The majority of Mg^{2+} absorption occurs in the thick ascending limb.

posed mechanisms have included an apical membrane Mg^{2+} channel in series with a basolateral membrane Mg^{2+} pump and a Na/Mg exchanger.

The thick ascending limb is an important site of regulation of Mg^{2+} transport. Mg^{2+} absorption here is increased in Mg^{2+} deficiency and inhibited in hypermagnesemia. Mg^{2+} absorption is also stimulated by PTH, calcitonin, glucagon, and ADH. Loop diuretics inhibit Mg^{2+} absorption in this segment by inhibiting the lumen-positive voltage and thus inhibiting passive Mg^{2+} absorption.

The distal convoluted tubule mediates reabsorption of an additional 2–5% of the filtered Mg^{2+} load. This flux is also stimulated by PTH, glucagon, vasopressin, and calcitonin. Magnesium absorption in the collecting duct appears to be minimal and is poorly characterized.

PHOSPHATE TRANSPORT

Almost all of plasma phosphate is freely filtered at the glomerulus. Under normal metabolic conditions approximately 20% of the filtered load of phosphate is excreted in the urine.

Approximately 70% of the filtered load of phosphate is reabsorbed in the proximal tubule. In this segment, phosphate is actively transported from lumen to cell by an apical membrane Na/PO_4 cotransporter. A number of Na/PO_4 cotransporter isoforms have now been cloned. Apical membrane transporter activity appears to be mediated by a type 2 transporter, encoded in the rat by the isoform NaPi-2. NaPi-2 normally operates in an electrogenic manner and accepts HPO_4^{2-} or $H_2PO_4^-$ as substrates, being highly specific for phosphate. A second type of Na/PO_4 transporter has been cloned and designated type 1, as exemplified by NaPi-1. This carrier is less specific and transports several solutes in addition to phosphate. It appears that NaPi-2 is the key regulated phosphate transporter. Following entry across the apical membrane, phosphate exits across the basolateral membrane, most likely via a Na-independent anion exchanger.

The proximal tubule is a key site of regulation of PO_4 excretion. Two important factors which regulate phosphate transport are dietary phosphate intake and parathyroid hormone levels. Decreases in dietary phosphate intake lead to enhanced phosphate reabsorption, while increases in dietary phosphate inhibit phosphate reabsorption. Both effects occur independent of PTH. In addition, PTH inhibits phosphate reabsorption. Both of these regulatory factors modulate the activity of the apical membrane Na/phosphate cotransporter. Proximal tubule phosphate handling is also regulated by acid–base status, with respiratory and chronic metabolic acidosis inhibiting transport, and respiratory and chronic metabolic alkalosis stimulating reabsorption.

The phosphaturic effects of diuretics in the proximal tubule appear to correlate with the ability of the diuretic to inhibit carbonic anhydrase. Thus, *acetazolamide* has a potent phosphaturic effect. *Thiazides* and *furosemide*, which modestly inhibit carbonic anhydrase, are also mildly phosphaturic.

Phosphate reabsorption is virtually absent in the loop of Henle. A small fraction of phosphate is reabsorbed along the distal convoluted tubule and collecting duct, but the mechanisms by which this occurs have not been defined. However, it has been demonstrated that this reabsorptive process is inhibited by PTH.

WATER TRANSPORT

Water movement across membranes is determined by the permeability of the membrane to water and the driving force. The driving force for water movement consists of two components, hydrostatic and osmotic pressures. Along the nephron, the predominant driving force for water movement is osmotic pressure. In some segments of the nephron such as the proximal tubule, water permeability is so high that minimal osmotic pressure differences can drive large water fluxes. In other segments of the nephron, water permeability is more intermediate such that significant osmotic pressures are required for water movement; in still other segments of the nephron water permeability is close to zero.

It is now known that in many epithelia and cells, water transport occurs through pores, now referred to as aquaporins. A number of these water channels have been cloned. They have 6 membrane spanning domains, with N-terminal and C-terminal cytoplasmic domains. The first cloned water channel, aquaporin-1, mediates water transport in the proximal tubule and thin descending limb. Aquaporin-2 encodes the *apical* membrane water channel of the collecting duct, a water channel whose activity is regulated by vasopressin. Aquaporin-3 encodes the *basolateral* membrane water channel of the collecting duct, most likely a site of minimal regulation.

Although it is beyond the scope of this chapter to present a thorough discussion of urinary concentration and dilution, we will discuss it briefly as diuretics have significant effects on these processes. In the proximal tubule water is reabsorbed isoosmotically with solute. This process is driven by small osmotic gradients that are generated by active solute (Na^+) transport. In the thin descending limb water is reabsorbed in response to high medullary tonicity, leading to a hypertonic luminal fluid. At the tip of the loop of Henle urinary dilution begins. The ascending limb of the loop of Henle is impermeable to water; solute absorption in this segment lowers luminal fluid osmolality to approximately 100 mOsm/liter.

The water permeability of the collecting duct is determined by the level of vasopressin. Vasopressin leads to exocytotic insertion of aquaporin-2 containing vesicles into the apical membrane. In addition, protein kinase A may directly phosphorylate aquaporin-2, further leading to its activation. Recent evidence suggests that the promoter of the aquaporin-2 gene is positively regulated by CREB, the cAMP response element binding protein. In the absence of vasopressin collecting duct water permeability is low and urine dilute, while in the presence of vasopressin collecting duct water permeability is high and the urine is concentrated by equilibration with the hypertonic contents of the renal medulla.

An integral component of urinary concentration is the generation of medullary hypertonicity. The nephron segment primarily responsible for this process is the medullary thick ascending limb. Active NaCl absorption in the absence of water absorption in this segment leads to hypertonicity in the *outer medulla.*

In addition to this process, hypertonicity in the *inner medulla* is generated by addition of NaCl and urea to the interstitium. The mechanism by which the inner medullary interstitium is made hypertonic is summarized in Fig. 15. NaCl absorption in the thick ascending limb leads to a low luminal NaCl concentration and low luminal fluid osmolality, without affecting luminal urea concentration. Vasopressin stimulated water absorption in the collecting duct, then causes luminal fluid osmolality and urea concentration to rise. Because the cortical and outer medullary collecting duct are impermeable to urea, there is little urea flux in response to the high luminal concentration. In the inner medullary collecting duct, vasopressin increases urea permeability, allowing passive urea diffusion into the interstitium. The high interstitial urea concentration draws fluid from the descending limb of the loop of Henle, increasing luminal fluid osmolality and NaCl concentration. At the tip of the loop of Henle, tubular and interstitial fluid are in osmotic equilibrium, but are very different in composition. Luminal fluid has a higher NaCl concentration and interstitial fluid has a higher urea concentration. In the thin ascending limb, NaCl permeability is large and the high luminal NaCl concentration provides a driving force for passive NaCl absorption and addition to the interstitium. The net result of these processes is that inner medullary interstitial osmolality is generated by urea diffusion from the inner medullary collecting duct and by NaCl diffusion from the thin ascending limb. It is important to understand that these processes are passive and all occur in response to driving forces established primarily by NaCl absorption in the thick ascending limb.

A number of diuretics significantly affect urinary concentration and dilution. In fact, the location of action of many diuretics was first identified based on their effects on urinary concentration and dilution. Loop diuretics inhibit both urinary concentration and dilution. Inhibition of NaCl absorption in the thick

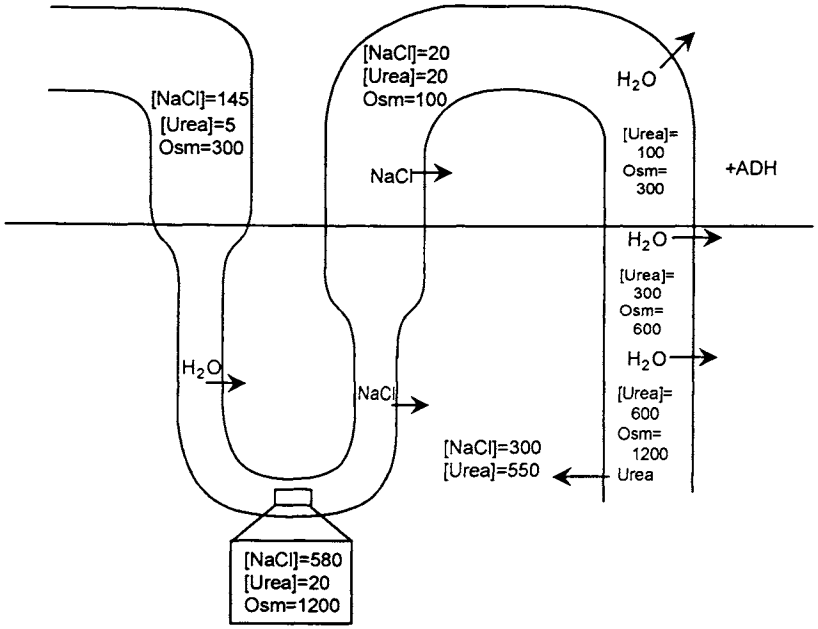

FIGURE 15. Urinary concentration: generation of medullary hypertonicity. The thin descending limb is highly permeable to water and relatively impermeable to solutes. As tubular fluid travels along the thin descending limb, luminal NaCl and urea are concentrated by water abstraction. The thin ascending limb has a high NaCl permeability, and low permeabilities to urea and water. As the tubular fluid travels along the thin ascending limb, there is passive NaCl absorption. Active NaCl absorption occurs in the thick ascending limb leading to a hypotonic luminal fluid. In the presence of vasopressin, water exits from the lumen of the collecting duct, allowing osmotic equilibration and concentrating luminal urea, leading to high luminal urea concentrations in the inner medullary collecting duct. In the presence of vasopressin, the inner medullary collecting duct is highly permeable to urea, allowing urea to diffuse into the medullary interstitium, and generating a high interstitial urea concentration. It is this high medullary urea concentration which provides the driving force for osmotic water efflux in the thin descending limb, leading to luminal Na^+ concentrations at the tip of the loop of Henle that are higher than those in the interstitium. All solute concentrations are in mM and all osmotic concentrations are in mOsm/liter.

ascending limb interferes with the operation of the major component of urinary dilution and prevents the addition of NaCl to the outer medullary interstitium, thus removing a significant driving force for water absorption in the collecting duct. These events lead to failure to increase urea concentration in the lumen of the collecting duct. This prevents urea diffusion into the inner medullary interstitium, inhibits water reabsorption in the thin descending limb, and lastly curtails the generation of the gradient for passive NaCl diffusion in the thin ascending limb. Urine frequently becomes isosthenuric in patients treated with loop diuretics.

Thiazides also inhibit urinary dilution, but have no effect on urinary concentration. This is related to the fact that they inhibit NaCl absorption distal to the tip of the loop of Henle, but have no effect on NaCl absorption in the medulla. The tubule site of thiazide action was originally defined by studying its effects on urine dilution. Thiazides inhibit urinary dilution by causing *volume depletion,* which leads not only to decreased distal delivery of filtrate to the tip of the loop of Henle but also to increased vasopressin secretion. The significant inhibitory effect of thiazides on urinary dilution, without an effect on urinary concentration, explains the high incidence of hyponatremia. Conversely, the effects of loop diuretics on both urinary concentration *and* dilution explain the significantly lower incidence of hyponatremia seen with these diuretics.

DIURETIC TRANSPORT

Most diuretics are highly protein bound in the plasma and thus are poorly filtered at the glomerulus. Because most diuretics work from the luminal fluid, their action depends critically on tubule secretion. In general, secretion of diuretics occurs predominantly in the proximal tubule. Organic *anion* diuretics, such as acetazolamide, bumetanide, ethacrynic acid, furosemide, metolozone, and thiazides are secreted predominantly in the S2 segment of the proximal tubule by processes that involve apical and basolateral membrane anion exchangers. Diuretics such as amiloride and triamterene are organic *cations.* These agents are secreted predominantly in the S1 and S2 segments of the proximal tubule by mechanisms that involve facilitated diffusion across the basolateral membrane and H^+/diuretic exchange on the apical membrane.

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PART III

Physiology of Diuretic Action

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CHAPTER IIIA

Site and Mechanism of Diuretic Action

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INTRODUCTION

Diuretics are a diverse group of chemical compounds that share the ability to augment net renal sodium excretion. These agents are widely used in clinical medicine for the treatment of hypertension, pulmonary or cerebral edema, and other disorders that are characterized by the accumulation of fluid in the interstitial or extracellular compartments. Detailed discussions of the therapeutic use of diuretics can be found elsewhere in this text. The goal of the present chapter is to provide the reader with an understanding of the site and mechanisms of diuretic effects, with particular emphasis on recent insights into their cellular mechanisms of action and the molecular biology of the transport proteins that they inhibit.

Diuretics can be conveniently divided into four classes: *osmotic diuretics* and *carbonic anhydrase inhibitors* like mannitol and acetazolamide, respectively, which act in proximal tubules; *loop diuretics* such as furosemide that inhibits sodium transport in thick ascending limbs of Henle's loop; *thiazide and thiazide-type diuretics* that act in distal tubules; and the *weak diuretics* amiloride and triamterene that act in collecting ducts and are used primarily for their potassium-sparing action. The nephron sites of action of these different agents are summarized in Fig. 1.

Diuretic Agents: Clinical Physiology and Pharmacology

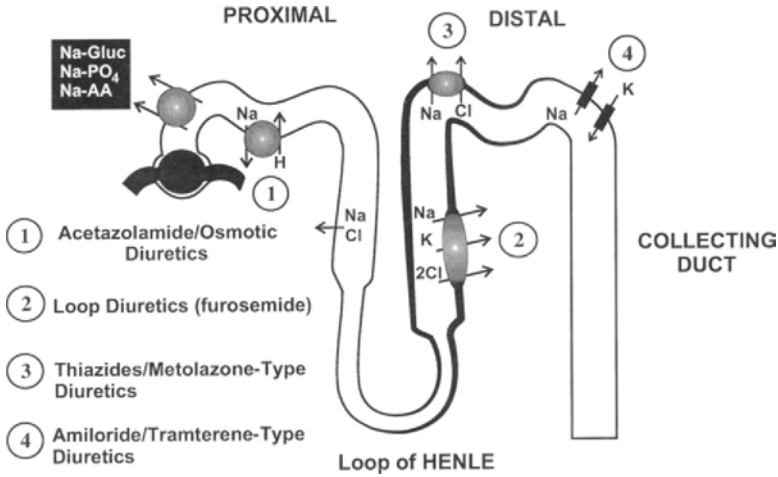

FIGURE 1. Sites of action of the four classes of diuretics.

When these compounds were initially developed there was little understanding of cellular ion transport mechanisms and hence few details known of how they work. Physiological investigations over the past 25 years, however, have revealed that each class of diuretic inhibits a specific ion transport protein in the kidney. Moreover, the NaCl absorption mechanisms along the mammalian nephron from proximal tubule to papillary collecting duct have been defined and characterized. In this regard, the most exciting new information has come from the cloning of members of each class of diuretic-sensitive Na^+ transporter, as well as other transporters or enzymes important to salt absorption and diuretic action. Many laboratories are currently engaged in research focusing on defining the structural sites for ion transport and diuretic binding and the molecular mechanisms of transport regulation. This information may enable the design of new diuretics and provide the basis for improved use of diuretics.

OSMOTIC DIURETICS

Drugs that owe their diuretic effects to the physical retention of fluid within the nephron rather than to a direct action on cellular sodium transport are called osmotic diuretics. Osmotic diuretics are nonelectrolytes that are freely filtered at the glomerulus and not reabsorbed to a significant extent. Any poorly absorbable solute whose transport maximum is exceeded can also effect such a diuretic action. For instance, in severe hyperglycemia the filtered load of glu-

cose (the product of GFR and plasma glucose) exceeds the maximal glucose reabsorptive capacity of the proximal tubule, resulting in a glucose diuresis. In this setting, glucose acts as a nonabsorbable osmolyte. Similarly, radiocontrast agents such as sodium iothalamate, iopamidol, or sodium methylglucamine ioxaglate may also promote an osmotic diuresis by virtue of their limited transport in the nephron. Practically speaking, however, few osmotic diuretics are available for therapeutic use. The prototype is mannitol (*Osmitrol*), a nonmetabolizable polysaccharide derivative of sucrose. Other clinically available osmotic diuretics include glycerin (*glycerol, Osmoglyn,* and the topical agent *Ophthalgan*), isosorbide (*Ismotic*) (not to be confused with its derivative, isosorbide dinitrate, an antianginal drug), and urea (*Ureaphil, Urevert*). The chemical structures of these compounds are shown in Fig. 2.

The ability of mannitol and other osmotic diuretics to reduce solute and fluid absorption depends primarily on the high water permeability of proximal tubules and thin descending limbs of Henle's loop. In proximal tubules, solute transport proceeds in an isosmotic fashion with sodium and water being absorbed in a fixed ratio; the tubular fluid remains at virtually the same tonicity as the surrounding interstitial fluid. Mannitol is freely filtered at the glomerulus and contributes to the total solute concentration of the luminal fluid. In this setting, sodium and fluid absorption proceed normally. However, mannitol is not transported and since the fluid remains isosmotic, the concentration of

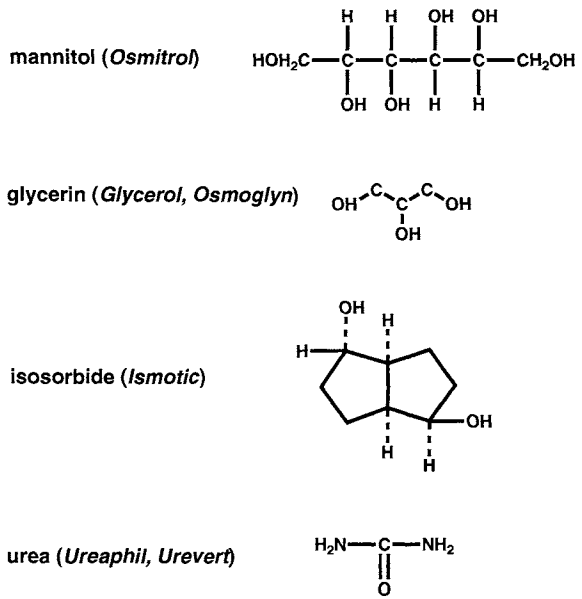

FIGURE 2. Chemical structures of representative osmotic diuretics.

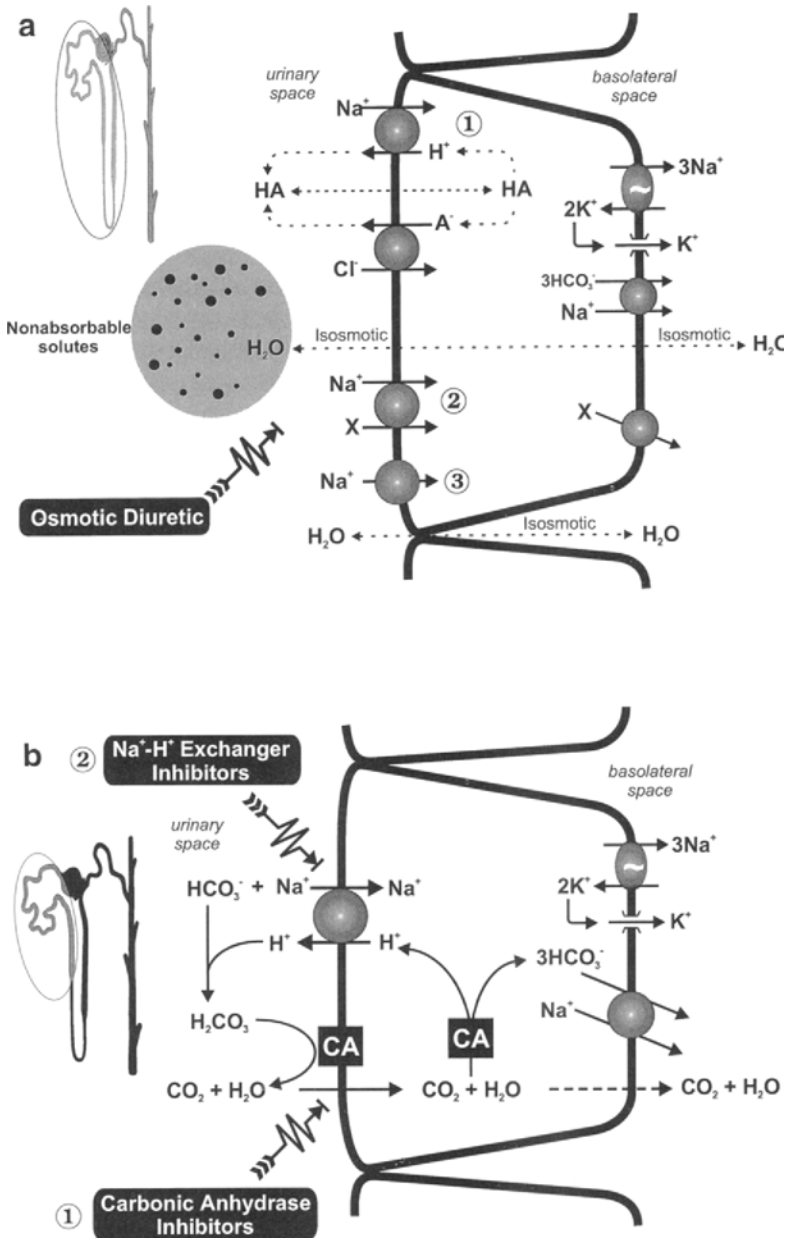

FIGURE 3. Model for solute and fluid reabsorption in the proximal tubule. (a) Sodium transport is mediated by Na^+/H^+ exchange (1), Na^+-coupled cotransport (2), and by other electroneutral transporters (3). Osmotic diuretics such as mannitol nonspecifically inhibit fluid absorption by retaining water in the lumen. (b) Carbonic anhydrase inhibitors (1) block the dehydration of H_2CO_3, which accumulates in the lumen, thereby limiting the secretion of H^+ions by the Na^+/H^+ exchanger (2).

mannitol increases as the tubular sodium concentration decreases, thereby producing an initial dissociation between sodium and fluid absorption (see Fig. 3).

Mannitol in the tubular lumen diminishes net fluid absorption, while the continued absorption of sodium lowers its concentration in the lumen until a limiting gradient is established, against which sodium is no longer absorbed. Similar physical–chemical effects are responsible for reduced fluid absorption by thin descending limbs of Henle's loop, where osmotic water permeability is as great as in proximal tubules. In contrast to proximal tubules, however, sodium absorption is negligible in thin descending limbs. Therefore the action of osmotic diuretics in water-permeable thin limbs is simply to retard fluid absorption without an effect on sodium transport. The overall consequence of mannitol administration is to augment the rate of urine flow, with relatively modest increases of sodium excretion and, notably, without the intense loss of potassium that accompanies the action of diuretics that directly inhibit sodium transport by thick ascending limbs or distal convoluted tubules.

Distal and Hemodynamic Effects of Mannitol

Evidence now supports the conclusion that the proximal tubular actions of mannitol on sodium absorption are insufficient to account for its diuretic effect, especially when mannitol is administered as a hypertonic solution. Under these conditions the ensuing diuresis and sodium excretion are considerably greater than the relatively modest decline in proximal reabsorption. It is generally accepted that inhibition of absorption by thick ascending limbs accounts for the majority of the additional sodium excretion. However, mannitol has no known direct action on sodium absorption by thick ascending limbs, which is mediated by the Na/K/2Cl cotransporter (see Fig. 7). It may be surmised, therefore, that suppression of sodium absorption in thick ascending limbs is an indirect, dynamic phenomenon that is due to the dilution of tubular sodium. Sodium dilution is secondary to the inhibition of fluid reabsorption by thin descending limbs as well as to diminished delivery of sodium to the thick ascending limbs. It has been firmly established that sodium absorption by thick ascending limbs is load-dependent, i.e., the more sodium that reaches the thick limb, the more that is absorbed. Conversely, when less sodium reaches the thick ascending limb its ability to absorb sodium is reduced. The same phenomenon contributed to the reduced diuretic action of the furosemide and bumetanide under circumstances such as severe dehydration, where proximal tubules absorb more solute and water, resulting in diminished delivery to thick ascending limbs and an attendant decrease in the ability of these "loop" diuretics to inhibit

salt transport. Thus, the decrease of tubular sodium absorption by more proximal segments, as described above, reduces sodium delivery and absorption by thick ascending limbs and distal convoluted tubules, where the rate of sodium absorption is proportional to the amount delivered. Furthermore, by replacing sodium in proximal tubules mannitol preserves fluid isotonicity while allowing the tubular sodium concentration to fall. When the concentration of luminal sodium reaching the thick limb falls, NaCl absorption is impaired because the tubular transport mechanism is operating near the limiting concentration for sodium entry, below which it cannot be transported.

Several other actions contribute and are necessary to explain fully the osmotic diuresis induced by mannitol. These include increased blood flow to the renal medulla and papilla and free radical scavenging, which may account for the vasodilation and the elevated blood flow. The increase in renal medullary blood flow is associated with a reduction of the interstitial osmolality, a phenomenon generally known as "washout." As a consequence of the reduced medullary interstitial osmolality, renal concentrating capacity is impaired. Thus, administration of hypertonic mannitol during hydropenia causes urine osmolality to decrease asymptotically toward isotonicity. The fact that free water reabsorption plateaus at high rates of osmolar clearance is consistent with the view that mannitol may inhibit sodium reabsorption by thick ascending limbs of Henle's loop.

Effects of Increased Distal Delivery

The rejection of NaCl by proximal tubules and loops of Henle results in increased delivery of fluid and greater tubular flow rates to more distal nephron segments. The consequence of such augmented distal delivery is enhanced potassium secretion. The magnitude of potassium secretion by distal tubules and collecting ducts is regulated, in part, by the supply of sodium reaching these nephron locations and flow of tubular fluid through them. Increases in net sodium absorption, for instance, are accompanied by elevated potassium secretion, while decreases of sodium absorption cause diminished rates of potassium secretion. Similarly, parallel changes of fluid flow and potassium secretion occur. Under most circumstances alterations of flow and of sodium delivery occur hand-in-hand. However, when they are experimentally dissociated, either flow rate alone or sodium delivery alone was sufficient to stimulate potassium secretion. Indeed, potassium secretion increased even when net sodium absorption decreased. These findings may help explain the effects of mannitol on potassium excretion. Compensatory mechanisms, especially hormonal regulation of distal sodium and potassium transport by aldosterone, and the volume of extra-

cellular fluid may partially attenuate or exaggerate the actions of mannitol on urinary potassium excretion.

Maximum Osmotic Diuresis Is Linked to Amount Filtered

As described above, mannitol and other osmotic diuretics are freely filtered at the glomerulus and are not appreciably absorbed during their passage through the nephron or, in the case of urea, exceed the ability of the tubular transport mechanisms to reabsorb them. Consequently, the filtered load of the osmotic diuresis increases proportionately with the plasma concentration. The rate of urine flow is ultimately a function of the rate at which fluid is reabsorbed from the renal tubules. Hence, as the tubular concentration of mannitol increases, fluid reabsorption is correspondingly diminished with an attendant and commensurate rise of urine flow. Thus, the magnitude of the induced osmotic diuresis is proportional to the concentration of infused mannitol.

Effects on Concentrating and Diluting Capacity

Osmotic diuretics have complicated actions on urinary concentration and dilution. The magnitude and direction of these effects are dictated by the state of hydration at the time the agent is administered as well as on inherent physical and chemical properties of mannitol on tubular fluid movement and on renal blood flow. Increased renal medullary blood flow, as mentioned earlier, results in washout of renal interstitial solutes. Decreased tissue solute concentrations, in turn, dissipate the osmotic gradient that favors fluid abstraction from the collecting ducts. During dehydration or hydropenia, vasopressin increases the water permeability of collecting ducts, thereby permitting fluid absorption down its osmotic concentration gradient in to the renal medulla and return to the systemic circulation. By reducing the magnitude of the medullary interstitial solute concentration, osmotic diuretics decrease fluid absorption and depress maximal urinary concentrating capacity. Thus, as noted above, administration of mannitol during hydropenia causes urine osmolality to decrease asymptotically toward isotonicity. Conversely, mannitol depresses the capacity of the kidney to elaborate dilute urine during states of antidiuresis. Urine is diluted as a consequence of salt absorption without concomitant water movement in thick ascending limbs of Henle's loop (see Loop Diuretics Affecting

Thick Limb Salt Transport, below). In the absence of vasopressin, this dilute urine is excreted. By inhibiting the magnitude of salt absorption by thick ascending limbs, osmotic diuretics reduce the magnitude of maximal urinary dilution during states of volume hydration. In this setting urine, osmolality to increases curvilinearly toward isotonicity.

CARBONIC ANHYDRASE INHIBITORS

A second group of drugs that reduce proximal salt and water absorption are inhibitors of carbonic anhydrase. This enzyme is present on plasma membranes (apical and basolateral) of proximal convoluted tubule cells and within the cytoplasm. Carbonic anhydrases are produces of a gene family that encodes seven isozymes (CA I–VII) and several homologous carbonic anhydrase-related proteins. All seven isozymes have been cloned, sequenced, and mapped (see Table 1). Types II and IV have been identified in the kidney. CA II represents the majority of both membrane-bound and cytoplasmic carbonic anhydrase, while a smaller fraction is CA IV. Proximal straight tubules express CA II on basolateral but not on apical cell membranes. CA II is also present in the cytoplasm of thin descending limbs of Henle's loop, apical and basolateral membranes and cytoplasm of thick ascending limbs (except in the rabbit), basolateral membranes of distal convoluted tubules and connecting tubules, cytoplasm of intercalated cells, and, to a far lesser extent, principal cells. In contrast, CA IV is strictly a membrane-associated form that is restricted to apical

TABLE 1 Carbonic Anhydrase Genes

Carbonic anhydrase isoform	Species	Size (amino acids)	Chromosome	GenBank No.
CAI	Human	260	8q22	M33987
	Mouse	261	3	M32452
CA II	Human	261	8q22	J03037
CA III	Human	261	8q22	M29452
CA IV	Human	312	17q	M83670
	Mouse	305		U37091
CA V	Human	356	16q/p	L19297
CA VI	Human	308	1p36.22–p36.23	M57892
CA VII	Human	263	16q22–q23	M76420

Note. Numbering is based on human CA I. Size is based on cDNA sequence and does not necessarily represent that of the mature protein.

and basolateral plasma membranes of proximal convoluted tubules and thick ascending limbs of Henle's loop and is not found in intercalated cells.

Carbonic anhydrase is a zinc metalloenzyme that operationally mediates the reversible formation of water and carbon dioxide from carbonic acid (H_2CO_3):

$$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$$

The reaction as it is catalyzed physically by the enzyme is thought to involve binding of OH^- with one of the four zinc valances. The bound OH^- reacts with CO_2 to form HCO_3^-, which is then released from the zinc and replaced by a molecule of H_2O. One of the hydrogen ions in the water is removed to regenerate the OH^-.

Carbonic anhydrase serves an important, though not entirely intuitive, role in proximal tubule salt absorption. A number of proteins are involved in mediating sodium transport. Most proximal sodium transport, about one-third or more, is attributable to Na^+/H^+ exchange, which proceeds in parallel with Cl^-/OH^- or Cl^-/base exchange. Low intracellular Na^+ and Cl^- are the respective primary driving forces for these exchange reactions. The Na^+ that is taken up by the cell is exchanged for an H^+ ion (as shown in Fig. 3), which is buffered by HCO^-_3 to form carbonic acid. In the presence of carbonic anhydrase, H_2CO_3 is rapidly dehydrated to $H_2O + CO_2$. The CO_2 diffuses into the cell where, in the presence of cytoplasmic carbonic anhydrase, it is converted back to $H^+ + HCO^-_3$. The HCO^-_3 is transported across the basolateral membrane by an $Na/3HCO^-_3$ cotransporter (Fig. 3) and the H^+ becomes available for another cycle of apical membrane Na^+/H^+ exchange. Thus, the luminal enzyme prevents acidification of the tubular fluid by permitting continuous buffering of secreted H^+, while the cytoplasmic enzyme regenerates H^+ ion for exchange with Na^+. The net result of these operations is the absorption of $NaHCO_3$. Furthermore, by facilitating the preferential absorption of bicarbonate in the early portion of the proximal tubule, a Cl^- concentration gradient develops that enhances the passive absorption of NaCl in later portions of the proximal tubule by establishing favorable driving forces for its diffusion.

Effects of Carbonic Anhydrase Inhibition

The consequences of inhibiting these transport reactions that are dependent on carbonic anhydrase now become predictable. First, carbonic acid accumulates in the tubular fluid, thereby causing a limiting H^+ gradient against which no further H^+ ions can be introduced by the Na^+/H^+ exchanger (Fig. 3b). Second, inhibition of cytoplasmic carbonic anhydrase diminishes the rate of formation of H^+ ions that can participate in apical membrane Na^+/H^+ exchange. As a result, bicarbonate along with an equivalent amount of sodium remains in the

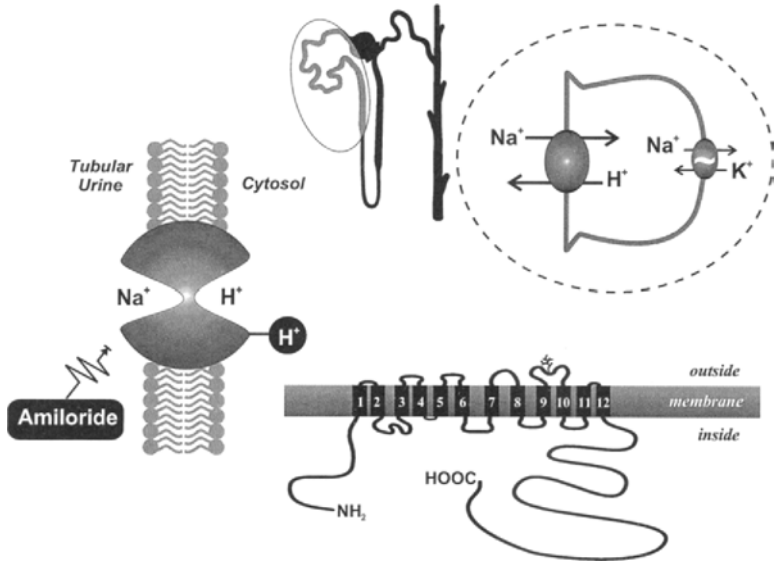

FIGURE 4. Molecular model of the Na^+/H^+ exchanger present in the proximal tubule.

proximal tubule. Thus, carbonic anhydrase inhibitors directly diminish sodium and bicarbonate absorption. A third consequence of inhibiting carbonic anhydrase is that the luminal chloride gradient is not developed, thereby reducing passive sodium chloride absorption in later portions of the proximal tubule. Therefore, carbonic anhydrase inhibitors not only diminish sodium absorption that normally attends bicarbonate recovery but, by preventing the development of a chloride concentration gradient, also reduce sodium transport that accompanies chloride absorption in the S2 and S3 portions of proximal tubules.

Insight into the spatial orientation of carbonic anhydrase within proximal tubule cells was obtained by preparing inhibitors of carbonic anhydrase that were complexed to impermeant dextrans. The results indicated that the impermeant dextran-bound drug was as effective as acetazolamide in inhibiting bicarbonate absorption. Thus, the active catalytic site of membrane-associated carbonic anhydrase is accessible to the luminal fluid. Dextran-bound carbonic anhydrase inhibitors blocked proximal tubule bicarbonate absorption by some 80% and resulted in significant acidification of the luminal fluid. These findings corroborate the earlier observation that membrane-associated carbonic anhydrase accounts for the majority of bicarbonate absorption. When the permeant parent compound was tested, bicarbonate absorption was inhibited, but the pH of the luminal fluid was unchanged indicating that the unbound drug had access to both the membrane-delimited and the cytoplasmic enzyme.

Carbonic anhydrase inhibitors were the first useful orally active diuretics. They were systematically developed when it was recognized that the recently introduced sulfanilamide antibiotics caused acidosis and increased the volume of voided urine. Carbonic anhydrase diuretics containing the sulfonamide group, however, are devoid of antibacterial action. Numerous chemical derivatives have been prepared. The most commonly used agents are shown in Fig. 5. Replacement of the *N*-sulfamyl group ($H_2NO_2S^-$), as in the antibacterial sulfonamides, abolishes carbonic anhydrase activity. From a functional point of view, the carbonic anhydrase inhibitors may be categorized according to their liposolubility. The relative liposolubility of representative carbonic anhydrase inhibitors is ethoxzolamide (25) > methazolamide (0.035) > acetazolamide (0.001) > benzolamide (0.0001), where the value in parentheses is the $CHCl_3$: H_2O partition coefficient, an index of solubility; the lower the number the greater the aqueous solubility.

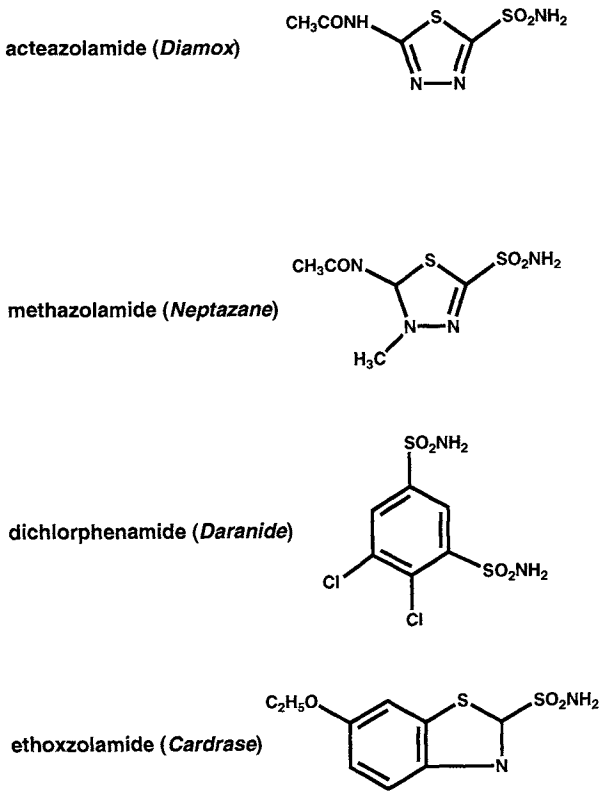

FIGURE 5. Chemical structures of the carbonic anhydrase inhibitors.

LOOP DIURETICS AFFECTING THICK LIMB SALT TRANSPORT

General Aspects

Pharmaceutical agents inhibiting NaCl reabsorption by the thick ascending limb of the loop of Henle are the most potent clinically useful diuretics. These drugs are often referred to as loop diuretics, since their major effect is on the thick ascending limb of the loop of Henle, or as "high ceiling" diuretics because of their *highly potent* natriuretic effects. The most widely used loop diuretics are *furosemide* (*Lasix*) and bumetanide (*Bumex*), torsemide (*Demadex*), and ethacrynic acid (*Edecrin*). These and functionally related compounds are shown in Fig. 6.

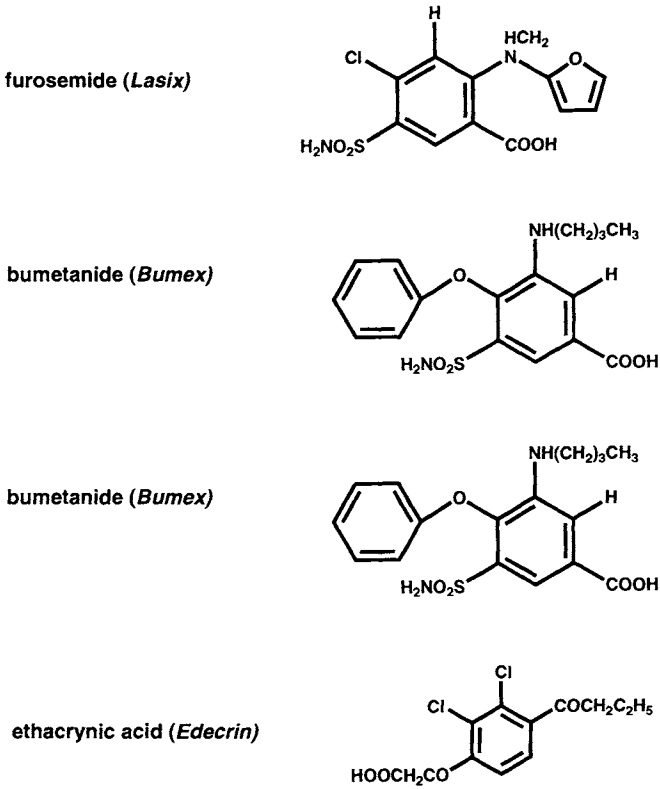

FIGURE 6. Chemical structures of the loop diuretics.

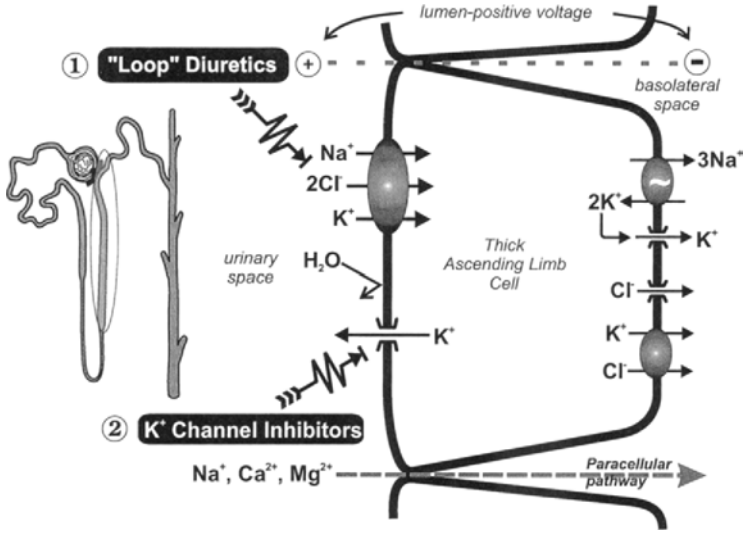

FIGURE 7. Model for NaCl absorption in the thick ascending limb of Henle.

Model of NaCl Transport

The mechanism of all salt reabsorption by the *thick ascending limb of Henle* is well understood and is shown schematically in the model depicted in Fig. 7. The thick ascending limb reabsorbs about 10–15% of the filtered NaCl. The entry of each sodium ion across the apical membrane of thick ascending limb cells is directly and tightly coupled to one potassium ion and two chloride ions by the Na/K/2Cl cotransporter, a process that is electroneutral. The entry of these ions is a secondary active transport process since it depends on the low intracellular Na^+ that is maintained by the primary active extrusion of Na^+ from the cell by the basolateral (Na^+/K^+/ATPase (Na^+-pump). Since the luminal membrane is relatively impermeable to water, NaCl absorption is responsible both for urinary dilution and for generating the classic "single" effect (active transport step) for countercurrent multiplication that is essential for urine concentration.

Much of the potassium that enters the cell by Na/K/2Cl cotransport recycles back to the tubular urine through potassium channels, a process that has two major consequences. First, it replenishes the urinary K^+ that would otherwise be lost through absorption by the Na/K/2Cl cotransporter. This step ensures a virtually inexhaustible supply of tubular K^+ necessary for reabsorption of the large fraction of Na^+ load transported by the thick ascending limb. Thus, without K^+ recycling, tubular fluid K^+ concentrations in the thick ascending limb

would fall to levels that would limit the amount of NaCl that could be reabsorbed by this nephron segment. In addition, K^+ recycling across the apical membrane produces an electrical current that results in a lumen-positive transepithelial voltage. This voltage, in turn, provides the driving force for a *paracellular* current that carries 50% of the total Na^+ reabsorbed by the thick ascending limb (see Fig. 7). Studies of the rabbit, rat, and mouse thick ascending limb have shown that blockade of these apical K^+ channels both abolishes the transepithelial voltage and substantially reduces net NaCl reabsorption.

From the salt transport model of the thick ascending limb shown in Fig. 7 it is evident that pharmaceutical agents could function as loop diuretics if they effectively interfered with any of the steps crucial for transepithelial NaCl movement. Although this can be accomplished in isolated thick ascending limb cells or tubule segments by the application of drugs that inhibit basolateral transport processes (e.g., inhibition of the Na^+/K^+/ATPase by cardiac glycosides such as ouabain or inhibition of the Cl^- channel by a variety of anion channel blockers) no such compounds have yet been found that are clinically useful as diuretics. On the other hand, certain pharmaceutical agents affecting apical transport processes do make clinically useful diuretics. These apical transport processes are especially vulnerable to inhibition in the clinical setting because they face a specialized compartment (urinary space) in which the concentrations of diuretic drugs can achieve effective inhibitory levels as a result of both proximal tubular secretion and proximal volume reabsorption. Only drugs directly inhibiting the apical Na/K/2Cl cotransporter [i.e., furosemide (*Lasix*), bumetanide (*Bumex*), torsemide (*Demadex*), and ethacrynic acid (*Edecrin*)] have found their way into clinical practice in this country. Several others, notably, piretanide, and azosemide, have comparable action but have not been approved for clinical use in the United States.

These drugs are extensively bound to plasma proteins. Nonetheless, the primary mode of elimination is urinary excretion. Because they are bound to plasma proteins, their entry into the tubular fluid is dependent on active secretion of the diuretics by the proximal tubule. Systemic effects of these agents on Na/K/2Cl cotransport processes in nonrenal tissues are generally absent or minimal since plasma concentrations usually are below effective inhibitor levels. High plasma concentrations leading to systemic toxic effects such as deafness can result, however, when large quantities of these loop diuretics are given to patients with impaired renal function. Potassium channel inhibitors should also make potent diuretics but clinically effective and selective agents are not yet available. One class of agents, sulfonylureas, which can inhibit these K^+ channels (see discussion below) have been shown in loop perfusion studies to inhibit NaCl absorption in the thick ascending limb and result in natriuresis and chloruresis.

Other Physiological Consequences of Inhibiting NaCl Absorption in the Thick Ascending Limb

A number of other transport processes are affected by inhibition of NaCl reabsorption by the thick ascending limb. Some of these effects can be readily understood from the transport model of the thick ascending limb shown in Fig. 7. First, since NaCl absorption is essential to both the concentrating and the diluting processes loop diuretics result in excretion of urine with an osmolality approaching that of plasma. Second, the NaCl transport-related lumen-positive transepithelial voltage drives passive calcium and magnesium reabsorption through the paracellular pathway. Thus, loop diuretics can result in frank calciuria and magnesuria, with attendant hypomagnesemia in some instances. Comparable effects on serum calcium do not occur. Conversely, because of their effects on calcium and magnesium excretion, loop diuretics are used clinically in treating hypercalcemia or hypermagnesemia.

The action of loop diuretics on the thick ascending limb also results in increased delivery of NaCl to more distal nephron segments. A variable fraction of this salt is reabsorbed by the *distal convoluted tubule* and *collecting duct*. This additional NaCl reabsorption can modulate the magnitude of the natriuresis produced by diuretics like furosemide. During clinical conditions resulting in heightened renal NaCl absorption (such as states of extracellular fluid volume depletion from vomiting, diarrhea, or blood loss; congestive heart failure; or cirrhosis) this distal reabsorption may severely limit loop diuretic-mediated natriuresis. The reduced effectiveness of loop diuretics is due to at least two consequences of volume-depletion states. First, as described earlier, the increased fraction of NaCl and volume reabsorbed by proximal tubules reduces the delivery of NaCl to the thick ascending limb and consequently the amount of NaCl that can be inhibited by diuretics is diminished. Second, NaCl reabsorption by the distal convoluted tubule and collecting duct (see Figs. 11 and 14), which, like that in the thick ascending limb, is also load-dependent, is enhanced so that larger absolute and fractional amounts of delivered NaCl are reabsorbed. The interplay of many hormonal systems (e.g., renin–aldosterone, atrial natriuretic peptides, antidiuretic hormone, kinins, and prostaglandins) can alter these distal NaCl reabsorption processes and affect the natriuretic effectiveness of loop diuretics.

There are two major physiological consequences of the increased delivery of NaCl to more distal nephron segments. First, NaCl reabsorption in the distal convoluted tubule is load- and flow-dependent so that increased delivery results in greater NaCl reabsorption by this nephron segment. Second, calcium reabsorption by both the distal convoluted tubule and *connecting tubule*, in contrast, is inversely related to NaCl reabsorption. Thus, increased NaCl delivery

results in reduced reabsorption of calcium by both these nephron segments. This latter effect significantly enhances the calciuric potential of loop diuretics. Moreover, increased NaCl delivery to the cortical collecting duct (see Fig. 14) enhances K^+ secretion and increases kaluresis (see Diuretics Affecting Collecting Duct Salt Transport, below, for further details). The loop diuretic-induced kaluresis and extracellular fluid volume depletion can, in turn, lead to significant hypokalemia and metabolic alkalosis.

The Na/K/2Cl Cotransporter Genes and Proteins

Major advances have been made over the past few years in our understanding of the actions of loop diuretics. This is due in large part to the molecular identification of a family of cationchloride cotransporters to which the Na/K/2Cl transporters belong (see Table 2). This information has revolutionized our thinking about these transporter proteins. It is now clear that Na/K/2Cl cotransport activity is the function of a single membrane protein, dispelling the earlier speculations that a complex of separate proteins (e.g., Na/Cl and K/Cl cotransporter proteins) might be required. In this regard, however, the cloning of distinct Na/Cl and K/Cl cotransporters has shown that these transport functions do exist and depend on membrane proteins that are closely related to the

TABLE 2 **Diuretic-Sensitive Cation-Chloride Cotransporter Genes**

Cotransporter	Alternative nomenclature	Species	Size (amino acids)	Chromosome	GenBank No.
TSC		Human	1021	16q13	U44128
(thiazide-	NCCT	Flounder	1023		L11615
sensitive	SLC12A3	Rat	1002		U10097
Na/Cl		Mouse	1002	8	U61085
cotransporter)					
BSC1		Human	1099	16	U58130
(bumetanide-	NKCC2	Rat	1095		U10096
sensitive	SLC12A1	Rabbit	1099		U07547
Na/K/2Cl		Mouse	1095	2	U20975
cotransporter)					
BSC2		Human	1212	5q23.3	U30246
(bumetanide-	NKCC1	Mouse	1205	18	U13174
sensitive	SLC12A2	Shark	1191		U05958
Na/K/2Cl					
cotransporter)					

Na/K/2Cl cotransporters. Thus, the Na/K/2Cl, Na/Cl, and K/Cl cotransporters comprise a newly identified family of proteins, the electroneutral cation/chloride cotransporters.

Cotransporter Genes and Tissue Expression

Two distinct Na/K/2Cl cotransporter genes (*Slc12a1* and *Slc12a2*) have been cloned with the encoded proteins exhibiting only about 50% overall amino acid identity (see Table 2). Both of these Na/K/2Cl cotransporter genes are expressed in the mammalian kidney although in different regions. One of these genes, *Slc12a1* (see Table 2), is apparently expressed exclusively in the thick ascending limb. Polyclonal antibodies directed against the rat protein (BSC1) demonstrated cotransporter-specific fluorescence only on apical membranes of thick ascending limb and macula densa cells in rat kidney. Ion transport function and diuretic sensitivities of BSC1 were determined using *Xenopus laevis* frog oocytes injected with synthetic messenger RNA made from this cotransporter complementary DNA. Cotransporter RNA-injected oocytes exhibited high levels of potassium- and chloride-dependent tracer sodium uptake. This sodium uptake was specifically inhibited by bumetanide, while thiazides such as hydrochlorothiazide (*Diuril*) or metolazone (*Zaroxolyn*) had no effect. Thus BSC1 is kidney-specific and encodes the loop diuretic-sensitive Na/K/2Cl cotransporter that mediates NaCl absorption in the thick ascending limb.

The second Na/K/2Cl cotransporter gene, *Slc12a2* (Table 2), was originally cloned from shark rectal gland (NKCC1) and then subsequently from human and mouse (BSC2). The messenger RNA and cotransporter protein encoded by the *Slc12a2* gene are expressed in a wide variety of cells including kidney, brain, thymus, eye, trachea, lung, choroid plexus, heart, skeletal muscle, esophagus, stomach, jejunum, colon, and testis. Consistent with this distribution of *Slc12a2,* this cotransporter serves several different functions including Cl^- and fluid secretion, cell volume regulation, and acid secretion. Antibodies raised against this cotransporter showed that BSC2 was expressed in two distinct regions of the kidney. In cortex, the cotransporter was localized to renin-containing granular cells and vascular smooth muscle cells of afferent arteriole, glomerulus, and extraglomerular mesangium. Because of this renal cortical pattern of expression, the BSC2 cotransporter was suggested to be involved in the tubuloglomerular feedback (TGF) and/or renin secretion. In this regard, it is well recognized that Cl^- is involved in these functions, and thus it is not surprising that furosemide both blocks TGF and modulates renin secretion. Inhibition of TGF secondary to administration of loop diuretics would potentially enhance the diuretic action of these agents by diminishing the effect of the diuretic to increase luminal Cl^- in the thick ascending limb, thereby reducing GFR by the TGF mechanism.

The BSC2 protein is also expressed on basolateral membranes of type A (acid secreting) intercalated cells of the rat collecting duct and on basolateral membranes along the terminal one-third of the mouse *papillary collecting duct*. What effects loop diuretics would have on acid secretion and/or NaCl transport by the PCD is at present unclear, although many years ago furosemide had been shown by an *in vivo* duct cannulation technique to reduce Na^+ transport by rat papillary collecting ducts. The question of how such possible actions of loop diuretics would affect their natriuretic potencies remains unresolved.

Cotransporter Stoichiometry, Topology, and Diuretic Interactions

The proposed order of ion binding to the Na-K-2Cl cotransporters and the overall topology of the cotransporter protein is shown in Fig. 8. The stoichiometry of $1Na^+:1K^+:2Cl^-$ for the cotransporter was worked out more than 15 years ago in Ehrlich ascites tumor cells. More recent kinetic studies of ion

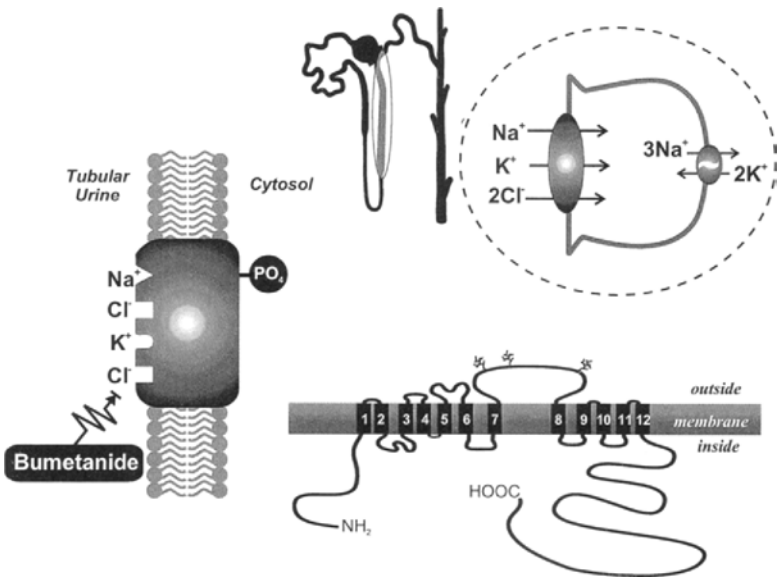

FIGURE 8. Molecular model of the Na/K/2Cl cotransporter present on apical membranes of thick ascending limb cells. This transporter is a member of the electroneutral cation/chloride cotransporter family that includes two bumetanide-sensitive Na/K/2Cl cotransporters, the thiazide-sensitive Na/Cl cotransporter and two K/Cl cotransporters (see Table 2. for description of these genes and the transporters they encode). The Na/K/2Cl cotransporter protein model consists of a central region with 12 membrane spanning helices flanked by two hydrophilic segments that are thought to be facing the cytosol. Three potential N–O linked glycosylation sites are predicted to be present in the large extracellular loop between membrane helices 7 and 8.

transport in several cell types suggested that the order of ion binding-interaction with the cotransporter protein is as shown in Fig. 8A. Sodium binds first, then one Cl^- followed by K^+ and the second Cl^- ($Na^+ \rightarrow Cl^- \rightarrow K^+ \rightarrow Cl^-$). Loop diuretics like bumetanide appear to bind at or near to the second Cl^- site on the transporter protein. In fact, bumetanide binding has been shown to depend on the presence of all three ions (Na^+, K^+, and Cl^-). Thus it is likely that the diuretic binding site is unavailable unless all ions (or at least the first three ($Na^+ \rightarrow K^+ \rightarrow Cl^-$) bind to the protein. Limiting any of these ions severely reduces bumetanide binding to the cotransporter. The second Cl^- may interfere with diuretic binding, possibly by competing at or near the diuretic binding site.

The Na/K/2Cl cotransporters are large proteins with a core molecular weight of about 120–140 kDa. Each also has a similar overall topology with a large hydrophobic central region of many (possibly 12) membrane-crossing helices flanked by large hydrophilic regions that appear to face the interior of the cell (see Fig. 8B). Sugar residues are linked to an extracellular loop between the 7th and 8th membrane-spanning segment, rendering these cotransporters glycoproteins and increasing their apparent molecular weight on Western blotting to 150–195 kDa. The specific ion and diuretic binding regions of these proteins have not yet been identified but such studies are currently underway in several laboratories.

Apical K^+ Channels

Electrophysiological experiments in rabbits and rats have identified two types of K^+ channels that are involved in the K^+ recycling process: a channel with a 30–40 pS conductance (low-conductance channel) and another with a higher conductance of 70–80 pS (moderate conductance channel). High conductance (> 100 pS), or maxi-K^+ channels, have also been identified in apical membranes of rabbit thick ascending limb cells in culture and they are thought to function in cell volume regulation, but not in K^+ secretion or recycling. Both the low and the moderate conductance K^+ channels are weak inward rectifiers, i.e., they conduct more current in the absorptive than the secretory direction. Although this would seem to imply that these channels might not function very well in K^+ secretion and K^+ recycling, they do in fact have a significant secretory conductance and can effectively transport K^+ in the secretory direction. Moreover, these channels exhibit a long open (conducting) state or high open probability (> 0.9), which means that they are effectively transporting (secreting) K^+ almost continuously at the usual intracellular potentials of -30 to -60 mV found in transporting thick ascending limb cells.

Apical membrane K^+ channels in thick ascending limbs are metabolically

regulated by changes in cellular MgATP concentrations or the MgATP/ADP ratio. Since increases in MgATP or the MgATP/ADP ratio leads to channel inhibition, these channels are sometimes referred to as ATP-sensitive or K_{ATP} channels. Like K_{ATP} channels in other tissues (e.g., pancreatic β-cells), the thick ascending limb K_{ATP} channels are sensitive to sulfonylureas like glibenclamide (*Glyburide*), though considerably less sensitive to glibenclamide than those present in β-cells. This has led to the suggestion that certain sulfonylureas or similar agents may function as diuretics. Furthermore, since similar low conductance K_{ATP} channels are thought to mediate K^+ secretion in principal cells of the cortical collecting duct these drugs might exert a K^+ sparing action. However, to date no K^+ channel targeted diuretics have made their way to clinical practice.

The ATP-sensitivity of these K^+ channels is thought to provide a system for functionally coupling the rate of Na^+ entry mediated by the Na/K/2Cl cotransporter with the rate of K^+ secretion by apical membrane K^+ channels. The model for this "cross-talk" is as follows (see Fig. 7). Increases in Na/K/2Cl cotransporter activity cause enhanced Na^+ entry into thick ascending limb cells and a rise in cytoplasmic Na^+. The latter stimulates basolateral Na^+/K^+/ATPase activity, thereby providing for enhanced Na^+ exit. The increased ATP utilization by the Na^+-pump would lower cytosolic MgATP concentrations or reduce the MgATP/ADP ratio, leading to a rise in apical K^+ channel activity. Since increased Na^+ entry is matched one-to-one with K^+ entry by the Na/K/2Cl cotransporter the rise in apical K^+ channel activity ensures that apical Na^+ entry matches K^+ secretion.

The low conductance K^+ channel is activated by PKA-dependent phosphorylation processes, a mechanism that probably accounts for the increase in apical K^+ channel activity that accompanies vasopressin-dependent increases in cyclic AMP production. Since Na/K/2Cl cotransporter activity is also increased by vasopressin (as well as other hormones that stimulate adenylyl cyclase), the increase in apical K^+ channel activity could help maintain adequate K^+ recycling during hormone-enhanced cotransporter activity and NaCl reabsorption. Finally, both the low and the moderate conductance K^+ channels are inhibited by reductions in cytosolic pH within the physiological range, an effect that probably contributes to alterations in K^+ secretion during acidosis.

Model of the Low Conductance K^+ Channel-ROMK

To date only the low conductance K^+ channel in the thick ascending limb has been molecularly cloned. Complementary DNA encoding this channel was first isolated from the rat outer medulla and is called ROMK. The biophysical, electrophysiological, and regulatory characteristics of the cloned channel correspond closely to that of the native low conductance, inwardly rectifying (and ATP- and pH-regulated) K^+ channels found in the apical membranes of both

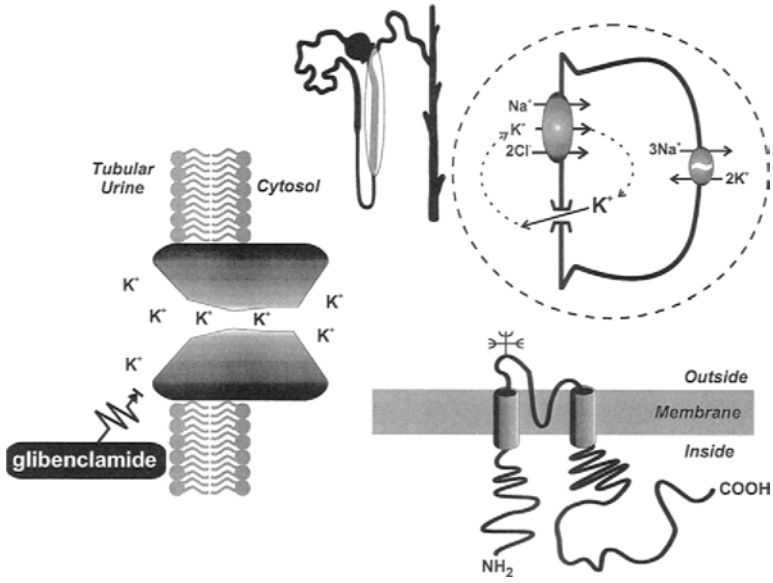

FIGURE 9. Molecular model of the low conductance, inwardly rectifying K^+ channel present in apical membranes of thick ascending limb cells. This channel is a member of the rapidly expanding family of inward rectifier K^+ channels (KIR channels) and the one present in the thick ascending limb is termed ROMK or Kirl.1. KIR channels have a unique topology with only two membrane-spanning helices making them structurally distinct from the voltage- and ligand-gated K^+ channels with six membrane helices. This channel is thought to provide a potassium secretory pathway in apical plasma membranes of the thick ascending limb and participate in apical K^+ recycling. Mutations in ROMK (Kirl.1) have been found in some patients with antenatal Bartter syndrome, providing strong evidence that this K^+ channel plays a significant role in the NaCl transport process in the thick ascending limb. See text for detailed discussion. Also see Fig. 7 for a model of ion transport in the thick ascending limb.

thick ascending limb and principal cells of the cortical collecting duct. The channel protein is rather small, about 45 kDa (397 amino acids), and exhibits an unusual topology with only two proposed membrane spans (see Fig. 9). This protein model was quite novel since earlier cloned voltage-gated and ligand-gated K^+ channels generally had six proposed membrane spans. It has been suggested that the functional ROMK channel may be composed of four identical subunits that form a central pore but this has not been verified. Several alternatively spliced isoforms of ROMK have been identified in the rat and human kidney. These isoforms either alter the initial part of the amino-terminus of the protein or involve only noncoding regions. In the rat, three ROMK proteins with distinct amino-termini have been identified that are differentially expressed along the nephron from medullary thick ascending limb to outer medullary collecting duct. Recent studies using an antibody directed against ROMK

have localized the channel to apical membranes of these nephron segments, including thick ascending limb cells and principal cells of the cortical collecting duct. Structure–function studies of ROMK should add considerably to our understanding of the distal K^+ secretory mechanisms and may provide a model for developing K^+ channel-specific diuretics.

Lessons from Mutations in the Thick Ascending Limb Na/K/2Cl Cotransporter (Slc12a1) and Apical K^+ Channel (KCNJ1 or ROMK) Found in Human Disease

Richard Lifton and co-workers at Yale University and the *International Collaborative Study Group for Bartter-Like Syndromes* have identified mutations in both the *Slc12a1* (Na/K/2Cl cotransporter) and the *KCNJ1* (ROMK apical K^+ channel) genes in a number of families with Bartter syndrome, including the antenatal hypercalcemic variant. The syndrome is associated with a hypokalemic alkalosis and in the classic and antenatal variants is accompanied by hypercalciuria. Some of these mutations were missense, resulting in alterations in single amino acids, while others resulted in deletions of portions of the transporter proteins. These mutations apparently result in loss of transporter (Na/K/2Cl or K^+ channel) function although actual functional studies have not yet been reported.

These exciting discoveries demonstrate that Bartter syndrome is genetically heterogeneous and provide clear evidence that the *Slc12a1* (BSC1) gene encodes the apical Na/K/2Cl cotransporter in thick ascending limbs. Loss of cotransporter function by gene mutation or inhibition of its activity by loop diuretics results in the same clinical presentation: salt wasting volume depletion, hypokalemic metabolic alkalosis, and hypercalciuria. Likewise, the finding that mutations in *KCNJ1* (ROMK) also leads to an identical clinical syndrome provides strong evidence that ROMK encodes the apical K^+ channel in thick ascending limb and that normal function of this channel is vital to maintenance of NaCl reabsorption by the thick ascending limb.

Thiazide or Thiazide-Like Diuretics Affecting Distal Convoluted Tubule Salt Transport

General Aspects

The Na/Cl cotransporter represents the major target site for clinically useful benzothiadiazine (or thiazide) type diuretics like chlorothiazide (*Diuril*). The thia-

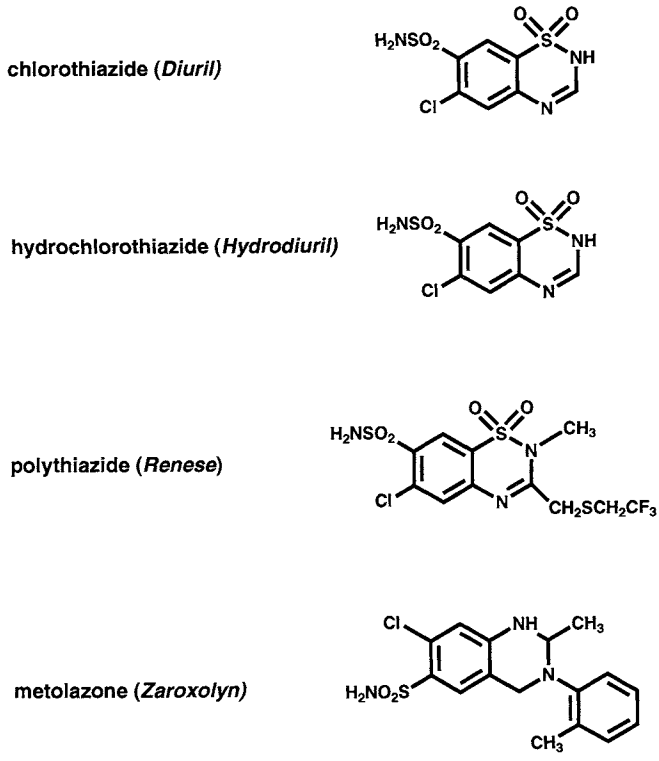

FIGURE 10. Chemical structures of selected thiazide and thiazide-like diuretics.

zide diuretics are analogs of 1,2,4-benzothiadiazine-1,1-dioxide and evolved from chemical modification of sulfonamides that were noted to produce diuresis and chloruresis. Many of these thiazide diuretics retain a sulfamyl sidegroup on the benzene ring (see Fig. 10), which imparts varying carbonic anhydrase inhibiting activity to these compounds. The order of potency for carbonic anhydrase inhibition by commonly used diuretics is chlorthalidone (67) > benzthiazide (50) > polythiazide (40) > chlorothiazide (14) > hydrochlorothiazide (1) > bendroflumethiazide (0.07). The carbonic anhydrase inhibiting capability of certain thiazides has caused confusion and resulted in incorrect conclusions in some studies. Caution should be exercised when interpreting results of experiments where reductions in NaCl transport were caused by thiazides with the highest carbonic anhydrase inhibiting potencies since the thiazide effect may be due to carbonic anhydrase inhibition rather than a direct action on the Na/Cl cotransporter. For example, some thiazides reduce proximal tubule sodium reabsorption. As detailed below, the thiazide-sensitive Na/Cl cotransporter protein is not expressed in the proximal tubule so that these

thiazide effects on proximal tubules likely relate to their carbonic anhydrase inhibiting capacity in a manner identical to that for acetazolamide (see Carbonic Anhydrase Inhibitors, above).

Model of NaCl Transport

The generally accepted mechanism of salt reabsorption by the *distal convoluted tubule* is shown schematically in Fig. 11. About 5–7% of filtered NaCl is reabsorbed by the distal convoluted tubule. The entry of each sodium ion across the apical membrane of distal convoluted tubule cells is directly and tightly coupled in an electroneutral fashion to one chloride ion by the Na/Cl cotransporter. As in the case of NaCl absorption by the thick ascending limb, the entry of these ions is a secondary active transport process because it depends on the favorable electrochemical Na^+ gradient that is maintained by the active extrusion of Na^+ from the cell by the basolateral Na^+/K^+/ATPase. The specific mechanism of Cl^- exit across the basolateral membrane is less clear but probably involves a Cl^- channel, although other mechanisms such as K/Cl cotransport have not been excluded.

The two most important modulators of the rate of sodium absorption and potassium secretion by the distal convoluted tubule and cortical collecting duct are the amount of sodium delivered and the plasma mineralocorticoid level. The magnitude of NaCl reabsorption increases *pari passu* with salt delivery. Absolute sodium reabsorption, measured during *in vivo* microperfusion experiments, was proportional to the distal load. Evidently, the sodium load delivered

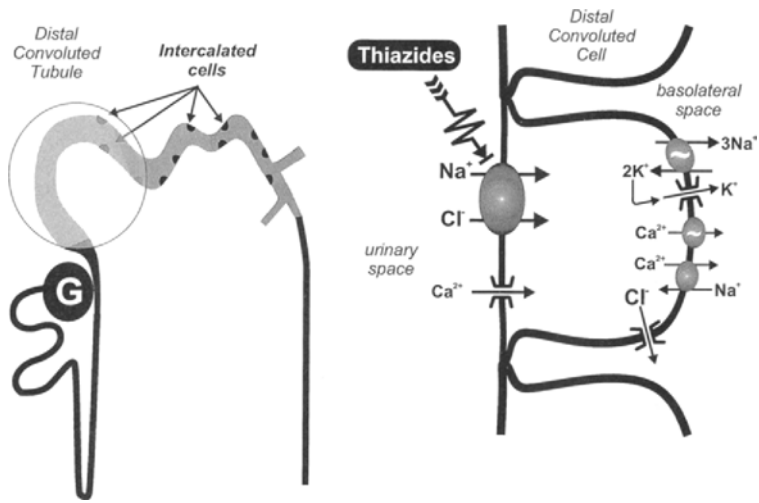

FIGURE 11. Model of NaCl absorption by the distal convoluted tubule.

to these nephron segments is elevated by diuretics acting on more proximal nephron segments. Both the transepithelial electrical conductance and the passive sodium permeability of these tubular segments are low. Hence, sodium absorption by late distal and cortical collecting tubules may lead to the development of a steep transtubular sodium concentration gradient, which, in turn, diminishes the electrochemical driving force for sodium entry across apical plasma membranes and limits further sodium reabsorption. As the load of sodium presented is raised by increasing the luminal sodium concentration or the tubular urine flow rate (or both), the point at which this limiting gradient is achieved is deflected further downstream with an attendant increase in the absolute amount of sodium that is reabsorbed. Such dynamic actions represent one form of tubular compensatory response to the diminution of NaCl reabsorption at upstream sites. This is the same type of load- or flow-dependence of NaCl reabsorption as described above for the thick ascending limb. Clearly, potassium secretion is also altered secondary to the changes of sodium absorption as described elsewhere.

A recent study showed that the density of the rat Na/Cl cotransporter, estimated by the specific binding of [^{3}H]metolazone, decreased by 70% after adrenalectomy, while selective glucocorticoid or mineralocorticoid replacements increased thiazide receptor density. Thus, both the density of the renal thiazide "receptor" (presumably equivalent to the extent of Na/Cl cotransporter protein) and the quantity of NaCl reabsorbed by the renal Na/Cl cotransporter are under adrenocortical regulation. Moreover, both the gender of the animal and the application of sex hormones appear to regulate the density of thiazide-sensitive cotransporter in rats such that thiazide "receptor" density is higher in females and is decreased by removal of the ovaries.

Other Physiological Consequences of Inhibiting the NaCl Absorption Process in the Distal Convoluted Tubule

One of the most significant effects of changing the rate of NaCl transport by the distal convoluted tubule (as with thiazide diuretics) is an alteration in Ca^{2+} reabsorption. An inverse relationship has been demonstrated between the rates of NaCl and Ca^{2+} reabsorption. Thus, thiazide diuretic-mediated reductions in NaCl reabsorption by the distal convoluted tubule result in enhanced rates of Ca^{2+} reabsorption. This is believed to account for the beneficial effect of thiazides in individuals with calcium nephrolithiasis associated with idiopathic hypercalciuria. Although the precise origin of this inverse relationship between NaCl and Ca^{2+} reabsorption remains somewhat controversial, two mechanisms have been proposed to account for it. First, studies using cultured mouse distal convoluted tubule cells have shown that Ca^{2+} entry is mediated by voltage-gated Ca^{2+} channels with the unusual characteristic of being activated by membrane hyperpolarization. In these cells, thiazide diuretics inhibit Na^+ entry

mediated by the Na/Cl cotransporter, which in turn hyperpolarizes the cell and activates apical membrane Ca^{2+} channels (see Fig. 11). An alternate proposal implicates enhanced Na^+/Ca^{2+} exchange as responsible for the dissociation of sodium and calcium absorption. According to this scheme, by inhibiting apical membrane sodium entry, thiazide diuretics reduce the intracellular Na^+ concentration. The decrease of intracellular Na^+ increases the electrochemical gradient for basolateral sodium entry, thereby augmenting calcium efflux through the Na^+/Ca^{2+} exchanger.

Increased NaCl delivery to the *cortical collecting duct* (see Fig. 14) as a consequence of thiazide-mediated inhibition of NaCl reabsorption in the distal convoluted tubule enhances K^+ secretion and results in heightened kaliuresis (see Diuretics Affecting Collecting Duct Salt Transport, below, for further details). As with the loop diuretics, the thiazide diuretic-induced kaluresis can lead to significant hypokalemia.

The Na/Cl Cotransporter Gene and Protein

Major advances have been made over the past few years in our understanding of the actions of thiazide diuretics and this is due in large part to the molecular identification of a family of cation/chloride cotransporters to which the Na/Cl transporter belongs (see Table 2). This information has enhanced our thinking about these transporter proteins. It is now clear that Na/Cl cotransport activity represents the function of a single membrane protein belonging to the newly identified family of proteins, the electroneutral cation/chloride cotransporters.

Cotransporter Gene (Slc12a3) and Tissue Expression

A single distinct Na/Cl cotransporter gene (*Slc12a3*) has been cloned from mammalian tissue (see Table 2). Transcripts encoding the Na/Cl cotransporter are expressed predominantly in the kidney. Extrarenal expression has been shown in osteoblast-like cells and preliminary observations have suggested expression in some other cells (e.g., pancreatic β cells and testis). The overall extent of extrarenal expression of the Na/Cl cotransporter is currently under intense investigation but potential roles for Na/Cl cotransport in nonrenal tissues in the systemic actions or adverse effects of thiazide diuretics remains speculative. In the kidney, Na/Cl cotransporter expression is restricted to distal convoluted tubule cells in the rat and rabbit kidney. Polyclonal antibodies raised against the rat Na/Cl cotransporter show that the protein is normally limited to the apical surface of distal convoluted tubule cells. Electron micrographs reveal cotransporter protein on the short microplicae and in subapical

vesicles. It is not known whether the subapical vesicles represent a pool of cotransporter that can cycle into the membrane and become functional in NaCl transport or are merely part of the protein degradation pathway. Interestingly, this Na/Cl cotransporter antibody was used in a recent study by Kaissling and co-workers showing that thiazide diuretic treatment of rats provoked apoptosis of distal tubule cells. In the rat, Na/Cl cotransport is the sole mechanism of Na^+ entry in distal convoluted tubule cells. It is possible that this may represent a part of remodeling of the distal convoluted tubule epithelium when NaCl entry into cells is dramatically reduced (e.g., with thiazide diuretics). However, more work is needed to examine this hypothesis and to determine if the same effect obtains in other species, such as mice, where Na^+ entry is mediated both by Na/Cl cotransport and by apical membrane amiloride-sensitive Na^+ channels (see below).

Ion transport function and diuretic sensitivities of the rat Na/Cl cotransporter, TSC1, were characterized in *Xenopus laevis* frog oocytes injected with synthetic messenger RNA made from cotransporter complementary DNA. Cotransporter RNA-injected oocytes exhibited high levels of chloride-dependent tracer sodium uptake. This sodium uptake was specifically inhibited by thiazides such as hydrochlorothiazide (*Diuril*) or metolazone (*Zaroxolyn*), whereas the loop diuretic bumetanide had no effect. Thus *Slc12a3* (TSC1) is predominantly expressed in the mammalian kidney and encodes the thiazide diuretic-sensitive Na/Cl cotransporter protein that mediates NaCl absorption in the distal convoluted tubule.

Cotransporter Stoichiometry, Topology, and Diuretic Interactions

The proposed order of ion binding to the thiazide-sensitive Na/Cl cotransporter is shown in Fig. 12A. For the rat distal convoluted tubule a stoichiometry of $1Na^+:1Cl^-$ for the cotransporter was established by *in vivo* perfusion. Sodium binds first and then Cl^- ($Na^+ \rightarrow Cl^-$). Thiazide-like diuretics such as metolazone (*Zaroxolyn*) appear to bind at or near the Cl^- site on the transporter protein in a competitive fashion.

The Na/Cl cotransporter is a relatively large protein with a core molecular weight of about 110 kDa. This thiazide-sensitive Na/Cl cotransporter protein has an overall topology (Fig. 12B) that is similar to the Na/K/2Cl cotransporters (Fig. 8B) with a large hydrophobic central region of many (possibly 12) membrane-crossing helices flanked by large hydrophilic regions that appear to face the interior of the cell. At least two sugar residues are linked to an extracellular loop between the 7th and 8th membrane-spanning segment, making this cotransporter a glycoprotein and increasing its apparent molecular weight on Western blotting to ~140–150 kDa. The specific ion and diuretic binding regions of the thiazide-sensitive Na/Cl cotransporter have not been distinguished.

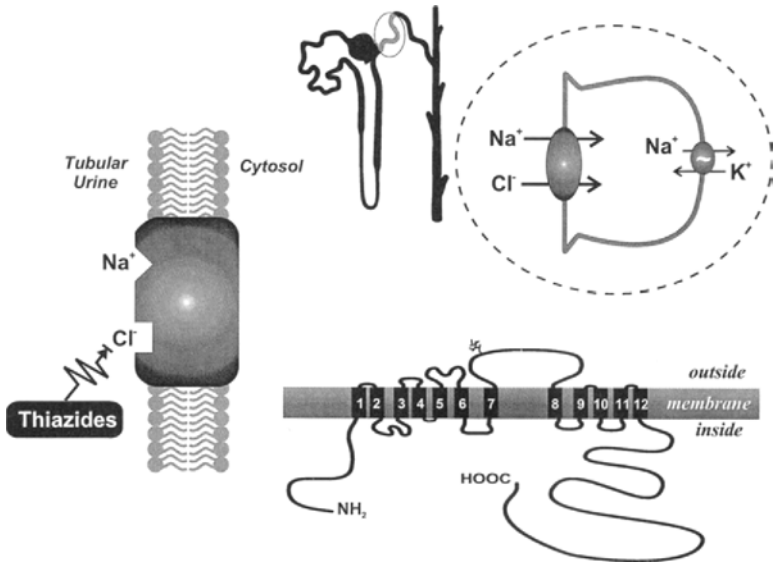

FIGURE 12. Molecular model of the Na/Cl cotransporter expressed in apical membranes of the distal convoluted tubule. This protein is the target site for thiazide and thiazide-like diuretics. See Fig. 8 and Table 2 for further descriptions of the gene and protein.

Lessons from Mutations in the Distal Convoluted Tubule Na/Cl Cotransporter (*Slc12a3*) Found in Human Disease

Lifton and coworkers at Yale University and the *International Collaborative Study Group for Bartter-Like Syndromes* as well as others have identified mutations in the *Slc12a3* (Na/Cl cotransporter) gene on human chromosome 16 in kindreds with the Gitelman variant of Bartter syndrome. It has been proposed that these mutations in the cotransporter gene result in Na/Cl cotransporter proteins that function poorly or not at all (i.e., these are loss-of-function mutations). Individuals with Gitelman's variant exhibit the same renal salt wasting with subsequent volume depletion and hypokalemic metabolic alkalosis as the other variants of Bartter's syndrome. Unlike the classic or antenatal variants, who are hypercalciuric, the Gitelman's variant individuals exhibit hypocalciuria. The latter is characteristic of the Gitelman's variant and is used to distinguish this form from the classic Bartter's syndrome. The characteristic hypocalciuria of the Gitelman's variant can be understood from the model of NaCl reabsorption in the distal convoluted tubule shown in Fig. 11. Since the magnitudes of NaCl and Ca^{2+} reabsorption are inversely related to each other in the distal convoluted tubule, significant reductions in (or complete loss of) Na/Cl cotransporter function would result in enhanced Ca^{2+} reabsorption and con-

sequent hypocalciuria. Individuals with Gitelman's variant also usually present with significant hypomagnesemia.

DIURETICS AFFECTING COLLECTING DUCT SALT TRANSPORT

General Aspects

The group of drugs acting on the collecting duct, also called "potassium-sparing diuretics," constitute an important part of the modern diuretic armamentarium. Because of their potassium-sparing effect, these weak diuretics are often used in combination with loop or thiazide diuretics to reduce or avoid potassium loss and hypokalemia that can develop with the latter diuretics. The epithelial Na^+ channel expressed in apical membranes of connecting tubule cells and principal cells of the collecting duct is the target of amiloride and triamterene (see Fig. 13).

Model of the Sodium Transport

The mechanism of Na^+ reabsorption by the principal cell of the cortical collecting duct is shown in Fig. 14. Sodium enters the cell across the apical plasma membrane down its electrochemical gradient through highly Na^+ selective pores or channels. The favorable electrochemical gradient for Na^+ entry is

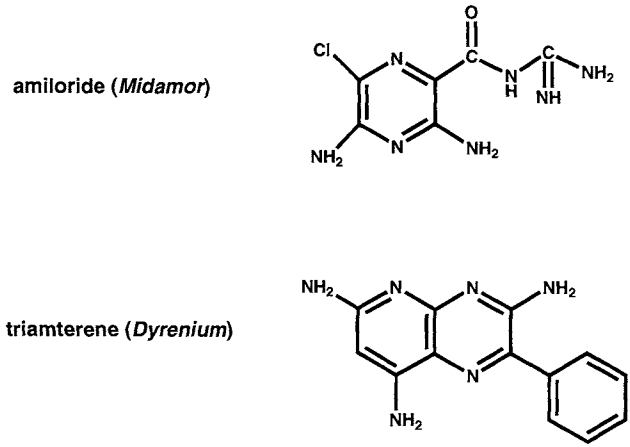

FIGURE 13. Chemical structures of diuretics inhibiting Na^+ transport in the cortical collecting duct (Site 4).

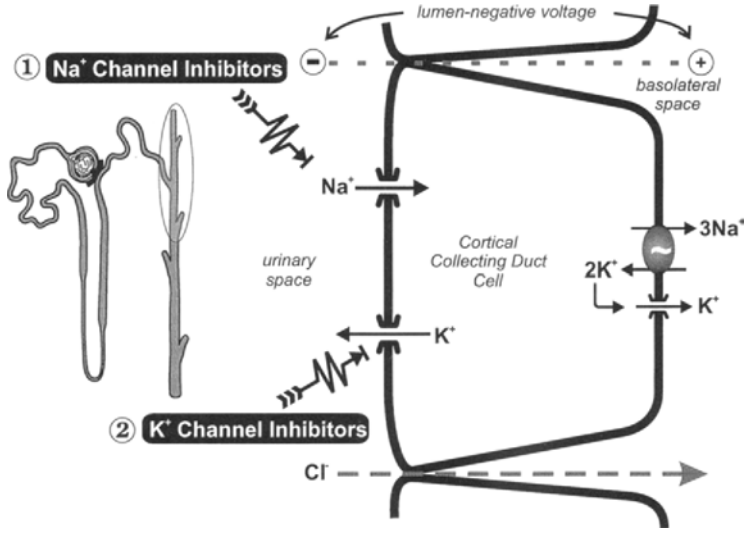

FIGURE 14. Model of Na^+ transport in principal cells of the cortical collecting duct.

achieved by active extrusion of Na^+ from the cell across the basolateral membrane via Na^+/K^+/ATPase.

Other Physiological Consequences of Inhibiting NaCl Absorption in the Collecting Duct

The major physiological effect of inhibiting Na^+ entry into principal cells is the associated reduction in potassium secretion. Inhibition of Na^+ channel activity results in depolarization of the voltage across the apical cell membrane (and also reduction in the lumen-negative transepithelial voltage) and a reduction in K^+ entry into principal cells via the basolateral Na^+/K^+ATPase. These effects result in a diminished driving force for K^+ secretion. The decrease in Na^+/K^+/ ATPase activity is a consequence of a lower intracellular Na^+ activity resulting from diminished Na^+ entry.

Modulation of active K^+ secretion can also occur when nonreabsorbable charged compounds are present in the collecting duct tubular urine. Sulfate, phosphate, and anionic antibiotics (e.g., many penicillin derivatives) enhance the secretion of K^+ by increasing lumen electrical negativity. Conversely, trimethoprim, an organic cationic antibiotic, reduces K^+ secretion. Trimethoprim is often used for infection prophylaxis of AIDS patients and a common side-effect of this therapy is hyperkalemia. Recent studies demonstrate that trimethoprim mimics amiloride and triamterene and blocks apical membrane Na^+

channels in the mammalian distal nephron and collecting duct. As a consequence, the transepithelial lumen-negative voltage is reduced and potassium secretion is inhibited. In addition, trimethoprim-mediated inhibition of basolateral Na^+/K^+/ATPase activity may also contribute to the reduced K^+ secretion in collecting ducts.

The Epithelial Na^+ Channel Genes and Proteins

Molecular cloning and human genetics have provided important insights regarding Na^+ reabsorption by collecting ducts. As with the other transporters described above, this work has uncovered the molecular identity of the Na^+ channel mediating reabsorption and has also begun to define the molecular site of channel inhibition by amiloride.

Na^+ Channel Genes and Tissue Expression

The amiloride-sensitive epithelial Na^+ channel is formed by the assembly of three homologous subunits (Table 3): alpha-ENaC (*SCNN1A*), beta-ENaC

TABLE 3 Channels

Channel	Alternative nomenclature	Species	Size (aa)	Chromosome	GenBank No.
Potassium secretory channel					
ROMK	Kir1.1	Human	391	11	U12541-5
(inwardly rectifying K^+ channel)	KCNJ1	Rat	391		L29403
Amiloride-sensitive sodium channel					
ENaC	SCNN1A	Human	669	12p13	L29007
alpha-subunit		Rat	698		X70521
(amiloride-sensitive		*X. laevis*	632		P51167[a]
NA^+ channel)					
ENaC	SCNN1B	Human	640	16p12–p13	L36593
beta-subunit		Rat	638		X77932
(amiloride-sensitive		*X. laevis*	647		P51169[a]
NA^+ channel)					
ENaC	SCNN1G	Human	649	16p12–p13	L36592
gamma-subunit		Rat	650		X77933
(amiloride-sensitive		*X. laevis*	660		P51171[a]
NA^+ channel)					

[a] SWISS-PROT Accession No.

SCNN1B), and gamma-ENaC (*SCNN1G*). This Na^+ channel is characterized by: (i) sensitivity to amiloride and to some amiloride derivatives, such as phenamil and benzamil; (ii) low single channel conductance of approximately 5 pS; (iii) high selectivity for lithium and sodium over that for potassium; and (iv) slow kinetics that result in long periods where the channel is open. The three subunit proteins share significant similarity with degenerins, a family of proteins found in the mechanosensory neurons of the nematode. *Caenorhabditis elegans*. The activity of the epithelial Na^+ channel is highly regulated by several hormones, including mineralocorticoids and vasopressin. In kidney and colon, aldosterone is the major sodium-retaining hormone and stimulates Na^+ reabsorption across the epithelium. In kidney, mRNA levels of the three subunits are not altered by aldosterone, suggesting that other mechanisms are responsible for controlling Na^+ channel activity.

The human alpha-ENaC gene was mapped to chromosome 12 (Table 3) and the encoded protein has an amino acid sequence that is 83% identical to rat. Transcripts of alpha ENaC have been detected in human kidney, lung, liver, and pancreas. Expression of alpha ENaC in *Xenopus oocytes* produces currents that are amiloride sensitive and Na^+ selective and that exhibit properties consistent with the function of epithelial Na^+ channels in native tissues.

Polyclonal antibodies have been raised against the alpha, beta, and gamma subunits of the amiloride-sensitive Na^+ channel. The three subunits have been detected by immunohistochemistry at the apical membrane of epithelial cells in distal convoluted tubules, connecting tubules, cortical collecting ducts, and outer medullary collecting ducts. In the collecting duct, the subunits are expressed in principal, but not intercalated, cells. This localization correlates with the previously described physiological expression of amiloride-sensitive electrogenic sodium transport.

Na^+ Channel Topology and Diuretic Interactions

The overall topology of the epithelial Na^+ channel protein is shown in Fig. 15. The Na^+ channel is composed of three homologous subunits termed alpha-, beta-, and gamma-ENaC. The specific subunit stoichiometry forming the native channel has not yet been unequivocally defined. All subunit proteins contain a large, highly glycosylated extracellular loop that is located between two membrane spanning α-helices. The amino- and carboxy-terminal segments are cytoplasmic and contain potential regulatory segments that may modulate channel activity.

The Na^+ conductance generated upon expression of all three subunits in *Xenopus* oocytes is sensitive to both amiloride and triamterene. The amiloride binding site appears to reside on the large extracellular loop of the alpha subunit of ENaC. Since expression of an alpha-ENaC mutant that lacks the puta-

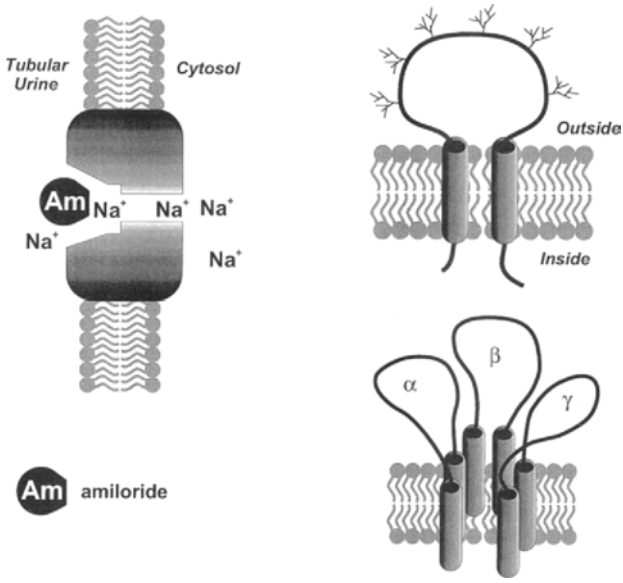

FIGURE 15. Molecular model of the amiloride-sensitive, epithelial Na^+ channel (ENaC) expressed in apical membranes of principal cells. This channel provides the major pathway for sodium entry into principal cells from tubular urine. Channel activity can be inhibited by the diuretics, amiloride and trimterene. The channel consists of a complex of three related subunit proteins (alpha-ENaC, beta-ENaC, and gamma-ENaC).

tive amiloride-binding site exhibited a greatly reduced affinity for both triamterene and amiloride, it seems likely that both weak diuretics interact with alpha-ENaC by very similar mechanisms and probably share a similar or identical binding site.

Lessons from Mutations in the Epithelial Na^+ Channel (SCNN) Found in Human Disease

Mutations in the human ENaC subunit genes result in inherited diseases characterized by either "gain-of-function" or "loss-of-function" of the epithelial Na^+ channel in distal convoluted tubules and collecting duct. Mutations causing overactivity of the Na^+ channel result in NaCl retention and hypertension (Liddle's syndrome), whereas other mutations leading to reduction or loss of channel activity result in renal salt wasting and hyperkalemic acidosis (pseudohypoaldosteronism type I). These "experiments of nature" provide convinc-

ing evidence that the epithelial Na^+ channel genes (*SNCC1A, -1B,* and *-1G*) encode the crucial amiloride-sensitive Na^+ absorptive channel found in connecting tubules and collecting ducts.

Pseudohypoaldosteronism type I is a rare autosomal recessive disease that is characterized by severe neonatal renal salt wasting, hyperkalemia, metabolic acidosis, and unresponsiveness to aldosterone. Mutations have been found in both the alpha- and beta-subunit genes of ENaC and, as expected from the inheritance, affected individuals are homozygous.

Liddle's syndrome is an uncommon cause of familial hypertension that is transmitted in an autosomal dominant pattern. The syndrome is characterized by a defect in renal distal tubular sodium handling, resulting in excessive sodium absorption and concomitant potassium wasting and hypokalemia resembling primary aldosteronism. Serum and urine aldosterone concentrations are, however, low. Rapidly following the molecular cloning of *SNCC* (*1A, 1B,* and *1G*) genes, it was shown that Liddle's syndrome is caused by mutations in the beta- and gamma-subunit genes of the human epithelial Na^+ channel.

The mutation identified in the original kindred described by Liddle introduces a premature stop codon in the ENaC channel beta-subunit that results in a loss of almost all the COOH-terminus of the encoded protein. When RNA encoding the truncated beta and gamma human ENaC subunits is expressed in *X. laevis* oocytes, Na^+ currents are increased compared to oocytes injected with normal (wild-type) ENaC RNA. This appears to be due, largely, to an increase in the number of active (functional) channels in plasma membranes of oocyes injected with the mutant ENaC. Increases in Na^+ current are also seen following expression of subunits with point mutations in a conserved motif located in the region of the subunit $COOH^-$terminus that is absent in the Liddle's mutations. Thus, by deleting or mutating a conserved motif, the number of Na^+ channels in the cell membrane is increased leading to enhanced renal Na^+ reabsorption. The latter results in a predisposition to develop hypertension. These studies of Liddle's syndrome provide direct genetic and physiological evidence that the ENaC (*SCNN*) channel subunits form the amiloride diuretic-sensitive Na^+ channel expressed in the connecting segment and collecting duct.

SUMMARY

In conclusion, the molecular identification of the cellular targets of diuretic action has provided definitive evidence regarding the mechanisms responsible for sodium absorption along the nephron. Two major advances have already emerged from this work. First, the basis for the selective effects of different diuretic agents, notably the loop and thiazide-type diuretics, becomes clear. Second, the genetic origin of the salt-wasting diseases. Bartter's and Gitelman's syndromes, has been elucidated. The former involves the Na/K/2Cl cotrans-

porter located in the thick ascending limb, where Na^+ and Ca^{2+} absorption proceed in parallel, whereas the latter is associated with mutations in the distal Na/Cl cotransporter, where Na^+ and Ca^{2+} transport are inversely related. This information explains why the salt-wasting that accompanies Bartter's disease is associated with concomitant urinary calcium losses, while in the Gitelman variant, the salt wasting is accompanied by diminished calcium excretion.

Knowledge of molecular structures of the Na/K/2Cl and Na/Cl cotransporters, and the amiloride-sensitive epithelial sodium channel will surely usher in a new age of chemical structures that provide even more selective and efficacious diuretics with fewer adverse actions.

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CHAPTER IIIB

Special Diuretics

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Unlike standard diuretics, the agents described in this chapter do not block specific transporter proteins, but tend to alter the physiological control processes which govern salt and water excretion in the normal animal. The increased specificity of action of these agents may make them useful in certain defined circumstances, but in general these agents act as weaker diuretics and are not in large-scale clinical use. Each of these agents acts on distinct portions of the nephron, which is shown schematically in Fig. 1.

AGENTS WHICH PRIMARILY INCREASE FREE WATER CLEARANCE

The kidney increases plasma osmolality by excreting a urine which is dilute with respect to the plasma (increased free water excretion) and reduces plasma osmolality by excreting a urine which is concentrated with respect to the plasma (increased free water reabsorption). As shown in Fig. 1, the nephron dilutes the urine by reabsorbing solute (predominantly NaCl) without water primarily in the thick ascending limb (TAL). In the absence of ADH, this dilute urine is mostly excreted. The reabsorption of solute in the absence of water in the thick ascending limb, coupled with the action of the countercurrent ar-

Diuretic Agents: Clinical Physiology and Pharmacology

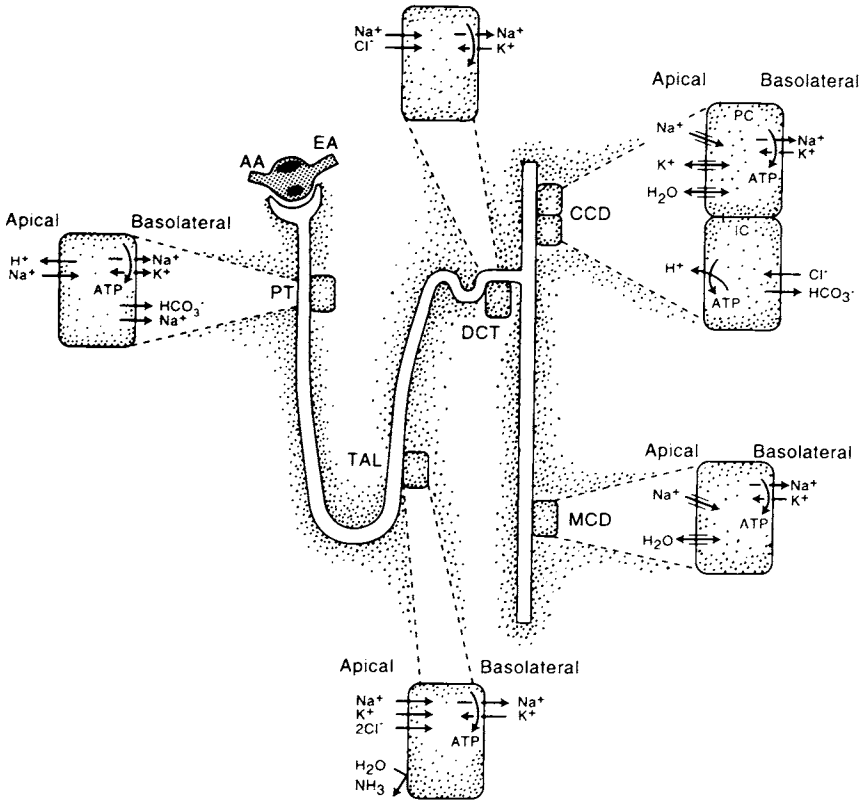

FIGURE 1. Schematic of the nephron with principal pathways of salt and water transport shown for several key segments. AA, afferent arteriole; EA, efferent arteriole; PT, proximal tubule; TAL, thick ascending limb; DCT, distal convoluted tubule; CCD, cortical collecting duct; MCD medullary collecting duct. For PT, TAL, DCT, CCD, and MCD, representative epithelial cells with transport pathways are shown, including the Na/K-ATPase in all cell types, the Na^+/H^+ exchanger in the PT, the $Na^+/K^+/2Cl^-$ cotransporter in TAL, the Na^+/Cl^- cotransporter in DCT, as well as apical Na^+, K^+, and water channels in collecting duct segments.

rangement of the vasculature and tubules in the medulla, lead to the development of an interstitial osmolality which is markedly hypertonic with respect to the plasma. In response to increases in plasma osmolality, a fall in blood pressure, and reduced effective circulating volume, ADH is released from the posterior pituitary. ADH stimulates insertion of water channels into the apical membranes of the collecting duct (see Fig. 2), permitting reabsorption of water from the lumen into the hypertonic interstitium and excretion of a concentrated urine. In some species ADH also promotes the development of a hypertonic interstitium by stimulating thick ascending limb salt reabsorption.

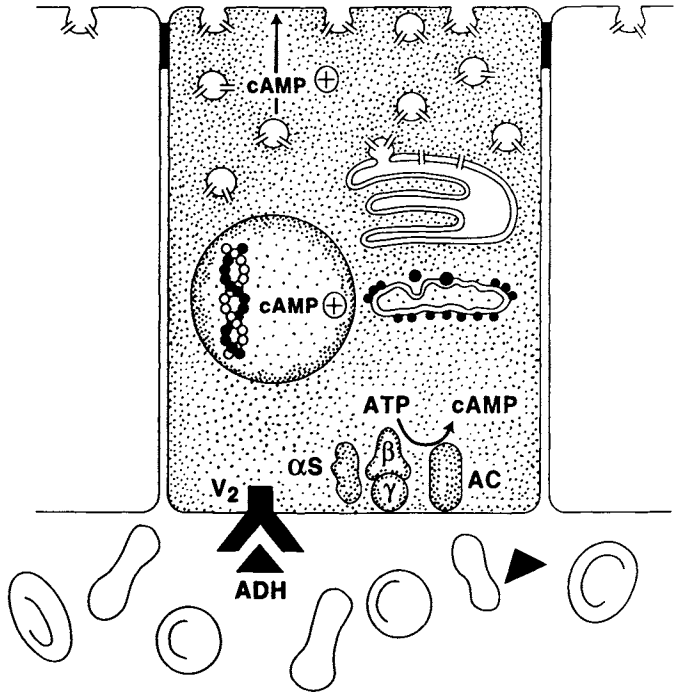

FIGURE 2. ADH regulation of collecting duct water permeability. A principal cell from the cortical or inner medullary collecting duct is shown. ADH binds to a basolateral V_2 receptor, triggering the association of the three subunits of the stimulatory G protein heterotrimer (α_s, β, and γ subunits) with adenylate cyclase (AC), leading to stimulation of cAMP generation. cAMP augments transcription of Aquaporin II mRNA chronically, increading the levels of water channel proteins. cAMP acutely augments insertion of water channel containing vesicles into the apical membrane as well.

Most diuretic agents increase urine volume by reducing net reabsorption of NaCl and obligating excretion of increased water. However, in salt-retentive conditions such as congestive heart failure, cirrhosis, and nephrotic syndrome, effective circulating volume is decreased. The neurohypophyseal and renal responses to reduced effective circulating volume include increased circulating levels of ADH, resulting in increased free water reabsorption and hyponatremia. The availability of agents which block specifically free water reabsorption in response to ADH would prevent hyponatremia in these conditions and also in patients with the syndrome of inappropriate ADH secretion [31]. As shown in Fig. 2, there are several sites at which agents could potentially block the water-reabsorptive response, including antagonists of ADH, agents which disrupt the transmission of the ADH signal via cAMP and protein kinase A, and agents which block water channels [60].

ADH Antagonists

Since the synthesis of ADH (shown in Fig. 3) by Du Vigneaud and colleagues [19], innumerable modifications of the peptide structure have been attempted, in order to develop specific antagonists to the different ADH receptor subtypes [31]. There are three receptor subtypes, all of which are membranes of the 7 membrane spanning G-protein-linked receptor family. V_{1A} receptors are present in vascular and hepatic tissues, where they mediate vasoconstriction and glycogenolysis. V_{1B} receptors, located in the anterior pituitary, mediate release of ACTH in response to ADH [60]. Both types of V_1 receptors act via the phosphoinositide pathway. V_2 receptors are located in collecting duct cells, where they stimulate insertion of water channel-containing vesicles into the normally water-tight apical membrane via stimulation of adenylate cyclase and its attendant protein kinases (protein kinase A) [60]. With the recent cloning of the V_2 receptor, it has become clear that most patients with congenital nephrogenic diabetes insipidus lack a functional V_2 receptor, emphasizing the potential therapeutic value of V_2 receptor antagonists [7]. Initial attempts to design selective V_2 antagonists focused on peptide derivatives [31]. Although some selective derivatives were developed that were successful in rats, these demonstrated agonist properties in humans and dogs [31]. In addition, peptide analogs were suitable for parenteral administration only.

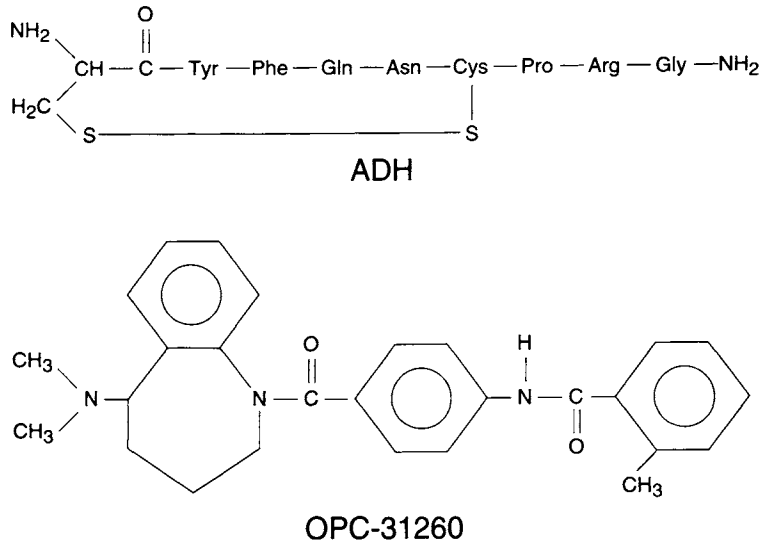

FIGURE 3. Structures of antidiuretic hormone (ADH) and the selective V_2 antagonist, OPC-31260.

Recently, selective nonpeptide ADH antagonists have been developed by extensive drug screening programs [57]. Following the successful development of V_1 receptor antagonists, further derivatization yielded a compound, OPC-31260 (see Fig. 3), which bound selectively to V_2 receptors, exhibiting 50% inhibition of [^{3}H] ADH binding at 1.2×10^{-6} *M* for V_1 receptors and at 1.4×10^{-8} *M* for V_2 receptors [57]. Unlike earlier peptide-based inhibitors, the compound exhibited no antidiuretic agonist activity when injected into rats with hereditary diabetes insipidus (Brattleboro rats) and strikingly raised urine volume and lowered urine osmolality in hydrated conscious rats [57]. In humans, oral doses of 1 mg/kg increased urine volume to a similar degree as was observed with 0.33 mg/kg furosemide, but did so primarily by increasing free water clearance [41]. Thus, the oral dose of OPC-31260 stimulated excretion of 500 ml of urine of osmolality below 70 mOsm/kg, while furosemide resulted in excretion of a similar amount of isosthenuric urine. The fact that OPC-31260 did not prevent dilution of urine when it was administered suggests that the stimulatory effect of ADH on thick ascending limb salt reabsorption is relatively minor in the human. Interestingly, OPC-31260 raised circulating ADH levels to double to triple their basal values, either by effecting a modest rise in serum osmolality or by another, possibly direct, effect on neurohypophyseal cells [41]. In addition, the compound elicited a modest increase in $U_{Na}V$, suggesting that its antagonism of ADH binding blocked ADH-stimulated Na^+ reabsorption in the collecting duct. At present, the effects of chronic administration of OPC-31260 are unknown, and it is apparently undergoing clinical trials [41].

Water Channel Blockers

By homology to the red cell water channel CHIP 28 or, by its more recent designation, Aquaporin 1, a second water channel, Aquaporin 2, was cloned and demonstrated to function as the ADH-dependent water channel of the collecting duct [21, 60]. This protein is abundant in apical membranes and subapical vesicles of collecting ducts. It is inserted into and removed from the apical membrane in response to the addition or removal of ADH, respectively [36, 60]. Moreover, some patients with congenital nephrogenic diabetes insipidus were recently shown to possess normal ADH V_2 receptors, but lacked functional Aquaporin II molecules [17]. Like Aquaporin I, this protein has cysteine residues at sites likely to be near the active site, and therefore its water channel function is inhibited by mercuric chloride and organic mercurials such as parachloromercuribenzoate (pCMBS) [21, 59]. At present, however, there are no compounds which selectively inhibit the function of this channel. Such compounds would offer several advantages. First, if they were filtered but not reabsorbed, they would tend to be concentrated in the urine to extent that free water

absorption via the channels is permitted. This raises the possibility of allowing precise adjustment of dosage so as to maintain urinary osmolality within certain limits. Moreover, concentration in the urine would likely lead to a higher therapeutic index for such inhibitors, since their levels in urine at any given dosage would be higher than those in blood.

LITHIUM

Lithium salts have been used in the treatment of manic–depressive disorders since 1949, and treatment is frequently complicated by the development of polyuria and polydipsia [49]. When patients on lithium are dehydrated, they exhibit impaired concentrating ability which is not responsive to exogenous vasopressin. Moreover, ADH levels in these patients are elevated. Therefore, lithium induces nephrogenic diabetes insipidus. Although acute administration of lithium can impair renal concentrating ability to a moderate degree, chronic administration tends to make the defect more severe. Clearance studies have shown that lithium does not alter diluting capacity, and sections of medulla from rats with lithium-induced diabetes insipidus exhibit normal hypertonicity. These results localize the defect to the collecting duct [49] because medullary tonicity, everything else being equal, is dependent primarily on salt transport by the thick ascending limb. In isolated perfused rabbit cortical collecting ducts, luminal but not basolateral lithium reduced the water-reabsorptive response to ADH, but not to cAMP analogs, suggesting that lithium impairs acutely the ability of ADH to stimulate accumulation of cAMP within the cell [15]. This impression was confirmed in studies of cAMP generation in microdissected single tubules, in which lithium inhibited ADH stimulation of cAMP synthesis [15]. Further studies suggest that lithium reduces adenylate cyclase activity by enhancing the activity of the inhibitory G protein (G_i) associated with the enzyme. Similar results have been obtained in cultured collecting duct cells as well as in tubules dissected from rats which developed diabetes insipidus on lithium, as compared with controls [15, 56].

An important feature of lithium-induced nephrogenic diabetes insipidus is its progressive nature and the delay in recovery of concentrating ability following cessation of therapy [49]. With the cloning and identification of aquaporin II, the mechanism for these more chronic effects are being clarified. Rats subjected to long-term lithium-induced diabetes insipidus exhibited striking reductions in levels of aquaporin II in their collecting duct cells [32]. These levels were diminished despite supplementation with the V_2 agonist, dDAVP [32]. These results suggest that prolonged lithium exposure downregulates the response of collecting duct adenylate cyclase to ADH, leading to chronically low levels of intracellular cAMP. Since the gene for aquaporin II has a cAMP-

responsive promoter, it is possible that long-term reductions in cAMP attenuate transcription of aquaporin II message and decrease levels of channel protein [32]. These chronic reductions may explain, in part, the delay in recovery of concentrating capacity following cessation of lithium therapy.

AGENTS WHICH PRIMARILY INCREASE SALT EXCRETION

Atrial Natriuretic Peptide and Related Peptides

The original peptide (see Fig. 4) was discovered by purification of atrial extracts which exhibited striking diuretic and natriuretic properties [6, 58]. Atrial natriuretic peptide is stored in secretory granules of the atrial myocyte as a 126-amino-acid propeptide (pro-ANP) which is cleaved during or soon after secre-

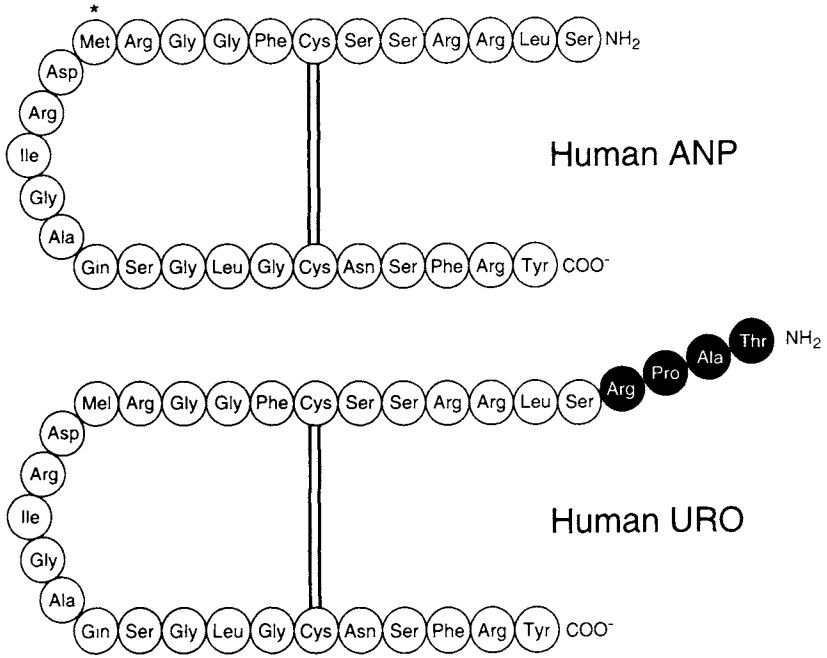

FIGURE 4. Structure of human atrial natriuretic peptide (human ANP) and urodilatin (Human URO). Darkened amino acid residues on human URO represent an amino terminal extension when compared with human ANP.

tion into several fragments including ANP_{99-126} and ANP_{31-67}, both of which have natriuretic and diuretic properties [6, 24, 58]. Urodilatin (URO) arises from the same gene product but is synthesized in the renal cortex, where it undergoes different processing from ANP, resulting in a 4 amino acid extension, and is secreted into the luminal fluid in the connecting segment [47, 58]. Whether URO is also secreted into the renal circulation is unclear.

Three ANP_{99-126} or natriuretic peptide receptor (NPR) subtypes have been identified. Two, NPR-A and NPR-B, contain cytoplasmic guanylyl cyclase domains which become active, converting GTP to cGMP, when ligand is bound to the extracellular domain. A third subtype, NPR-C, lacks the cytoplasmic guanylyl cyclase domain, and may participate mostly in clearance of bound ANP [1]. Although a lack of specific antisera has hampered localization studies, differential binding and detection of specific mRNAs have localized NPR-A to the renal cortex, including glomeruli, and medulla, while both NPR-A and NPR-B are found in peripheral vasculature and the adrenal gland. NPR-C is present in glomeruli and large renal vessels and absent in the medulla [55, 58].

ANP exhibits significant hypotensive, natriuretic, and diuretic effects (see Table 1). It lowers blood pressure by reducing cardiac output and peripheral vascular resistance [58]. ANP diminishes cardiac output by reducing preload and by blunting the hypotension-induced reflex rise in sympathetic efferent nerve activity and heart rate. ANP decreases preload by reducing intravascular volume, both by stimulating salt and water excretion and by stimulating redistribution of intravascular volume into the interstitial space. ANP either lowers peripheral vascular resistance or prevents a reflex rise in intravascular resistance (which would occur due to its hypotensive effect) by reducing renin secretion, thereby diminishing the circulating levels of the vasoconstrictor, angiotensin II. ANP can also effect relaxation of preconstricted vascular smooth muscle *in vitro*, but the importance of this effect *in vivo* has been difficult to establish. The importance of ANP in long-term blood pressure regulation was recently emphasized in studies of transgenic mice with a disruption of the pro-ANP gene and an inability to synthesize ANP (and urodilatin and ANP_{31-67}) [27]. Homozygotes for disrupted pro-ANP gene exhibited no atrial granules and were hypertensive on standard and high salt chow. Heterozygotes showed an intermediate number of atrial granules, and were hypertensive only on high salt chow [27].

ANP enhances salt and water excretion via several synergistic mechanisms involving both direct renal effects and several extrarenal effector mechanisms. ANP attenuates sympathetic activity and lowers the levels of circulating catecholeamines [58]. This effect plus a direct effect on the macula densa inhibits release of renin, lowering circulating and renal levels of angiotensin II. Diminished sympathetic nerve activity and circulating angiotensin II levels, combined

TABLE 1 Effects of ANP on Blood Pressure and Renal Salt and Water Excretion

I. Actions of ANP to reduce blood pressure

A. Reduced cardiac output
  1. Reduced preload
    a. Reduced total body volume by natriuresis/diuresis
    b. Redistribution of volume from vascular to extravascular space
    c. Reduced tone of capacitance veins, reducing venous return
      i. Reduced sympathetic nerve activity
      ii. Possible direct relaxation of venous vascular smooth muscle
  2. Reduced contractility and heart rate
    a. Reduced sympathetic nerve activity
    b. Reduced circulating catecholeamines

B. Reduced peripheral vascular resistance
  1. Direct relaxation of smooth muscle of resistance arterioles
  2. Reduced sympathetic nerve activity
  3. Reduced circulating catecholeamines
  4. Reduced renin production, leading to reduced angiotensin II

II. Actions of ANP to increase renal salt and water excretion

A. Increased glomerular filtration rate
  1. Increased glomerular capillary pressure (P_{GC})
    a. Afferent arteriolar vasodilatation
    b. Efferent arteriolar vasoconstriction
  2. Increased glomerular surface area for filtration by actions on mesangial cells

B. Inhibition of tubular reabsorption of salt and water
  1. Inhibition of proximal tubule Na^+ reabsorption
    a. Direct inhibition of tubule response to angiotensin
    b. Reduced sympathetic nerve activity
    c. Reduced circulating catecholeamines
    d. Reduced renin production, leading to reduced angiotensin II
  2. Inhibition of cortical and inner medullary collecting duct Na^+ reabsorption
    a. Direct inhibition of amiloride-sensitive cation/Na^+ channels
    b. Reduced circulating levels of aldosterone
      i. Direct inhibition of aldosterone production
      ii. Reduced renin production, leading to reduced angiotensin II
      iii. Reduced circulating catecholeamines
      iv. Reduced sympathetic nerve activity
  3. Antagonism of ADH-stimulated water reabsorption
    a. Direct inhibition of ADH-stimulated water reabsorption in collecting duct.
    b. Reduction of ADH release in response to osmotic or volume stimuli

Note. Reported effects of ANP relevant to blood pressure and salt and water excretion are listed. Actions are detailed in the text and reviewed in [6, 58]. The importance of these effects in determining the physiological response to ANP will depend on factors such as the circulating concentration of ANP and the underlying state of the subject.

with a direct inhibitory effect on the adrenal glomerulosa cells reduce aldosterone release and circulating levels. The decreases in both renal sympathetic nerve activity and in angiotensin II levels lower proximal tubular reabsorption of salt and water. Reductions in aldosterone levels diminish renal salt reabsorption, principally in the distal convoluted tubule and collecting duct. Direct and coordinated effects of ANP along the nephron act synergistically with the reductions in salt-retaining stimuli to stimulate markedly salt and water excretion. Thus ANP directly enhances glomerular filtration rate (GFR), attenuates proximal tubular sodium reabsorption in response to catecholamines and angiotensin II, and blocks collecting duct Na^+ and water reabsorption.

ANP increases GFR by increasing both the glomerular capillary pressure and the ultrafiltration coefficient [58]. Glomerular capillary pressure rises as a result of dilatation of the arcuate, interlobular, and afferent arterioles in a setting where efferent arteriolar tone is unaltered or even increased. ANP may raise the ultrafiltration coefficient by enhancing the relaxation of mesangial cells, thereby expanding the surface area available for ultrafiltration. There is some controversy as to whether the glomerular actions of ANP occur at levels of the peptide which circulate physiologically, or whether they represent a pharmacologic effect. The vasorelaxant effects of ANP are mediated by stimulation of NPR-A, resulting in increased cGMP within vascular smooth muscle and mesangial cells.

ANP reduces tubular Na^+ reabsorption in the proximal tubule and collecting duct [58]. In the proximal tubule, studies involving micropuncture in intact animals and microperfusion of isolated proximal tubule segments demonstrated that ANP did not alter basal Na^+ reabsorption, but did inhibit catecholamine- and angiotensin II-stimulated Na^+ reabsorption, an effect which was duplicated by exogenous cGMP. It is of interest that proximal tubule cells do not appear to have high levels of NPR-A relative to other tubule segments, but it appears likely that ANP binding to NPR-A mediates these responses.

In cortical and inner medullary collecting duct, ANP binding to NRP-A leads to striking increases in intracellular cGMP. cGMP, in turn, inhibits Na^+ reabsorption [25, 62, 63]. In the inner medullary collecting duct, the apical cation channel (which conducts Na^+) appears to be amiloride-sensitive and resembles that of the regina; cGMP itself can reduce the open probability of the channel. An additional portion of the response to cGMP appears to be mediated by a cGMP-dependent protein kinase [29, 30]. In the cortical collecting duct, where the Na^+ channel is made up of the highly Na^+ selective ENaC subunits (for epithelial Na^+ channels), the specific mechanism of action of cGMP remains unclear [12, 37, 39].

ANP also inhibits ADH-stimulated water reabsorption in both cortical and medullary collecting duct [18, 38]. In the rabbit cortical collecting duct, ANP appears to act by inhibiting cAMP generation in response to ADH, because forskolin, which stimulates cAMP accumulation independent of the ADH re-

ceptor, and exogenous cAMP gave equivalent increases in water flow in the absence and presence of ANP [18]. By contrast, ANP inhibited ADH and cAMP-stimulated water flow in rat cortical and medullary collecting duct, indicating that its effect of blocking water flow occurs at a site beyond the generation of cAMP [38]. In the rat, this action likely involves inhibition of trafficking of water channel containing vesicles to the apical membrane [60].

Because of its combined effect of counteracting antinatriuretic influences and inhibiting renal salt and water reabsorption, ANP is a potent natriuretic and diuretic. Efforts to apply these properties clinically have centered on infusions of ANP in edematous states. In cirrhosis with attendant ascites, basal ANP levels tend to remain normal. However, following head out water immersion or placement of a LaVeen peritoneovenous shunt, there is a rise in circulating ANP levels, an increase in urinary cGMP excretion (denoting ANP action in the kidney), and an increase in salt and water excretion [11, 20]. These results suggest that an increase in preload in cirrhosis leads to an increase in ANP levels which can augment salt and water excretion. However, infusion of ANP without measures to increase preload has led to severe hypotension which has precluded significant natriuretic responses. In congestive heart failure, ANP levels are high, likely in response to the chronic enlargement of the atria [14]. Despite the high levels of ANP, patients retain excessive salt, indicating that antinatriuretic influences such as increases in sympathetic outflow and angiotensin II and aldosterone levels override the natriuretic effect of ANP. Indeed, the high levels of ANP may dampen the salt retention, because infusion of anti-ANP antibodies into rats with congestive heart failure leads to increased salt and water retention [5]. As occurred in cirrhosis with ascites, infusion of ANP into patients with congestive heart failure led to intolerable hypotension, which prevented effective diuresis [14].

Because a major proportion of ANP degradation occurs via neutral endopeptidase, which is located in the proximal tubule brush border, several studies have examined the effects of increasing endogenous ANP levels by inhibiting ANP degradation. In normal man and rat, administration of inhibitors of neutral endopeptidase such as candoxatrilat can increase circulating ANP levels, increase urinary cGMP excretion, and stimulate natriuresis and diuresis [40, 48]. These effects are more pronounced in volume-loaded men and hypertensive rats. In humans, dogs, and rats with congestive heart failure, inhibition of neutral endopeptidase also gave an increase in salt and water excretion. The natriuretic and diuretic response was more pronounced in the setting of less severe heart failure, and symptomatic hypotension was also less severe [35]. Since inhibition of neutral endopeptidase also increases local levels of kinins, this dual action of the inhibitors may account for the salutary response. It is possible that these agents will find a role in the symptomatic treatment of congestive heart failure in the future.

Urodilatin is known to be secreted into the tubule fluid and does not appear systemically [43]. Since most actions of hormones including those of ANP are thought to be mediated via basolateral receptors, the urinary secretion of urodilatin was thought to be ineffective in mediating a natriuresis. however, microcatheterization studies have shown that luminal ANP can inhibit inner medullary collecting duct Na^+ reabsorption; similarly, ADH can also act via luminal receptors [50]. It is therefore possible that luminal urodilatin acts as a renal mediator of salt excretion. At present, the mechanisms governing urodilatin release into the urine are unclear. However, if the secretion of this peptide could be stimulated *in vivo,* the natriuretic effect might be observed. Such a response may be particularly beneficial in salt-retaining states, because urodilatin is confined to the urinary tract and therefore cannot alter systemic hemodynamics.

ANP_{31-67} is also released when pro-ANP is cleaved [54, 58]. Studies in rats and humans have demonstrated that this peptide circulates at levels close to those of ANP [54]. Infusions of this peptide to achieve levels close to those obtaining *in vivo* have led to diuresis and natruresis without a change in GFR [33]. Moreover, this peptide inhibits Na^+ transport in inner medullary collecting duct cells by a prostaglandin-mediated mechanism [24]. The role of this peptide in regulating Na^+ excretion *in vivo* remains unclear, and there have been no trials of the peptide as a potential natriuretic and diuretic agent.

Dopamine

Dopamine augments salt and water excretion by a combination of hemodynamic and tubule effects [3, 23]. Dopamine appears to be synthesized primarily in proximal tubule cells from its precursor, L-dopa, which enters the cells via a Na^+ cotransporter and is converted to dopamine by the enzyme, aromatic amino acid decarboxylase (see Fig. 5) [3]. Whether the proximal tubule is the source for dopamine acting in the medullary thick ascending limb and the cortical collecting duct is unclear; it is possible that luminal dopamine carried by the tubule fluid can regulate Na^+ transport in these segments. The mechanisms governing dopamine generation are unclear. During volume expansion, dopamine excretion is increased, and inhibition of dopamine receptors attenuates the natriuretic response to volume [3, 23]. These results suggest that dopamine release is governed in some way by volume status. Because uptake of L-dopa may be governed by the Na^+ gradient across the plasma membrane of the proximal tubule cell, it is possible that the level of intracellular Na^+ within the proximal tubule cell can regulate the rate of L-dopa uptake and therefore the rate of dopamine generation [3].

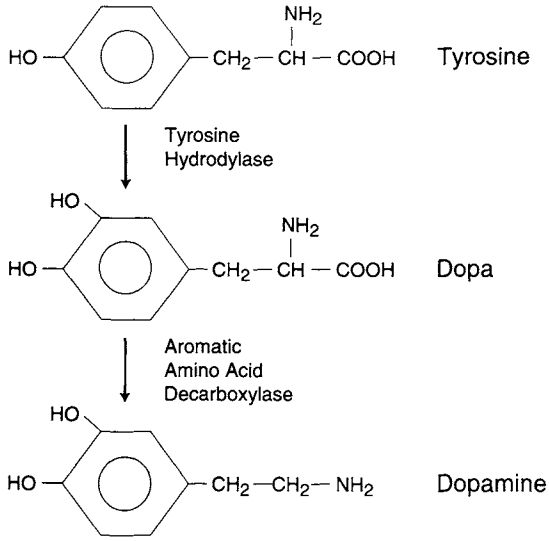

FIGURE 5. Generation of dopamine from tyrosine and Dopa. See text for details.

The molecular biology of dopamine receptors remains undefined, but pharmacologically, most renal actions appear to be mediated by DA_1 receptors, although specific agonists for DA_2 can also effect a natriuresis [3]. In several segments, including proximal tubule, medullary thick ascending limb, and cortical collecting duct, dopamine inhibits Na/K ATPase activity by stimulating the phosphorylation of the α or catalytic subunit of the pump [3, 4, 45]. In all segments, dopamine acts via DA_1 receptors to activate adenylate cyclase as well as phospholipases A_2 and C. Activation of adenylate cyclase may lead to direct phosphorylation of the α subunit, or, in the proximal tubule may alter the phosphorylation state of a cAMP-activated protein phosphatase I inhibitor, DARPP-32 (see Fig. 6) [4]. Increased activity of DARPP-32 would reduce the rate of dephosphorylation of α subunits, diminishing the activity of Na/K ATPase. In the cortical collecting duct, coupling of dopamine binding by DA_1 receptors to Na/K ATPase inhibition appears to occur via an interaction of protein kinase A with the phospholipase A_2 pathway [45]. Thus, dopamine reduces Na/K ATPase activity at several nephron sites. Although the rate-limiting step in transepithelial Na^+ transport is generally believed to be at the apical membrane Na^+ entry step, it has recently been shown that inhibition of Na/K ATPase leads to a prompt downregulation of apical Na^+ entry, indicating that downregulation of Na/K ATPase can diminish transepithelial Na^+ transport [52].

Dopamine, via DA_1 receptors, activates vascular adenylate cyclase and raises

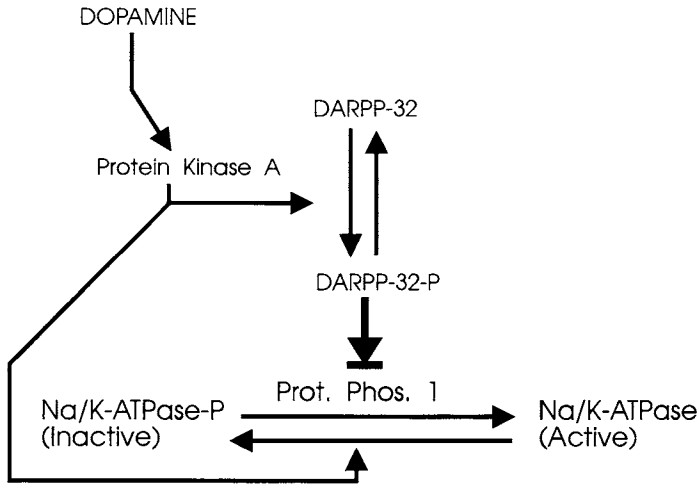

FIGURE 6. Regulation of Na/K-ATPase by Dopamine. Dopamine increases intracellular cAMP, activating protein kinase A. Activation of protein kinase A has dual actions to reduce Na/K-ATPase activity: 1. By phosphorylating DARPP-32, which, in turn inhibits protein phosphatase 1 (Prot. Phos. 1), the dephorphorylation (and activation) of Na/K-ATPase is reduced. 2. Direct phosphorylation of Na/K-ATPase increases the proportion of the enzyme which is inactive.

intracellular cAMP, leading to vasodilatation, particularly in the renal, mesenteric, and coronary vascular beds [3, 23]. The dilation of the renal vasculature augments renal plasma flow, increasing both glomerular capillary pressure and glomerular filtration rate. Importantly, at higher concentrations, dopamine also has a positive inotropic effect, which will likely enhance renal plasma flow, especially in situations when cardiac output is compromised [23]. The natriuretic effect of dopamine can occur in the absence of significant hemodynamic actions [3, 23]. At high concentrations, dopamine stimulates α_1 adrenergic vascular receptors, leading to vasoconstriction in all vascular beds. Thus, in the setting of systemic hypotension, where reflex vasoconstriction of all vascular beds is likely to result in reduced renal blood flow, dopamine is used at low and moderate concentrations to effect selective renal vasodilatation, thereby augmenting or preserving renal blood flow.

Because dopamine is degraded in the gastrointestinal tract, it is used only parenterally. In general, at low doses it increases renal perfusion and stimulates natriuresis in patients with poor cardiac output and hypotension [3, 23]. At higher doses, dopamine exerts a positive inotropic effect. Its ability to increase renal plasma flow may help prevent the onset of ischemic acute renal failure in some patients. Moreover, the inhibitory effect of dopamine on tubular Na/K

ATPase may reduce oxygen consumption by tubular epithelial cells and prevent hypoxic injury, particularly in the cells of the thick ascending limb of Henle [3].

Endogenous Ouabain

In the 1960s and 1970s, de Wardener and colleagues developed evidence for the existence of various natriuretic factors, which could stimulate salt excretion in the setting of volume expansion by inhibition of tubule Na/K ATPase [16]. While numerous extracts of plasma and urine from volume expanded animals inhibited Na/K ATPase activity and reduced transepithelial Na^+ transport in a number of renal model epithelia, the identity of these factors remained unclear [16]. Recent studies have provided strong evidence that at least one of these factors may closely resemble ouabain itself [8]. The structure of ouabain is shown in Fig. 7. Similar compounds have been found in extracts of numerous plant species, most prominent of which is digitalis, an extract of the foxglove plant (*Digitalis purpurea*). Ouabain binds to the α subunit of Na/K ATPase and inhibits pump activity. Ouabain was shown to be present in high concentrations in the adrenals of rats, cows, and humans and has been measured at levels of 0.2–0.7 n*M* in human plasma [8, 26]. At present, the factors governing release of endogenous ouabain from the adrenal cortex are unclear. Partial block-

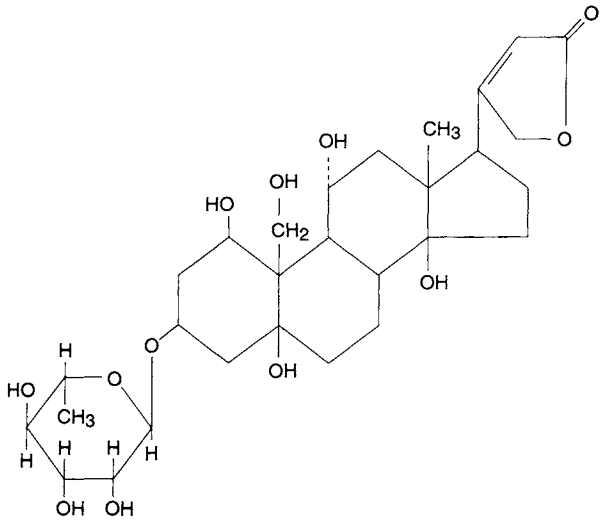

FIGURE 7. Structure of ouabain.

ade of vascular smooth muscle Na/K ATPase by circulating ouabain could increase intracellular Na^+ levels, stimulating calcium uptake by Na/Ca exchange [8, 53]. The increased levels of intracellular calcium would then increase vascular tone and vasoconstriction in response to other vasoconstrictive elements. Thus, higher levels of circulating ouabain would likely lead to hypertension. Importantly, renal Na/K ATPase is composed nearly entirely of α_1 β_1 heteromers. The α_1 isoform is thought to be least sensitive to ouabain [8]. From these considerations, endogenous ouabain would likely cause increases in blood pressure at levels far below those which would reduce renal tubular Na^+ reabsorption. Therefore, ouabain and ouabain-like agents are unlikely to serve as effective diuretic agents.

MERCURIALS

These were the first diuretic agents and were largely supplanted by the sulfonamide-based diuretics such as thiazides and loop diuretics. The structure of one of the more prominent mercurial diuretics, mersalyl, is shown in Fig. 8. Because these agents went out of use decades ago, before the advent of isolated perfused tubule techniques, we lack detailed information on their molecular mechanisms of action [10, 51]. Moreover, with different preparations, there were several variables such as the extent of secretion into the lumen in the proximal tubule and a variable degree of release of mercuric ion, which altered their mechanisms of action [10, 51]. Hg^{2+} binds to sufhydryl groups in a nonspecific manner and can inactivate numerous proteins [51]. Whole animal clearance and micropuncture studies on the mechanism of action of mersalyl demonstrated that it increased delivery of salt and water to the distal convoluted tubule without altering GFR or proximal tubular reabsorption [9, 10, 51]. Application of mersalyl to the lumina of thick ascending limb segments using the then-new isolated perfused tubule technique demonstrated that the drug directly inhibited net Cl reabsorption in a manner distinct from that observed with Hg^{2+} [9]. Because of the toxicity of these compounds and their relatively

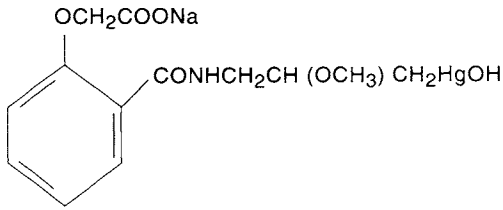

FIGURE 8. Structure of mersalyl, an organic mercurial compound.

low diuretic potency when compared with that of loop diuretics, mercurials are not used as diuretic agents. Interestingly, mercurials can also inhibit water flux through aquaporins, by binding to discrete cysteine residues which are likely located near the pore [61]. Because of their lack of specificity and toxicity, however, these agents do not appear promising as starting points for drug discovery projects designed to obtain inhibitors of aquaporin function.

XANTHINES

Xanthine derivatives such as theophylline (see Fig. 9) have multiple actions on cells, including blockade of uptake of calcium into sarcoplasmic reticulum, inhibition of degradation of cyclic AMP and cyclic GMP by phosphodiesterase, and blockade of adenosine receptors [42]. The effects on calcium transport and cyclic nucleotide degradation occur at methylxanthine concentrations in the range of 0.5–1 mM, far above the therapeutic range of 20–50 μM. By contrast, blockade of adenosine receptors occurs well within the therapeutic range of these compounds, so that their major actions result from antagonism of adenosine action [42].

Adenosine is generated locally within the kidney by the action of 5′-nucleotidases, from AMP [28]. The levels of adenosine are determined by the levels of AMP, which rises and falls depending on the energy state of the cell. Based on binding studies and more recent cloning results, two classes of

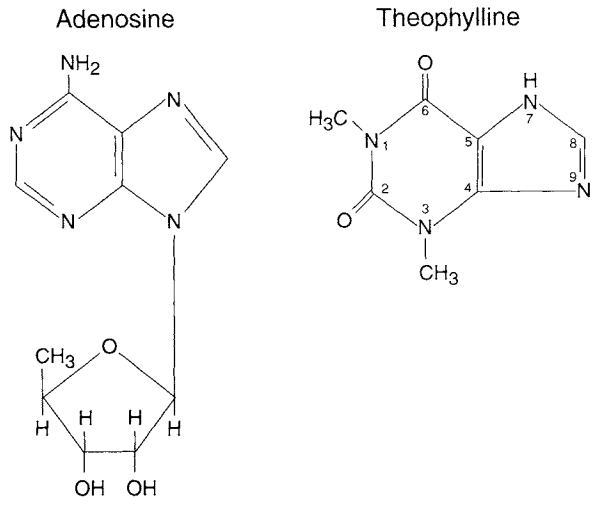

FIGURE 9. Structures of adenosine and theophylline.

adenosine receptors, A_1 and A_2 receptors, have been identified [34]. These are located throughout the nephron, and it appears that many cell types have both classes of receptors. A_1 receptors appear to link with inhibitory G proteins to reduce adenylate cyclase activity, while A_2 receptors stimulate the stimulatory G protein to active adenylate cyclase [34]. In epithelial cells, these different receptor subtypes may be differentially deployed on apical or basolateral membranes, raising the possibility that adenosine may mediate opposite effects when placed on the apical or basolateral sides of the cell [34]. Since most membranes are likely impermeable to adenosine, this localization of the different receptor subclasses permits an additional level of control of adenosine actions [28, 34].

Adenosine causes vasoconstriction of afferent glomerular arterioles via A_1 receptors, and more delayed vasodilation of efferent arterioles via A_2 receptors. These changes in vessel diameter lead to a fall in glomerular capillary pressure and a decrease in GFR [13, 44]. It appears that adenosine mediates tubuloglomerular feedback when it is released into the glomerulus by the macula densa in response to increased salt and water loads [46]. When NaCl delivery accelerates, transepithelial transport rises, leading to more rapid ATP consumption by the Na/K ATPase [34, 46]. Increased ATP consumption is thought to augment adenosine release, which will reduce GFR and lower the transport burden on the tubule. Adenosine can also stimulate (A_2 receptors) or inhibit (A_1 receptors) renin release by the juxtaglomerular apparatus [34]. Adenosine can also augment Na^+ reabsorption in thick ascending limb and salt and water reabsorption in collecting duct, likely by increasing cAMP [28, 34].

Theophylline and other methylxanthines can stimulate natriuresis and diuresis by blocking the effects of adenosine to reduce GFR and augment salt and water reabsorption. However, because the actions of adenosine may depend heavily on where adenosine is being generated and on the levels of other renal effector hormones and autacoids such as angiotensin II, the response to theophylline may also vary [28, 34]. In general, however, methylxanthines stimulate salt and water excretion by increasing GFR and inhibiting salt reabsorption along the thick ascending limb and collecting duct.

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CHAPTER IIIC

Renal Hemodynamic Effects of Diuretics

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INTRODUCTION

While diuresis specifically refers to increased urinary volume output, it is generally recognized that clinically important diuretics increase sodium excretion. This is because the main determinant of extracellular fluid volume is total extracellular sodium content. Thus, to be effective in correcting extracellular fluid volume, plasma volume and arterial pressure, diuretics must elicit natriuresis. Natriuresis can be achieved by either decreasing net tubular sodium reabsorption or increasing the filtered sodium load or some combination of these effects. Because plasma sodium concentration is regulated within a rather narrow range, increases in filtered sodium load are generally due to increases in glomerular filtration rate (GFR) which occur as a consequence of renal hemodynamic adjustments that increase glomerular pressure, net filtration pressure, and/or renal plasma flow.

Many vasodilator agents elicit natriuresis via direct effects to increase renal blood flow (RBF), GFR, and filtered sodium load. In other cases, however, natriuretic agents may decrease renal hemodynamic function by direct or indirect mechanisms and thus limit the efficacy of the treatment. Changes in renal hemodynamics also alter net sodium reabsorption through postglomerular mechanisms that remain incompletely understood. Increases in blood flow

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through the peritubular capillaries in the cortex or through the medullary blood vessels are associated with diminished net sodium reabsorption and increased sodium excretion. Thus, changes in renal hemodynamics may greatly influence the final effectiveness of natriuretic therapy. In this chapter, emphasis is placed on the changes in renal hemodynamics that are caused by or are the consequences of treatment with natriuretic agents.

GLOMERULAR AND POSTGLOMERULAR VASCULAR DYNAMICS

Because diuretics can affect renal hemodynamics by altering function at any of several levels of control, it is worthwhile to consider briefly the integrative and cellular control mechanisms. A variety of integrated physiological mechanisms maintain a highly regulated renal microcirculatory environment that establishes optimal conditions for glomerular filtration and peritubular capillary reabsorption. Extrinsic, neural and paracrine mechanisms ultimately exert their control by influencing the vascular smooth muscle cells that regulate vascular resistance of the various segments of the renal microcirculation [1, 17, 23, 25].

Glomerular Dynamics

Fluid exchange across the glomerular capillaries is a passive process driven by hemodynamic and oncotic forces which are controlled primarily by changes in vascular smooth muscle tone. As shown in the following equation, GFR is dependent on the net effective filtration pressure (EFP) across the glomerular capillary wall and the filtration coefficient (K_f). The filtration coefficient represents the product of the hydraulic conductivity of the filtering capillaries and the total surface area available for filtration:

$$GFR = K_f\,(EFP) = K_f\,(P_g - P_B - \Pi_g)$$

The main determinants of the effective filtration pressure are the glomerular pressure (P_g), which is the principal driving force, the pressure in Bowman's space (P_B), and the colloid osmotic pressure in the glomerular capillaries (π_g). Glomerular pressure is counteracted by P_B and π_g, thus leading to a relatively small effective filtration pressure compared to the glomerular pressure. As shown in Fig. 1, colloid osmotic pressure (π_g) within the glomerular capillaries increases progressively along the length of the capillaries as a consequence of the filtration of a protein free ultrafiltrate into Bowman's space. This causes a progressive decrease in effective filtration pressure along the length of the capillaries [1, 17, 23].

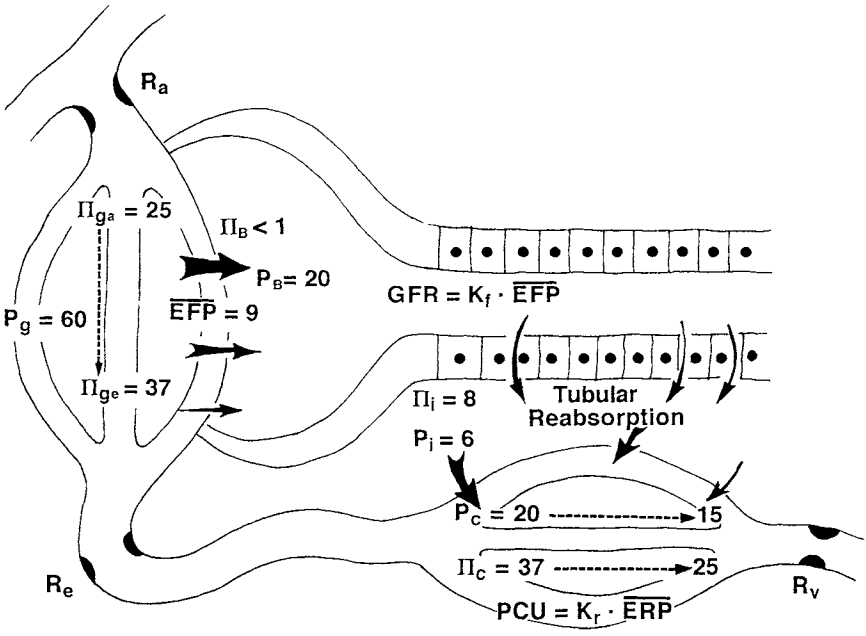


FIGURE 1. Description of forces governing filtration at glomerular capillaries and reabsorption into the peritubular capillaries and ways that diuretics can alter filtered load of sodium. Increases in filtered load: renal vasodilation, increases in glomerular pressure (P_g), decreases in colloid osmotic pressure (Π_g), and increases in filtration coefficient (K_f). Decreases in filtered load: renal vasoconstriction, increases in proximal tubule pressure (P_B), decreases in glomerular pressure (P_g), and decreases in filtration coefficient (K_f).

Indirect measurements from humans and data extrapolated from experimental animals suggest that glomerular pressure is 55 to 60 mm Hg and proximal tubular pressure is 18 to 22 mm Hg in the normal human kidney. Plasma colloid osmotic pressure in humans averages 25 mm Hg. The increase in colloid osmotic pressure along the glomerular capillaries depends primarily on the filtration fraction; for filtration fractions usually observed in humans (0.18 to 0.20), efferent arteriolar colloid osmotic pressure reaches values of 35 to 37 mm Hg. Accordingly, EFP varies from a high of 15 mm Hg at the afferent end of the glomerular capillaries to only a few mm Hg at the terminal end of the capillary network. When renal vascular tone is elevated substantially and the filtration fraction is high, the protein concentration may increase so much that the resulting colloid osmotic pressure at the terminal segments of the glomerular capillaries reaches a value sufficient to neutralize the transglomerular hydrostatic pressure gradient. If "filtration equilibrium" is achieved, no further filtration of fluid occurs in the more terminal segments of the glomerular capillaries.

Under these conditions, part of the glomerular filtering surface area is not used but may be recruited during increases in plasma flow [1, 17].

Vasopressin and other hormonal systems regulate plasma osmolality and sodium concentration within relatively narrow limits; therefore, increases in filtered sodium load occur primarily as a consequence of increases in GFR usually caused by increases in glomerular pressure which increase effective filtration pressure. In addition, the rate of rise in colloid osmotic pressure along the glomerular capillaries can be reduced by increases in blood flow which lead to reductions in filtration fraction. Although plasma protein concentration is reduced in some pathological processes such as the nephrotic syndrome, it is generally well regulated. Nevertheless, procedures that lead to reductions in plasma protein concentration such as volume expansion with protein free solutions can increase EFP markedly due to reductions in plasma colloid osmotic pressure.

Pressure in Bowman's space is determined by the filtered load, proximal reabsorption rate and tubular fluid flow out of the proximal tubular segment. Thus, inhibition of tubular reabsorption rate, in particular at the level of the proximal tubule or loop of Henle, causes substantial increases in proximal tubule pressure which reduces effective filtration pressure and GFR. Accordingly, diuretics that increase proximal tubule pressure may lower GFR even when there are no changes in renal vascular resistance. Indeed, changes in GFR are not a reliable reflection of changes in renal plasma flow when diuretics are administered because of the variable changes in pressure in Bowman's space.

Increases in K_f can also increase GFR; however, the effects of increases in K_f tend to be self-limiting because of the eventual achievement of filtration equilibrium. K_f is thought to be regulated, in part, by the vasoactive tone of the mesangial cells, and many agents have been shown to alter mesangial cell contractile activity. In particular, angiotensin II, endothelin, nitric oxide, and several arachidonic acid metabolites, such as thromboxane, exert powerful actions on mesangial cells and have been shown to reduce K_f. The exact means by which changes in mesangial cell contractility influence K_f has not been clearly delineated. Their effects on K_f not withstanding, most agents that increase GFR do so by either increasing glomerular pressure or increasing blood flow or both. These changes occur most effectively by vasodilation of the preglomerular vasculature. If there is also vasodilation of the efferent arterioles, renal blood flow will increase more than GFR, leading to reductions in the filtration fraction. It is important to emphasize that decreases in filtration fraction, such as are generally seen during treatment with angiotensin-converting enzyme (ACE) inhibitors and other vasodilator agents are caused by combined vasodilation of *both* preglomerular and postglomerular arterioles. Indeed, exclusive dilation of the efferent arterioles is rare and leads to profound decreases in glomerular pressure and near cessation of filtration [1].

Peritubular Capillary Dynamics

Peritubular capillary reabsorption rate (PCRR) may be analyzed in a similar manner, but the colloid osmotic pressures both within and outside the capillaries must be considered due to the presence of plasma proteins in renal interstitial fluid. The determinants of PCRR are related according to the equation

$$PCRR = K_R (\Pi_C - \Pi_i - P_C + P_i),$$

where P_C is the peritubular capillary pressure, P_i is the interstitial fluid hydrostatic pressure, π_C is plasma colloid osmotic pressure within the peritubular capillaries, and Π_i is the average colloid osmotic pressure of the surrounding interstitial fluid. K_R is the reabsorption coefficient of the peritubular capillaries [1].

As shown in Fig. 1, the plasma that emerges from the efferent arterioles has a colloid osmotic pressure of 35 to 37 mm Hg. Because of the efferent arteriolar resistance, intravascular hydrostatic pressure decreases to about 20 mm Hg. The resulting reversal of hydrostatic and oncotic forces allows intravascular colloid osmotic pressure to predominate in the peritubular capillaries. Interstitial fluid pressure averages 6 to 10 mm Hg and colloid osmotic pressure is 4 to 8 mm Hg. Thus, the effective reabsorptive force is 12 to 15 mm Hg at the initial part of the capillary bed. As fluid is reabsorbed into the capillaries, the plasma proteins are diluted and plasma colloid osmotic pressure progressively decreases toward systemic values. While there is also a small decline in capillary hydrostatic pressure, the predominant force responsible for return of fluid into the vasculature is the elevated colloid osmotic pressure within the peritubular capillaries. The effectiveness and magnitude of the colloid osmotic pressure gradient depends on the integrity of the peritubular capillaries to minimize protein leakage into the interstitium and on the ability of the renal lymphatics to remove proteins that leak into the renal interstitium [1, 23].

Intrarenal Distribution of Blood Flow

Increases in postglomerular blood flow lead to reduced peritubular reabsorptive capability which is associated with reduced tubular reabsorption and increased sodium excretion. Because the glomerular and postglomerular vascular systems are arranged in series, it is often quite difficult to determine the relative contributions of changes in glomerular dynamics and changes in peritubular capillary dynamics to the overall diuretic responses to a drug. Furthermore, there is a parallel postglomerular circulation that provides blood flow to the medullary vasculature, and increases in medullary blood flow are also associated with reduced net reabsorption by the loops of Henle and collecting ducts.

While the medullary blood flow component is rather low, comprising only about 10–15% of the total blood flow, its regulation is important in optimizing function of the loops of Henle and collecting duct systems. This relatively low medullary blood flow is maintained by a complex combination of paracrine influences including angiotensin II, arachidonic acid metabolites, and endothelial derived factors. Some studies suggest that medullary vessels have a greater sensitivity than cortical vessels to angiotensin II, nitric oxide, and other agents. Increases in medullary blood flow enhance loss of accumulated solutes in the interstitium and reduce the medullary concentration gradient that is critical for concentrating capability. Increases in medullary blood flow and the associated reduction in medullary osmolality are also associated with increases in sodium excretion. This natriuresis may be the consequence of diminished water abstraction from the descending loop of Henle as a result of reduced medullary tonicity caused by the washout, resulting in increased tubule fluid flow with diminished sodium concentration of fluid reaching the active transport sites in the ascending limb of the loop of Henle. Therefore, specific increases in medullary blood flow constitute a parallel hemodynamic mechanism by which drugs can cause natriuresis, and the natriuretic responses to angiotensin converting enzyme inhibitors, agents that increase nitric oxide formation, vasodilatory prostanoids, and loop diuretics are thought to be due, at least partially, to selective increases in medullary blood flow [1, 9, 25].

A long-standing, but still unproven, hypothesis is that the relative distribution of blood flow within the cortex among the superficial, mid-, and deep nephrovascular units is also of importance in the regulation of sodium excretion. Formerly, it was thought that alterations in the intrarenal blood flow distribution pattern serve as an important determinant of the magnitude of the natriuretic response to diuretics. Specifically, redistributing renal blood flow to the outer cortical nephrons was thought to enhance natriuresis and, conversely, redistributing blood flow to the inner cortical nephrons, which were thought to have greater sodium reabsorptive capability, was postulated to reduce sodium excretion. Indeed, the effects of diuretics on intrarenal blood flow distribution patterns were studied extensively in the 1960s and 1970s. Unfortunately, definitive evaluation of this concept was compromised by the substantial uncertainty regarding the validity of the methods used to determine intrarenal blood flow distribution and the inconsistencies between RBF and GFR distribution patterns [1, 30].

Detailed investigations revealed that alterations in intrarenal blood flow distribution could not be consistently correlated with the coincident changes in sodium excretion while the alterations in intrarenal blood flow distribution in response to specific manipulations were highly dependent on the method used to assess these changes. It was observed that most agents that cause vasodilation elicited redistribution of blood flow away from the cortical nephrons while

agents that cause overall vasoconstriction increased the relative blood flow to the outer nephrons. Studies in dogs showed that acetazolamide, which reduced overall RBF, increased relative blood flow distribution to the outer cortex while furosemide, which increased total RBF, reduced relative RBF distribution to the outer cortex. Agents that did not influence total RBF did not alter cortical blood flow distribution [30, 31]. These hemodynamic changes may be due primarily to the architectonics of the preglomerular arteriolar vasculature in that the length of the blood flow pathway to the outer cortical nephrons is substantially greater than to the inner cortical nephrons. During vasodilated states, there may be greater pressure drops along the length of the preglomerular arteriolar network leading to reduced perfusion of the nephrons in the most terminal locations. Aside from this physical explanation, it remains unclear if there are selective mechanisms that differentially regulate the vascular smooth muscle tone of the various nephron populations within the cortex.

Autoregulatory Mechanisms

Consideration of the forces operating at the glomerular and peritubular capillaries reveals that even relatively small changes in the pressures and flows can cause substantial alterations in filtered and reabsorbed volumes. To minimize the effects of external disturbances such as changes in arterial perfusion pressure, the renal vasculature has powerful mechanisms that maintain a stable intrarenal hemodynamic environment and a controlled filtered load. Through active adjustments of smooth muscle tone of the afferent arterioles, the autoregulatory mechanism helps maintain an optimum filtered load and also provides a reserve capability that can be utilized during pathological processes that compromise renal hemodynamic function [1, 23]. As shown in Fig. 2, both RBF and GFR demonstrate highly efficient autoregulation in response to changes in perfusion pressure. In addition, the intrarenal pressures in the glomerular and peritubular capillaries and in the proximal tubules exhibit autoregulatory behavior. These characteristics of the autoregulatory phenomenon indicate that the major site for autoregulatory resistance adjustments is preglomerular. Direct observations of afferent and efferent arteriolar diameters during changes in perfusion pressure have confirmed this conclusion [25, 36].

Two mechanisms interact to provide highly efficient renal autoregulation: the macula densa feedback mechanism and the myogenic mechanism. The macula densa mechanism, also known as the tubuloglomerular feedback (TGF) mechanism is depicted in Fig. 3. In response to perturbations that increase distal tubular fluid flow past the macula densa, signals are sent to afferent arterioles to elicit vasoconstriction, whereas decreases in flow will cause afferent vasodilation [1, 4, 5, 25, 38, 39]. Micropuncture experiments have shown that

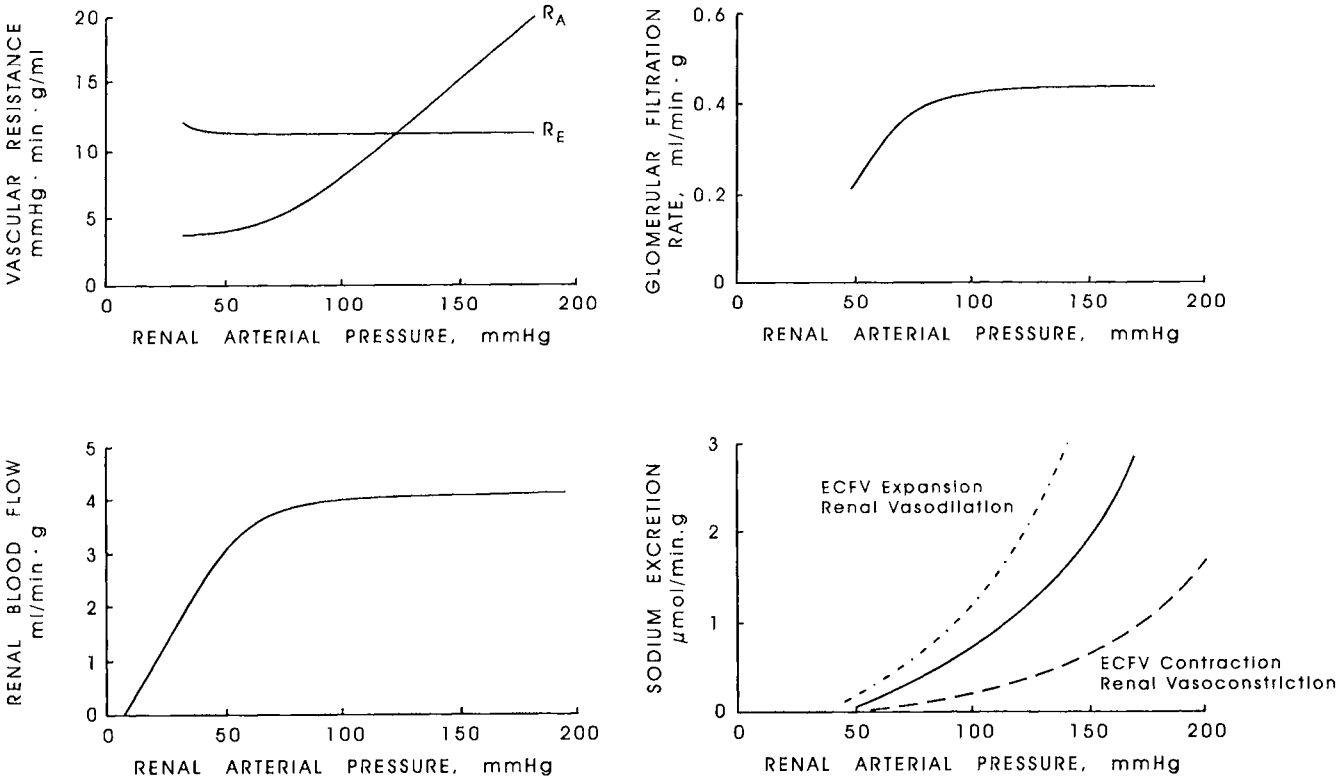


FIGURE 2. Renal autoregulatory responses to changes in RAP and associated changes in sodium excretion and segmental vascular resistances. The relationship between arterial pressure and sodium excretion is called the pressure natriuresis curve and can be adjusted by the intrarenal hemodynamic and hormonal status. States associated with ECFV expansion increase the slope of the curve, while conditions of dehydration and reduced ECFV will

increases in distal volume delivery in a single nephron elicit reductions in single nephron GFR (SNGFR) (Fig. 3), glomerular capillary hydrostatic pressure, and glomerular plasma flow. Furthermore, if there is residual tone in the afferent arterioles, interruption of fluid delivery to the distal nephron increases SNGFR above values obtained under conditions of maintained distal flow. This manipulation opens the feedback loop and attenuates autoregulatory efficiency of SNGFR and glomerular pressure, indicating that an intact TGF mechanism is required for efficient autoregulation. Autoregulatory responses seen at the level of the whole kidney represent one manifestation of this homeostatic mechanism, which maintains a balance between filtered load and the reabsorptive capabilities of each nephron.

The myogenic mechanism is based on the premise that preglomerular arterioles can sense changes in vessel wall tension and respond with appropriate adjustments in tone. An increase in wall tension, occurring in response to an elevation in arterial pressure, is thought to stimulate a vascular sensor element and initiate a sequence of events resulting in vascular smooth muscle contraction. Interlobular and arcuate arteries and afferent arterioles, but not efferent arterioles, exhibit myogenic responses to changes in wall tension. The residual autoregulatory capacity that exists during blockade of the tubuloglomerular feedback mechanism indicates that the myogenic mechanism contributes to autoregulatory responses of the renal vasculature [1, 25].

Autoregulatory behavior has been demonstrated in all regions of the kidney. Both cortical and juxtamedullary nephrons have a highly sensitive TGF mechanism, and deep nephrons autoregulate as efficiently as superficial nephrons. Since the medullary circulation is primarily a postglomerular circuit, its response should be similar to that of inner cortical nephrons. Although studies in rats indicate that medullary blood flow is less well autoregulated then cortical blood flow [9], studies in dogs have documented highly efficient autoregulation of the medullary circulation [25]. Under most circumstances the autoregulatory mechanism serves a critical function to stabilize the microcirculatory environment throughout the kidney.

Pressure Natriuresis

It is important to emphasize that while the autoregulatory mechanism maintains stable RBF and GFR during changes in renal arterial pressure, there is still a positive relationship between renal arterial pressure and sodium excretion. As illustrated in Fig. 2, this phenomenon of pressure natriuresis is characterized by progressively greater increases in urine flow and sodium excretion as renal arterial pressure is increased. Because GFR and filtered sodium load are very efficiently autoregulated over the same arterial pressure range, the changes

in sodium excretion are specifically due to progressive reductions in fractional sodium reabsorption [26]. Thus, arterial pressure, per se, is a natriuretic stimulus and a large number of studies have linked this pressure natriuresis phenomenon to the control of arterial pressure and extracellular fluid volume [9, 13, 41]. In essence, when one or more critical humoral mechanisms responsible for altering sodium excretion in response to increases in sodium intake are compromised or deranged, then retention of salt and water can lead to chronic plasma volume expansion and increases in arterial pressure. In response to the increases in arterial pressure, the kidney increases sodium excretion until a balance between sodium intake and excretion is reached [13]. In this sense, arterial pressure serves as the ultimate mechanism that can reestablish sodium balance even when renal function is severely compromised or when sodium retaining mechanisms such as the renin–angiotensin system are inappropriately stimulated. The actual slope of the pressure–natriuresis relationship can be influenced by a variety of factors including rapidly adjustable hormone systems such as angiotensin II (ANG II), arachidonic acid metabolites, and natriuretic peptides and physical mechanisms such as renal interstitial fluid pressure, peritubular capillary colloid osmotic pressure, and extracellular fluid volume [9, 26]. Furthermore, the efficacy of a diuretic is greatly influenced by the prevailing status of the pressure natriuresis relationship as well as the arterial pressure. The higher the arterial pressure or the greater the slope of the pressure natriuresis relationship, the greater will be the response to a natriuretic hormone or drug [6, 26, 29]. Thus, arterial pressure should always be considered in evaluating diuretic responsiveness, and it should be appreciated that hypotensive patients may have an attenuated response to a diuretic simply because of the lower renal perfusion pressure.

In spite of extensive experimentation in this area, the actual mechanism and tubule segment responsible for altering sodium reabsorption rate in response to changes in arterial pressure have not been firmly established. Some investigators have suggested that the changes in tubule reabsorption rate are mediated by subtle changes in renal interstitial fluid pressure, peritubular physical forces, or changes in medullary blood flow that occur even in the presence of whole kidney RBF and GFR autoregulation [9]. Other studies have implicated a local hormonal mechanism that responds to alterations in arterial pressure and elicits a change in tubule reabsorption rate. Interestingly, the tubular segment responsive to arterial pressure mediated signals also remains uncertain with some data supporting a major role for the proximal tubule and other data indicating that the changes in arterial pressure occur primarily in distal nephron and collecting duct segments [18]. Recent intriguing studies have supported the hypothesis that endothelial derived nitric oxide may be a principal mediator of pressure natriuresis. Increases in arteriolar shear stress caused by increases in pressure are thought to increase intrarenal production of nitric oxide which has

been shown to have direct effects on tubule sodium reabsorptive mechanisms as well as renal vasodilatory actions [18, 19, 26].

Tubuloglomerular Feedback Mechanism

In addition to its role in mediating renal autoregulation, the TGF mechanism contributes significantly to the regulation of GFR and ultimately to the long-term control of sodium balance and extracellular fluid volume [4, 5, 38, 39]. By operating in concert with glomerulotubular balance, the TGF mechanism stabilizes delivery of volume and solute to the distal nephron. As depicted in Fig. 3, flow-related changes in the tubular fluid composition at the macula densa are sensed and signals are transmitted to the afferent arterioles to regulate the filtered load. The specific steps involved in the transduction of changes in tubular fluid and solute load at the macula densa to alterations in smooth muscle activity remain under intensive investigation. Because of the powerful NaCl reabsorptive capability of the ascending loop of Henle coupled with an impermeability to water, early distal tubular fluid is hypotonic (~100 mOsm/kg H_2O). Furthermore, its composition is closely coupled to tubular fluid flow along the ascending loop of Henle such that increases in flow reduce net NaCl reabsorption per unit volume of flow leading to increases in tubular fluid osmolality and NaCl concentration at the macula densa [4].

The specific intraluminal constituent and the intracellular transduction mechanisms responsible for mediation of feedback signals remain uncertain with some data indicating that a specific NaCl entry step is required, while other results indicating that the macula densa cells respond to changes in total solute concentration of the tubular fluid. Regardless of the precise luminal activation step, it appears that the integrity of the $Na^+/2Cl^-/K^+$ cotransporter is essential for the manifestation of normal TGF signals. There is general agreement that furosemide and other loop diuretics prevent the transmission of TGF signals from the macula densa cells to the afferent arterioles [4–6, 12, 42]. These effects may be due, in part, to changes in macula densa cell membrane potential. When added directly, furosemide, piretamide, and torasemide caused a hyperpolarization of the membrane potential in macula densa cells evaluated with the whole cell patch clamp method. These results are consistent with the conclusion that these loop diuretics directly block the $Na^+/2Cl^-/K^+$ transporter on the luminal surface of macula densa cells [32]. Hydrochlorothiazide, which is known to not interfere with the TGF mechanism, did not alter macula densa membrane potential. At the cellular level, it has been postulated that increases in tubular fluid osmolality elicit increases in cytosolic $[Ca^{2+}]$ in macula densa cells, which result in release of a vasoconstrictive factor from these cells. Suggested mediators of the TGF mechanism include purinergic

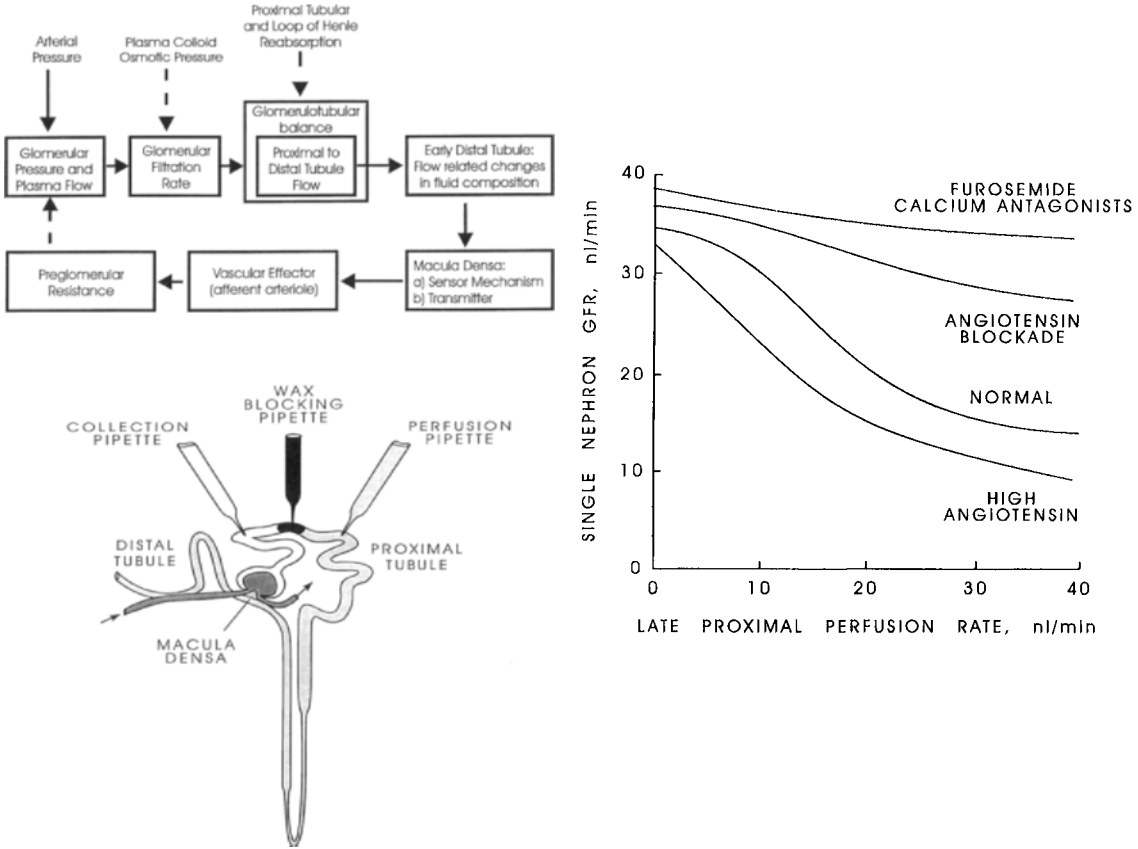


FIGURE 3. Components of the tubuloglomerular feedback (TGF) system. Macula densa delivery is controlled by alterations in

agents (e.g., adenosine or ATP) and one or more of the arachidonic acid metabolites. Although the actual factor mediating TGF responses remains to be characterized, it has been demonstrated that TGF mediated preglomerular vasoconstriction is blocked by calcium channel blockers, suggesting the participation of voltage gated Ca^{2+} channels [1, 4, 25].

The sensitivity of the TGF mechanism can be modulated by a variety of agents and circumstances, some of which are associated with changes in extracellular fluid volume [4]. TGF sensitivity is diminished during volume expansion, thus allowing a greater delivery of fluid and electrolytes to the distal nephron for any given level of GFR. By allowing GFR to be maintained or even augmented at elevated distal nephron volume delivery rates, reductions in TGF sensitivity allow correction of the volume expansion. In contrast, contraction of extracellular fluid volume is associated with an enhanced sensitivity of the TGF mechanism, which together with an augmented proximal reabsorption helps to conserve fluid and electrolytes. One major regulator of TGF sensitivity is ANG II. In states of low ANG II activity (i.e., extracellular volume expansion, high salt intake) the TGF mechanism is less responsive, whereas feedback sensitivity is enhanced during conditions of high ANG II activity [4, 22] such as occurs during dehydration, sodium depletion, hypotension, or hypovolemia. Several other hormones that are responsive to the status of extracellular fluid volume, such as atrial natriuretic peptide, may also participate in modulating TGF sensitivity. As will be discussed in a later section, diuretics, such as furosemide, that interfere with the transmission of macula densa feedback signals and agents that alter the solute and/or NaCl delivery to the macula densa exert influences on renal hemodynamics via their actions on the TGF mechanism [4, 5, 12, 27, 31, 32, 39, 40, 42].

CELLULAR MECHANISMS REGULATING RENAL VASCULAR RESISTANCE

Calcium Activation Mechanisms

Renal blood flow and intrarenal capillary dynamics are regulated by a variety of mechanisms that control vascular smooth muscle and mesangial cell contractile activity. As with other vascular smooth muscle cells, contraction of renal vascular cells is elicited primarily by increases in intracellular Ca^{2+} activity. Although extracellular fluid $[Ca^{2+}]$ is in the millimolar range, cytosolic $[Ca^{2+}]$ is maintained at considerably lower levels, (about 10^{-7} M) through active extrusion of Ca^{2+} from the cell and sequestration of Ca^{2+} from the cytoplasm into intracellular storage compartments.

Various hormones and drugs activate plasma membrane receptors to elicit an increase in cytosolic calcium. Increases in cytosolic calcium occur through a combination of enhanced calcium entry from the extracellular environment and mobilization of calcium from internal stores; however, the relative contributions of these two pathways can vary. Increases in calcium entry occur through a variety of pathways including receptor-operated channels, second messenger-operated channels, stretch activated channels, and voltage-dependent channels that are activated upon membrane depolarization. Depolarization results from influx of sodium and calcium following activation of receptor-operated cation channels, activation of chloride channels, or inactivation of potassium channels. Decreases in net calcium entry occur following dissociation of ligands from their receptors or as a consequence of membrane hyperpolarization, such as occurs when membrane potassium channels are activated. Several different potassium channels have been identified; those most prominent are calcium-activated and ATP-inhibitable potassium channels which mediate relaxation by hyperpolarizing the cell membrane and reducing calcium entry through voltage-gated calcium channels [25].

Release of Ca^{2+} from the intracellular storage pool occurs as a consequence of increases in inositol triphosphate (IP_3), a compound derived from plasma membrane lipids. The elevation of cytosolic [Ca^{2+}] resulting from these processes activates calmodulin, which activates myosin light chain kinase, thereby promoting actin–myosin interactions and contraction. As can be appreciated from this brief description, pharmacologic agents that interfere with Ca^{2+} entry into renal vascular smooth muscle cells will cause reductions in cytosolic Ca^{2+} either during basal states or in response to activating stimuli and consequently will elicit renal vasodilation. Furthermore, transport inhibitors that hyperpolarize the cell membrane may also decrease Ca^{2+} influx through voltage-dependent Ca^{2+} channels.

Agents that accelerate Ca^{2+} extrusion may also induce a vasodilatory response. Several important Ca^{2+} extrusion mechanisms help to maintain the normally low cytosolic Ca^{2+} levels. An important mechanism that is affected by diuretics is the Na^+/Ca^{2+} exchanger. This exchanger uses the Na^+ gradient to extrude Ca^{2+} against its concentration gradient. When the Na gradient is increased, there is increased Ca^{2+} extrusion which could potentially reduce steady-state intracellular Ca^{2+} levels and contribute to vasodilation. Because amiloride blocks sodium entry pathways, including sodium channels and the sodium–hydrogen exchanger, the hypotensive and vasodilatory actions elicited by amiloride and amiloride analogs may be due to a reduced intracellular sodium concentration and thus an enhanced sodium gradient [14].

Vascular smooth muscle cells in different segments of the renal vasculature vary in their dependence on Ca^{2+} entry versus Ca^{2+} release mechanisms. Cal-

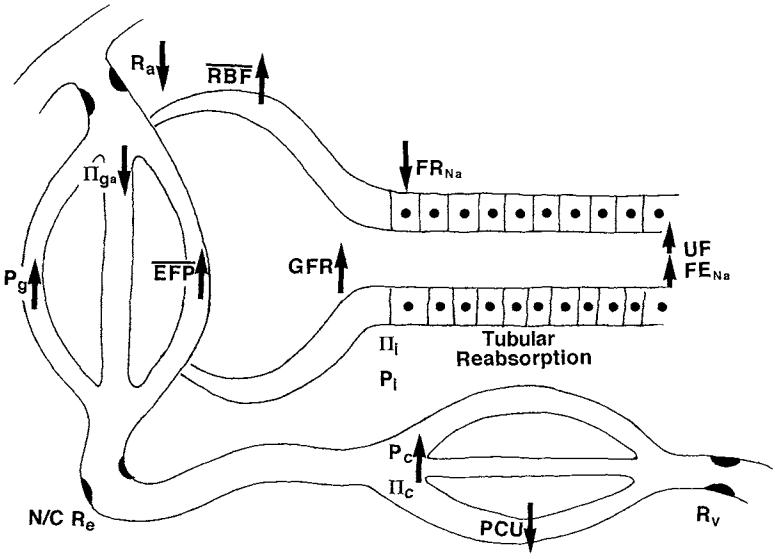


FIGURE 4. Effects of Ca^{2+} channel blockers on intrarenal hemodynamics and tubular sodium reabsorption.

cium channel blockers primarily reduce Ca^{2+} influx rather than interfere with Ca^{2+} release from intracellular storage pools. Recent studies indicate that there is a major difference in the mechanisms leading to calcium activation in the afferent and efferent arterioles. As illustrated in Fig. 4, preglomerular arterioles have a strong dependence on voltage-gated calcium channels, whereas efferent arterioles appear to not have this mechanism. Blockade of calcium influx through L-type, dihydropyridine-sensitive calcium channels primarily vasodilates preglomerular arterioles and selectively blocks agonist-induced constriction of afferent arterioles, without affecting efferent arteriolar contraction [7]. Calcium channel blockers such as nifedipine, diltiazem, and verapamil cause vasodilation and impair autoregulatory responses to changes in renal perfusion pressure and also attenuate or block tubuloglomerular feedback responses to increases in distal perfusion rate [7, 21, 24, 25, 36]. This effect is specific to calcium channel blockade because autoregulatory capability is not disrupted by agonists that act through other mechanisms, such as increasing cellular cAMP or cGMP. A primary action on the preglomerular vasculature can also explain the increases in GFR and glomerular capillary pressure as shown in Fig. 4. Thus, much of the natriuresis caused by calcium channel blockers can be explained by their hemodynamic actions to increase RBF, glomerular pressure, and GFR through effects primarily on preglomerular vascular smooth muscle

cells. However, calcium channel blockers also reduce proximal tubular reabsorption rate which would amplify the natriuretic effects of the hemodynamic actions.

Stimulation of cAMP and cGMP

Other vasodilatory influences on smooth muscle cells are associated primarily with formation of the cyclic nucleotides: adenosine 3′,5′-cyclic monophosphate (cAMP) and/or guanosine 3′,5′-cyclic monophosphate (cGMP). These compounds enhance Ca^{2+} sequestration into storage pools, extrusion of Ca^{2+} from the cell, and activation of protein kinase A to promote dephosphorylation of myosin light chain kinase. The calcium–calmodulin complex activates myosin light chain kinase, leading to phosphorylation of myosin light chains which interact with actin and ATP to elicit tension development. Relaxation occurs as a consequence of removal or sequestration of calcium from the cytosol and/or myosin dephosphorylation, which can result from alterations in the activity of several constituents of the cascade. Because of the multiple steps involved, many intracellular mechanisms can influence the magnitude of the contractile response to a specific stimulus. For example, both cAMP- and cGMP-dependent protein kinases will phosphorylate myosin light chain kinase and decrease the calcium sensitivity of myosin light chain phosphorylation. Drugs and hormones that increase cAMP and cGMP levels cause renal vasodilation and natriuresis as a consequence of both hemodynamic and tubular effects [1, 25].

INTERACTIONS OF ENDOTHELIUM-DERIVED VASOACTIVE AGENTS AND OTHER RENAL HORMONES WITH RENAL HEMODYNAMICS

In addition to exerting direct effects on tubular transport processes, diuretics may also activate cellular mechanisms leading to production and release of various vasoactive agents. Some of the major systems that can elicit hemodynamic effects are described briefly.

Nitric Oxide

The endothelium can respond to physical stimuli such as shear stress and to various hormones and drugs to release vasoactive factors including metabolites of arachidonic acid, vasoactive peptides, and nitric oxide. One agent currently under intense investigation is endothelium-derived relaxing factor which has

been identified as nitric oxide or a closely related substance. Nitric oxide (NO) is formed intracellularly by NO synthase which cleaves NO from L-arginine. In endothelial cells, NO is formed constitutively and diffuses out of the cell into adjoining cells. Through stimulation of soluble guanylate cyclase and cGMP levels in smooth muscle cells, NO and related nitrosamines exert powerful vasodilator actions. Intrarenal NO is important in maintaining the normally low renal vascular resistance and is also natriuretic. Agents that increase NO release such as acetylcholine, bradykinin, and various NO donors exert marked natriuresis in association with the renal vasodilation. Although much of the natriuresis is due to the enhanced renal hemodynamics, recent studies indicate that NO also exerts direct effects on the tubules to inhibit sodium reabsorption. In response to increases in renal perfusion pressure, intrarenal NO formation rate increases and may be responsible for the associated increases in sodium excretion. Nonmetabolizable arginine analogs that block the formation of NO cause substantial increases in renal vascular resistance, reduce renal blood flow by 20–40% and decrease sodium excretion. Both preglomerular and postglomerular arterioles are responsive to NO. Thus, NO blockade does not decrease GFR very much or decreases GFR proportionately less than it decreases RBF because both afferent and efferent arteriolar resistances are increased [19, 25, 26].

Endothelin

Another recently identified endothelium-derived vasoactive factor is endothelin, a 21-amino-acid peptide, which can exert marked and long-lasting renal vasoconstriction. There are three forms of endothelin (ET_1, ET_2, and ET_3), but humans primarily form ET_1. Stimulants for ET production include bradykinin, ATP, platelet activating factor, thrombin, and shear stress. Agents that increase endothelial cytosolic calcium and activate protein kinase C release endothelin. The two known receptor types, ET_A and ET_B, are G-protein coupled and lead to IP_3 formation, protein kinase C activation, and calcium mobilization in addition to calcium entry. ET_A receptors are predominately found on vascular smooth muscle cells. ET_B receptors are localized on endothelial and tubular cells.

Normal intrarenal ET levels are thought to be low and have little, if any, influence on basal renal hemodynamics. However, high levels associated with pathophysiologic conditions may contribute to renal vasoconstriction and sodium retention. Infusions of endothelin reduce both renal blood flow and GFR. Thus, diuretics that stimulate endothelin release may influence hemodynamics via this mechanism. Effects of endothelin on single nephron hemodynamics are

characterized by constriction of both preglomerular and efferent arterioles, with a decrease in K_f. Glomerular capillary pressure is either increased slightly or unchanged [25].

Renin–Angiotensin System

Renin is an aspartyl proteinase that cleaves the decapeptide angiotensin I (ANG I), from angiotensinogen, an α_2-globulin formed primarily by the liver but also in the kidney and other tissues. The major source of renin is the juxtaglomerular cells of afferent arterioles. ANG I generation is usually regulated by renin activity because of ample substrate availability. The decapeptide is subsequently cleaved to the octapeptide, ANG II, by angiotensin-converting enzyme (ACE). ACE is abundant in the lungs but is also found bound to endothelial cells in many other organs including the kidney. In addition to endothelial localization, ACE has also been found in the proximal tubules bound to the brush border [1, 22, 25].

ANG II is formed both intrarenally and extrarenally. The kidney converts about 20% of systemically delivered ANG I. ANG II may also be formed within the epithelioid cells of the afferent arteriole and in the proximal tubule cells, suggesting that formation of the peptide at different intrarenal sites may have specific roles. Recent studies have shown that intrarenal ANG II levels in certain compartments within the kidney, including the proximal tubules and the interstitium, are much higher than plasma levels.

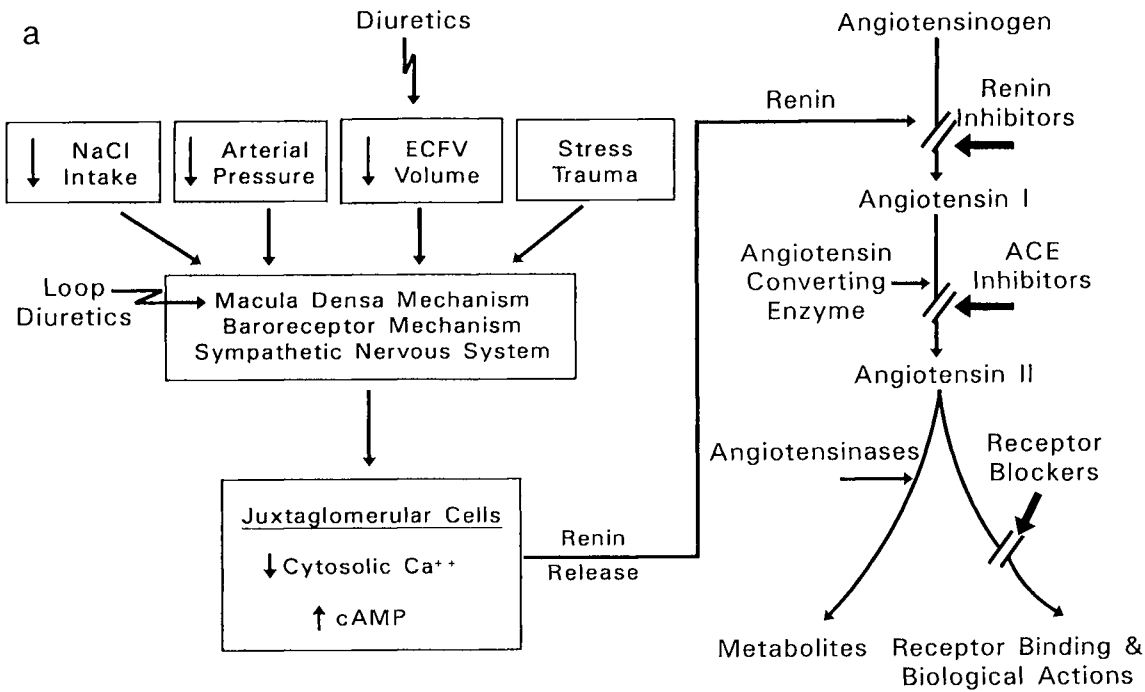
As depicted in Fig. 5, increased activity of the renin–angiotensin system is associated with circumstances that compromise body fluid volume homeostasis. Renin release is stimulated by decreases in sodium intake, reduced extracellular fluid volume, loss of blood volume, increases in sympathetic renal nerve activity, and decreases in renal arterial pressure. These conditions influence renin release by at least three distinct mechanisms: a macula densa signal, a baroreceptor mechanism, and a neurally mediated mechanism. The macula densa mechanism for renin release is distinct from the tubuloglomerular feedback mechanism controlling afferent arteriolar resistance previously described. In response to reductions in NaCl delivery to the macula densa cells, signals from the macula densa to the cells of the juxtaglomerular apparatus (JGA) in the afferent arterioles stimulate renin release. While the mechanism mediating this response remains uncertain, some studies suggest that adenosine released by macula densa cells during high NaCl delivery inhibits renin release by the JGA cells and that this inhibitory effect is diminished during reduced NaCl delivery to the macula densa [5, 22]. In this regard, furosemide and other loop diuretics that block the $2Na^+:2Cl^-:K^+$ cotransporter mimic the condition of

reduced NaCl delivery and accordingly, stimulate renin release. Renin release from the JGA cells is inhibited by ANG II, vasopressin, atrial natriuretic peptide, and potassium and is stimulated by PGE_2 and endothelin. These agents alter intracellular $[Ca^{2+}]$or cyclic AMP activity in the JGA cells. Decreases in cytosolic $[Ca^{2+}]$ and increases in cyclic AMP increase renin release. As shown in Fig. 5, diuretics can increase renin release via a direct effect on the macula densa mechanism or as a consequence of volume depletion [20].

The multiple actions of ANG II act in concert to minimize renal fluid and sodium losses and to maintain arterial blood pressure. In addition to its renal vascular effects, ANG II stimulates aldosterone release, directly enhances proximal and distal tubular reabsorption rate, stimulates thirst, and increases sympathetic nerve activity. The renal vasoconstrictive effects of ANG II result in decreases in RBF and, to a lesser extent, in GFR; thus, there is usually an increase in filtration fraction. Although it is sometimes stated that ANG II primarily constricts the efferent arterioles, the peptide has been shown to constrict preglomerular as well as postglomerular arteriolar segments. The preglomerular effects of ANG II are due to direct vasoconstrictive actions as well as to effects caused by increased sensitivity of the TGF mechanism (Fig. 3). As previously described, ANG II can also reduce K_F. In addition, medullary hemodynamics may be responsive to ANG II at concentrations lower than those required to elicit cortical vasoconstriction. The high sensitivity of the renal medulla may be related to the high ANG II receptor density found in the outer medulla [1, 5, 17, 22, 25, 41].

The renal vascular actions of angiotensin II are activated by at least two mechanisms. Afferent arteriolar responses are highly dependent on calcium entry, whereas efferent arteriolar responses are not dependent on calcium influx through voltage-gated channels. At the cellular level, ANG II has been shown to increase cytosolic $[Ca^{2+}]$ by enhancing Ca^{2+} entry as well as by mobilization of Ca^{2+} release from intracellular storage sites. ANG II-induced depolarization of preglomerular vascular smooth muscle cells, resulting in part from activation of chloride channels, leads to activation of voltage-gated Ca^{2+} channels and subsequent vasoconstriction. Accordingly, the preglomerular vasoconstrictor response to ANG II is blocked by calcium channel blockers. In contrast, efferent arterioles respond to ANG II even in the presence of calcium channel blockers [7, 25].

The overall influence of intrarenal ANG II on renal function is amplified by the powerful synergistic interactions that exist between the renal vascular and tubular actions of ANG II. The effects of ANG II to enhance proximal tubular reabsorption rate decrease solute and fluid delivery to the macula densa segment. While this decrease would elicit a TGF-mediated vasodilation, thus counteracting ANG II-mediated increases in proximal reabsorption rate, the


a
Diuretics
NaCl Intake
Arterial Pressure
ECFV Volume
Stress Trauma
Loop Diuretics
Macula Densa Mechanism
Baroreceptor Mechanism
Sympathetic Nervous System
Juxtaglomerular Cells
↓Cytosolic Ca++
↑cAMP
Renin Release
Renin
Angiotensinogen
Renin Inhibitors
Angiotensin I
Angiotensin Converting Enzyme
ACE Inhibitors
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Angiotensinases
Receptor Blockers
Metabolites
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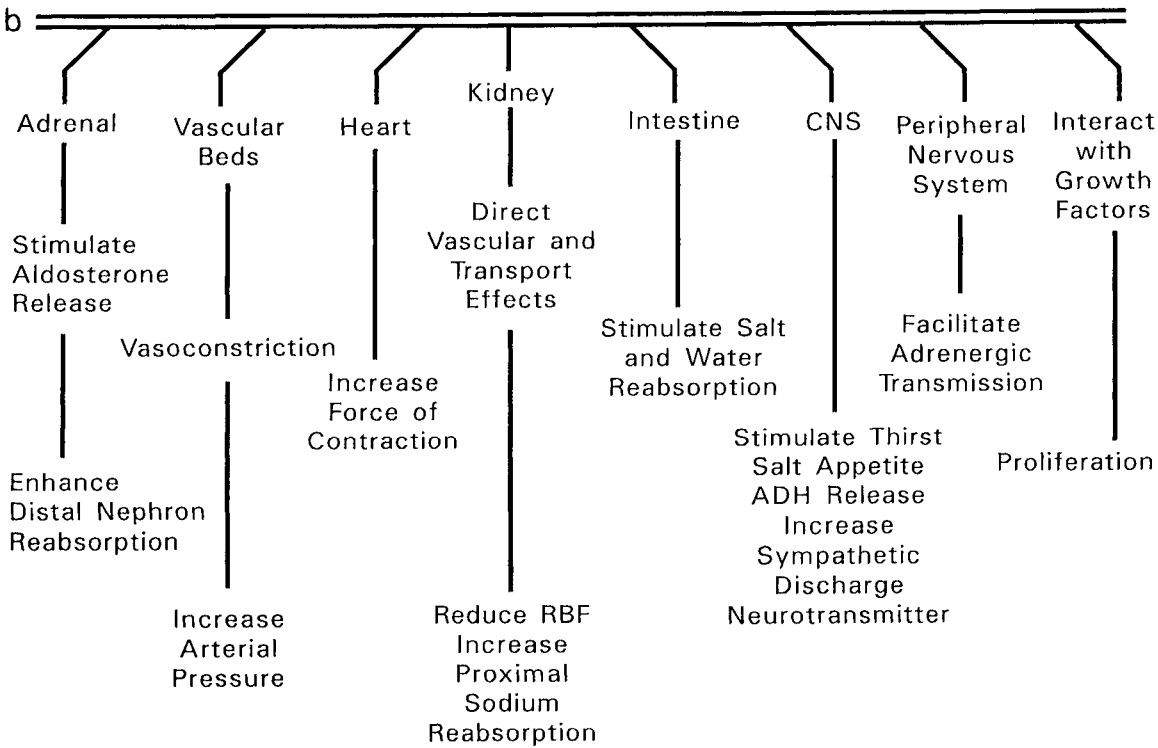

FIGURE 5. (a) Regulation of renin release and formation of angiotensin II. (b) Actions of angiotensin II and active metabolites.

concomitant modulatory influence of ANG II to enhance TGF responsiveness allows SNGFR to be maintained at a lower distal nephron volume delivery. This synergistic interaction between the renal vascular and proximal tubular effects of ANG II provides a powerful sodium conserving mechanism whereby increases in intrarenal ANG II levels can cause sustained decreases in distal nephron volume delivery and sodium excretion [22].

While it is well recognized that appropriate function of the renin–angiotensin system serves a powerful homeostatic function to conserve body fluids and electrolytes, inappropriate or pathological increases in the activity of the renin–angiotensin system are a major cause of sodium retention, hypertension, and vascular injury. Thus, diuretic therapy is often targeted at hypertensive and sodium retaining conditions caused by an inappropriately activated renin–angiotensin system. ACE inhibitors and, more recently, ANG II receptor antagonists are utilized either alone or in combination with diuretics to reduce the activity of the renin–angiotensin system or prevent its activation by the diuretic treatment.

Prostaglandins, Thromboxanes, and Other Arachidonic Acid Metabolites

Renal eicosanoids are synthesized from arachidonic acid at several sites within the kidney and influence renal vascular resistance, arterial pressure, and sodium and water excretion. Administration of PGE_2 or PGI_2 (prostacyclin) into the renal artery causes vasodilation, while thromboxane A_2 and leukotrienes C_4 and D_4 constrict the renal vasculature. Endoperoxides (PGE_2, PGF_{2a}, PGI_2, and thromboxane A_2) are synthesized by the cyclooxygenase enzymatic pathway, whereas the leukotrienes are formed by lipoxygenases. PGE_2 is synthesized in medullary interstitial cells, collecting tubule cells, and mesangial cells and has been shown to increase sodium and water excretion. Isolated glomeruli have been found to synthesize PGE_2, PGF_{2a}, and thromboxane A_2. PGI_2 is the major prostaglandin synthesized in the interlobular arteries and afferent arterioles. Other eicosanoids formed in the kidney through the cytochrome P450 monooxygenase enzyme system have also been identified. Several of the resultant epoxides and their derivatives are also thought to exert actions on both the renal vasculature and the tubules [1, 25].

In normal or expanded states of hydration and sodium balance, prostaglandin metabolites are formed at low rates and cyclooxygenase inhibitors do not appreciably alter RBF or GFR. Rather, prostaglandins exert protective effects in response to vasoconstrictor stimuli, hypovolemic states, or hypotensive epi-

sodes. When renal function is under the influence of vasoconstrictor stimuli (catecholamines, renal nerve activation, and ANG II), production of endogenous prostaglandins is increased and these agents partially counteract the vasoconstrictor effects [1, 28]. In this manner, prostaglandins take on a greater regulatory role in pathophysiologic conditions that compromise renal hemodynamics. Prostaglandin production is enhanced under several conditions such as acute renal failure, following hypotensive incidents, treatment with diuretics and immunosuppressive agents, or during compromised circulatory function. In particular, during long-term diuretic treatment, renal hemodynamic function may become more dependent on vasodilatory prostaglandins. Under such conditions, the blockade of prostaglandin formation with nonsteroidal anti-inflammatory drugs (NSAID) may leave unopposed the vasoconstrictor influences of coexisting elevated levels of ANG II and catecholamines, leading to reductions in RBF and GFR, which, in turn, contribute to reduced efficacy of diuretic treatments. Some combinations of NSAID with diuretics, such as triamterene, have been reported to cause rather marked decreases in renal function [28].

Kallikrein–Kinin System

Kallikreins are serine protease enzymes that act on kininogens (α_2-glycoproteins) to form bradykinin and kallidin, which have powerful vasodilator and natriuretic actions. Their vasodilator action is mediated, in part, by their effects on endothelial cells to stimulate NO formation and release. Infusion of bradykinin intravenously or into the renal artery increases RBF and sodium excretion with lesser effects on GFR. Renal kallikrein is produced by the distal nephron and released into the lumen and interstitium, where kinin formation occurs. The tubular lumen is a primary site of intrarenal kinin formation, suggesting that one major role of kinins is to regulate tubular transport function. Kinin degradation occurs through the action of kininase II, which is identical to ACE; therefore, some of the effects of ACE inhibitors (increase in RBF, sodium excretion, and urine flow) may be due to kinin accumulation. The effects of kinin blockade on normal kidney function, however, are relatively minor; thus the role of endogenously formed kinins in the control of renal vascular resistance and sodium excretion remains uncertain. In addition, intrarenal kinins are augmented during conditions of reduced sodium intake, thus suggesting that the natriuretic actions of kinins serve primarily to counteract powerful sodium retaining stimuli that exist during activation of the renin–angiotensin system [25].

Atrial Natriuretic Peptide (ANP)

ANP refers to a recently discovered 28-amino-acid peptide family that has major effects on renal function and sodium excretion. A high-molecular-weight precursor of ANP is constitutively synthesized in atrial cardiocytes. In response to atrial distention caused by plasma volume expansion or increased central blood volume, ANP is released into the circulation. Related peptides include brain and renal natriuretic peptides and urodilatin formed in the kidney. Atrial natriuretic peptide is a rapidly acting, potent natriuretic and diuretic hormone that is also capable of lowering arterial pressure by direct vasodilatory effects on the systemic vasculature. ANP infusions can increase GFR but the effects may not be sustained. There is some evidence for redistribution of RBF to the deep cortex and medulla during ANP infusion. ANP has vasodilatory effects on preglomerular vessels, which include the arcuate and interlobular arteries and the afferent arteriole. In contrast, the efferent arteriole constricts or does not respond. The reported effects of ANP on K_f are variable. The preglomerular vasodilation produced by ANP does not impair autoregulation of either RBF or GFR. ANP can also attenuate TGF sensitivity. The reduced TGF sensitivity allows an enhanced delivery of tubular fluid to the distal nephron and facilitates sodium excretion. Although it was initially suggested that the natriuresis caused by ANP was due primarily to increases in filtered load, additional studies demonstrated direct tubular actions to inhibit sodium and water reabsorption. Several tubular sites have been evaluated including an amiloride-sensitive sodium channel in the collecting duct and an angiotensin-sensitive Na^+/H^+ exchanger in the proximal tubule [1, 17, 29].

ANP receptors are concentrated in glomerular capillaries and the collecting duct; they are also present along cortical arterioles and medullary arterioles and vasa recta. A membrane-associated form of guanylate cyclase combined with protein kinases serves as a biologically active receptor of ANP that elicits physiologic effects by increasing cell cGMP levels. ANP reduces calcium influx and calcium mobilization in cultured mesangial cells. ANP buffers the action of vasoconstrictors such as ANG II and norepinephrine via an interaction of cGMP with intracellular calcium, perhaps secondary to stimulation of calcium efflux [1].

In summary, there are numerous hormonal mechanisms that may be activated or inhibited by diuretics. Vasodilator mechanisms such as nitric oxide, kinins, natriuretic peptide, and certain prostaglandins serve to preserve renal function and sodium excretion. Other systems, in particular the renin–angiotensin system and the sympathetic nervous system will exert major renal vasoconstrictor and antinatriuretic effects when they are activated and thus may counteract the actions of commonly used diuretics.

RENAL HEMODYNAMIC ACTIONS OF DIURETICS THAT ENHANCE NATRIURETIC RESPONSE

Ca^{2+} Channel Antagonists and Other Direct Vasodilators

The natriuresis caused by agents that directly increase GFR may be due largely to their hemodynamic effects. Calcium channel blockers or antagonists refer to a large class of drugs that directly interfere with entry of Ca^{2+} via voltage-dependent calcium channels. Thus, calcium channel blockers will directly vasodilate preglomerular arterioles, leading to increases in RBF and GFR and will also block vasoconstrictor responses to agents that activate L-type voltage-dependent Ca^{2+} channels. As mentioned earlier, activation of these calcium channels is an important component of the renal autoregulatory mechanism and, thus, these agents impair the ability to autoregulate RBF and GFR in response to increases in arterial pressure. In addition, they block the vascular responsiveness to vasoconstrictor signals from the macula densa cells that increase afferent arteriolar resistance [7, 21, 24, 25].

Figure 4 illustrates the effects of calcium channel blockers to enhance renal hemodynamic and excretory function. The overall renal responses to systemic administration of calcium channel blockers depends greatly on the dose and on the counteracting influence of the associated reductions in systemic arterial pressure. The sustained increases in RBF and sodium excretion may be modest due to incomplete blockade at the level of the kidney but their continued efficacy in preventing sodium accumulation and extracellular fluid volume retention depends, in part, on their natriuretic effects.

Diuretics may influence several transport mechanisms that contribute to membrane potential and/or the activity of Ca^{2+} extrusion and sequestration mechanisms. As mentioned earlier, amiloride has been found to exert a modest vasodilatory influence that is apparently independent of its natriuretic effects [14]. Since the primary actions of amiloride are to block sodium entry through amiloride sensitive sodium channels and, at higher concentrations, to block Na^+/H^+ exchange, the vasodilatory actions could be due to reductions in intracellular sodium which might enhance calcium efflux mechanisms or hyperpolarize the cell membrane.

Drugs that lead to increases in cAMP or cGMP in vascular smooth muscle cells represent another class of agents that may elicit natriuresis primarily by enhancing renal blood flow and GFR. These include methylxanthines (theophylline and aminophylline), the vasodilatory amines (dopamine), natriuretic peptides, nitric oxide donors, and vasodilatory prostaglandins. The methylxan-

thines include the older nonspecific drugs that block membrane bound adenosine receptors as well as inhibit intracellular phosphodiesterase activity which also increases intracellular cAMP levels [31]. Most of these agents also have tubular effects to inhibit sodium reabsorption rate at one or more segments of the tubule. Varied renal hemodynamic responses have been reported with some reports showing substantive increases in GFR and others failing to establish significant changes in filtered load. Nevertheless, for any given level of perfusion pressure, renal blood flow is slightly augmented by these agents. While older studies have often suggested marked hemodynamic effects of methylxanthines, more recent studies have not supported these earlier reports and, in a setting of normal hemodynamic function, only modest vasodilatory responses are observed with these agents. In a recent study comparing the effects of a newer more specific antagonist of adenosine receptors with aminophylline and theophylline, it was observed that renal blood flow increased significantly by up to 20%, while GFR was not significantly altered. Nevertheless, these agents elicited substantial natriuretic responses increasing fractional sodium excretion over fivefold from .5 to 3.0% [15]! Additional studies have shown that these agents also have direct tubular effects to inhibit net sodium reabsorption and thus amplify any hemodynamically mediated effects.

ACE Inhibitors and ANG II Receptor Antagonists

Angiotensin antagonists represent a major category of antihypertensive agents that exert their influence by interfering with the multiplicity of actions of ANG II on the systemic circulation as well as on the kidney (Fig. 5). There are a large number of ACE inhibitors and a growing number of nonpeptide ANG II receptor antagonists. Of the two main classes of ANG II receptors, the AT_1 receptor has been identified to be responsible for mediating most of the renal vascular and tubular effects. Thus, antagonists of AT_1 receptors are now being used as antihypertensive agents and also enhance sodium excretion for any given level of arterial pressure. Specific renin inhibitors have also been used to reduce the formation of ANG I and II.

Administration of pharmacological blockers of the renin–angiotensin system interferes with preexisting influences exerted by the prevailing endogenous ANG II levels; thus, the responses are highly dependent on the physiological status of the subject. Subjects on a low sodium diet (approximately 20 mmol Na/day) usually exhibit an increase in RPF and a natriuresis but the GFR responses have been much more variable. Indeed, GFR has been reported to be either increased, unchanged, or decreased. However, systemic blockade also causes substantial decreases in arterial pressure; and the GFR response to an-

giotensin blockade is partially dependent upon the magnitude of the associated decrease in arterial blood pressure. In contrast, subjects on a high sodium diet usually do not exhibit much of a hemodynamic or natriuretic response [22]. Careful attention should be given when ACE inhibitors or ANG II receptor antagonists are administered to subjects that have been taking diuretics since the renin–angiotensin system may be highly activated from chronic diuretic therapy. Accordingly, blockade of the renin–angiotensin system may cause profound hypotension and reductions in renal function.

In experimental studies designed to achieve maximal acute blockade of the intrarenal angiotensin effects with minimal hypotensive effects, combinations of a renin inhibitor, a converting enzyme inhibitor, and a receptor blocker were infused via the renal artery, resulting in marked increases in RPF, GFR, and sodium excretion [33]. This study demonstrated the marked effects of only blocking intrarenal ANG II in the absence of major systemic efforts. In other studies, it was shown that overall autoregulatory capability of RBF as well as GFR in response to decreases in renal perfusion pressure remains intact following treatment with ACE inhibitors or ANG II receptor antagonists, indicating that the autoregulation mechanism itself is independent of the prevailing ANG II levels. This effect of angiotensin blockers contrasts sharply with the actions of calcium channel blockers which do impair autoregulatory capability [25].

Because ACE is also kininase II, the enzyme that degrades bradykinin, ACE inhibitors reduce the degradation rate of kinins; and it has been suggested that enhanced kinin levels contribute to the renal vasodilator and natriuretic responses to ACE inhibitors. At present, the general consensus is that only a small fraction of the responses to ACE inhibitors is due to augmented kinin levels. Under conditions of sodium depletion where there is increased bradykinin synthesis, about 20% of the renal vasodilator response to ACE inhibition may be attributable to kinin activation.

The recent development of nonpeptide receptor antagonists has allowed a more specific delineation of the renal responses to angiotensin II receptor blockade. Responses to AT_1 receptor blockade include decreases in arterial pressure and increases in RBF. Some studies have indicated small decreases or nonsignificant effects on GFR, while other studies have demonstrated increases in GFR following treatment with AT_1 receptor antagonists. Decreases in both preglomerular and postglomerular resistances and increases in K_F have been reported in response to ANG II blockade with ACE inhibitors or ANG II receptor antagonists [17]. As previously mentioned ANG II does not directly mediate tubuloglomerular feedback responses but the prevailing ANG II levels do exert an important modulatory influence on the sensitivity of the vascular elements that respond to signals from the macula densa cells. Recent observations demonstrating that TGF responses are markedly attenuated by the nonpeptide

ANG II receptor antagonist, losartan, indicates that ANG II exerts its modulatory influence on tubuloglomerular feedback responsiveness via activation of AT_1 receptors [22, 25].

Treatment with either ACE inhibitors or ANG II receptor antagonists collectively causes a potent net effect because of the synergistic consequences of direct reductions in renal vascular tone, attenuation of tubuloglomerular feedback responses, inhibition of angiotensin II dependent tubular sodium reabsorption, and reductions of circulating aldosterone levels which further reduces distal nephron sodium reabsorption.

Effects of Loop Diuretics on Renal Hemodynamics via the Tubuloglomerular Feedback Mechanism

As discussed in other chapters, loop diuretics such as furosemide and bumetamide exert powerful actions to inhibit the $Na^+/2Cl^-/K^+$ cotransporter in the ascending loop of Henle. Accordingly, loop diuretics markedly increase NaCl load to the macula densa. While this would be expected to stimulate the TGF mechanism and lead to vasoconstrictor signals from the macula densa to reduce blood flow and GFR, this does not occur because the TGF mechanism is interrupted by these diuretics. Indeed loop diuretics have been reported to increase RBF and reduce renal vascular resistance [6, 10, 31]. This is due to the fact that the integrity of the $Na^+/2Cl^-/K^+$ cotransporter is essential for the proper function of the macula densa signaling mechanism. While the exact nature of the signal sensed by the macula densa remains uncertain, it is generally agreed that the loop diuretics block transmission of TGF signals [5, 12, 25, 32, 42]. The direct inhibitory action on macula densa cells prevents TGF mediated afferent arteriolar vasoconstriction and the reductions in GFR that might be expected to occur with increases in NaCl delivery to the macula densa segment. This ability of the loop diuretics to block the TGF mechanism may contribute to increased or preserved renal blood flow and GFR during therapy with loop diuretics. In studies on human subjects maintained on either low or high sodium intake, GFR was well maintained after treatment with furosemide [3]. Since furosemide has been shown to increase proximal tubule pressure, maintained GFR is suggestive of a renal vasodilatory response to increase glomerular pressure.

Consistent with the premise that the TGF mechanism mediates autoregulation of renal blood flow, it has also been shown that loop diuretics administered intrarenally in dogs increase RBF and attenuate the ability to autoregulate RBF in response to changes in renal perfusion pressure [6]. Thus, the magnitude of the increase in RBF in response to furosemide is dependent on the renal perfusion pressure with much greater increases in RBF occurring at higher arterial

pressures. It has also been suggested that part of the vasodilatory response elicited by loop diuretics is due to increased formation of vasodilatory arachidonic acid metabolites via stimulation of cyclooxygenase activity [31]. In a recent study using enantiomers of ozalinone, a furosemide-like diuretic, the hemodynamic effects of loop diuretics were dissociated from the natriuretic effects. While both enantiomers increased RBF, only one of them exerted natriuretic effects equivalent to those seen with furosemide, suggesting that the vasodilator actions of furosemide may not be mediated strictly via its effect on the TGF mechanism [2].

The loop diuretics are very powerful stimulators of renin release which may cause increased ANG II levels and reductions in renal blood flow [20]. This effect is thought to be mediated by the release of the inhibitory influence of the macula densa on renin secretion. Furosemide has also been reported to enhance activity of the sympathetic nervous system and the release of vasopressin, factors which cause renal vasoconstriction [16]. These interactions help explain how furosemide may also be associated with reductions in renal blood flow and GFR as has been reported [8, 16, 37]. It is possible that these indirect effects may predominate over the direct effects on the TGF mechanism when furosemide is given chronically. Thus, the actual renal hemodynamic response in any given subject to loop diuretics may be quite variable depending on the level of arterial pressure and on the relative influences of the vasodilatory and the vasoconstrictor systems that have been activated. In rats, renal vasoconstriction in response to furosemide has been observed often [8, 16, 20, 37]. However, in dogs and human subjects, furosemide has been shown to either have no significant effect on GFR or to increase GFR and RBF [3, 6, 31, 40]. In summary, natriuretic agents that exert a renal vasodilator action, either via direct or via indirect mechanisms, may exert a more profound and long-term effect on sodium excretion, especially when they are given in combination with an agent that interferes with tubular sodium reabsorption. However, continued treatment with such powerful diuretics ultimately leads to volume depletion, electrolyte imbalances, and enhanced activation of the renin–angiotensin system, the sympathetic nervous systems, and other vasoconstrictor systems. Optimal treatment should achieve the desired beneficial effects without inducing the deleterious consequences of excessive volume contraction.

HEMODYNAMIC CONSEQUENCES OF DIURETICS THAT COUNTERACT NATRIURETIC RESPONSE

Except for agents that directly cause renal arteriolar vasodilation or interfere with the transmission of tubuloglomerular feedback signals, most other diuretics have a greater potential for causing reductions in renal hemodynamics and

GFR by causing release of vasoconstrictor factors or by increasing the activity of the tubuloglomerular feedback mechanism. As already mentioned, nonspecific indirect effects to reduce RBF also result if diuretic therapy leads to excessive sodium loss and marked contraction of plasma and extracellular fluid volumes. Such decreases may activate powerful neural, hormonal, and local mechanisms leading to enhanced baroreceptor activity and renal sympathetic tone, increased catecholamine levels, and increased activity of the renin-angiotensin system [11, 40].

Reductions in GFR may occur not only as a consequence of renal vasoconstriction but may also be due to diuretic induced reductions in tubular reabsorption leading to increases in proximal tubule pressure. Osmotic diuretics, such as mannitol, and diuretics that interfere with either proximal or loop reabsorption rate cause substantial increases in proximal tubule pressure which will reduce effective filtration pressure and GFR. Reductions in GFR in conditions of maintained or increased renal blood flow are usually indicative of diuretic effects to raise proximal tubule pressure. Failure to recognize these effects of elevations in proximal tubule pressure may lead to incorrect interpretations regarding localization of the changes in segmental renal vascular resistance based on decreases in filtration fractions [2].

Diuretics that inhibit sodium reabsorption in the proximal nephron segments also cause marked increases in fluid delivery out of the proximal tubule [27, 31, 34, 39]. Increased volume delivery to the ascending loop of Henle will compromise the diluting capability of this segment and increase the solute and sodium concentration of the fluid flowing past the macula densa. This will lead to activation of the tubuloglomerular feedback mechanism resulting in TGF mediated afferent arteriolar vasoconstriction and reductions in GFR. Several agents that inhibit carbonic anhydrase activity, such as acetazolamide, benzolamide, and chlorothiazide have been shown to cause renal vasoconstriction and reductions in GFR due to increased activity of the tubuloglomerular feedback mechanism [4, 12, 27, 39]. That the effects are due primarily to an increased TGF activity has been shown by studies in which the SNGFR was measured from collections of distal or proximal tubule fluid samples. The reductions in SNGFR were reflected only in the measurements based on distal collections indicating that the TGF activity is increased by these diuretics. The effects of chlorothiazide to elicit renal vasoconstriction may be due primarily to its carbonic anhydrase activity in the proximal nephron segments since thiazides not having carbonic anhydrase activity, such as bendroflumethiazide, do not elicit perceptible alterations in either renal blood flow, GFR, or renal autoregulatory behavior [18].

Studies in normal human subjects have also demonstrated that acetazolamide causes significant decreases in GFR of about 18%. Lithium clearance, used as a reflection of volume delivery out of the proximal tubule, increased sug-

gesting an increased delivery out of the proximal nephron activating the TGF mechanism to elicit renal vasoconstriction and lower RBF and GFR [34]. This effect contributes to the diuretic resistance that develops with drugs that inhibit tubular reabsorption rate proximal to the macula densa but do not directly interfere with the tubuloglomerular feedback mechanism. In these cases, the TGF mechanism serves to protect from further volume losses by reducing GFR. In summary, chronic treatment with diuretics that do not have specific renal vasodilator action often leads to reductions in RBF and GFR mediated via several paracrine, hormonal and neural mechanisms. Such reductions may reduce the effectiveness of natriuretic therapy.

SYSTEMIC HEMODYNAMIC RESPONSES AND CONCLUSIONS

Many patients receiving diuretic therapy are hypertensive and a long-term goal of the therapy is to achieve sustained reductions in arterial pressure to normotensive levels. Indeed, monotherapy with diuretics has long been shown to be an effective treatment for many hypertensive patients. In more resistant cases, combinations of either ACE inhibitors or calcium antagonists with a diuretic have been effective in treating resistant patients. While the antihypertensive mechanisms for agents that directly elicit vascular smooth muscle relaxation are readily apparent, it is more difficult to explain the prompt antihypertensive effects of diuretics that primarily inhibit epithelial transport and do not have much direct effect on vascular smooth muscle to decrease peripheral vascular resistance. Studies in anephric subjects have shown that the direct systemic vasodilatory responses of most diuretics are rather modest. In addition, the immediate effects on arterial pressure of diuretics are rather minor. Thus, it is generally recognized that the antihypertensive effects of these agents result primarily as a consequence of their natriuretic actions [11, 35, 40]. Nevertheless, within 4 hr after administration of the thiazide or loop diuretics, systemic arterial pressure and cardiac index have been shown to decrease.

The actions of the diuretics on arterial pressure and cardiovascular function can be appreciated by recognizing the intimate associations between the regulation of salt and water balance and chronic control of cardiovascular function which are shown in Fig. 6 [9, 13, 41]. Diuretic induced increases in sodium excretion lead to reductions in extracellular fluid and plasma volumes which decrease effective blood volume, mean circulatory pressure, venous return, and cardiac output. There is often an early increase in total peripheral resistance that is partially attributable to enhanced sympathetic activity but this is eventually counteracted by local autoregulatory mechanisms which reduce vascular resistance and cause further decreases in arterial pressure. Additional factors

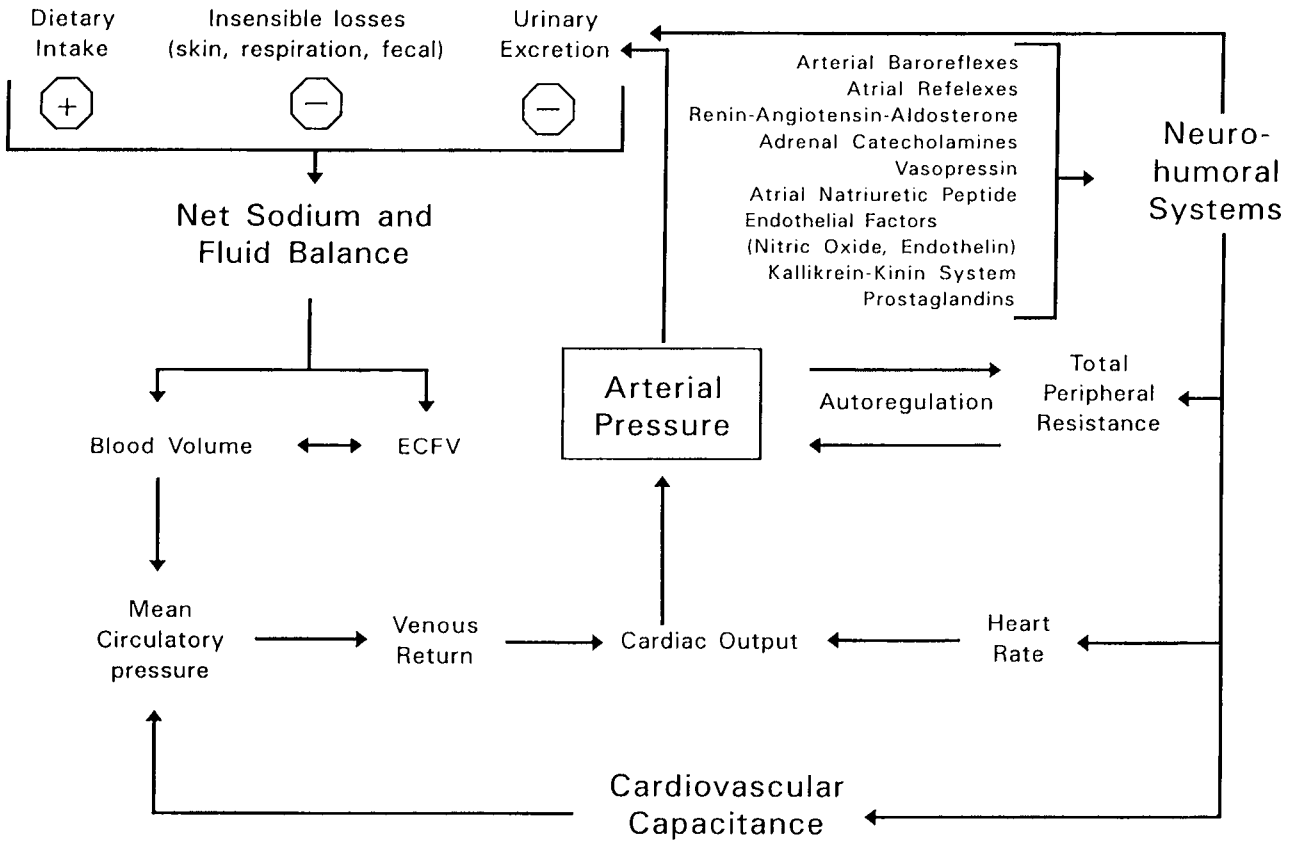

FIGURE 6. Relationships between sodium balance and arterial pressure.

such as enhanced production of endogenous vasodilator substances and adaptation of baroreflex activity have also been suggested to contribute to the reduced arterial pressure. In uncomplicated essential hypertensive subjects, effective antihypertensive action is usually associated with a sustained moderate reduction of extracellular fluid and plasma volumes. Thus, the correction of arterial pressure and effective blood volume depends on a complex interplay among neural, hormonal, and local regulatory mechanisms that amplify the effects of rather modest volume losses and lead to the normalization of the hemodynamic status of the subject [11, 13, 35, 40, 41].

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CHAPTER IIID

Extrarenal Effects of Diuretics

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INTRODUCTION

The primary clinical use of diuretics is to augment the renal excretion of salt and water. This effect is mediated by the ability of these drugs to interfere with transport mechanisms located at various sites along the nephron which are involved in the reabsorption of NaCl. Many of these same mechanisms are also found in cells and epithelial membranes throughout the body. In experimental studies, diuretics have been of great use in better defining the mechanisms of transport in these extrarenal epithelia. Of more clinical importance, the ability of these drugs to alter epithelial transport in extrarenal tissue has proven to be of therapeutic benefit in certain disease states. At the same time, however, such interactions account for some of the side-effects occasionally associated with the clinical use of these drugs. Rather than reviewing the large body of literature in which diuretics have simply been used as a tool in order to better define epithelial transport mechanisms, this chapter will focus on the extrarenal effects of diuretics which help to explain their potential therapeutic benefit or which explain their nonrenal side-effects. The vascular, otologic, and endocrine effects of diuretics will not be covered as these subjects are discussed in detail in other chapters.

Diuretic Agents: Clinical Physiology and Pharmacology

CENTRAL NERVOUS SYSTEM

Mannitol is an osmotic diuretic which is utilized clinically to decrease intracranial pressure. This agent is administered as a hypertonic solution such that an osmotic gradient is created favoring the movement of water from the brain parenchyma into the intravascular compartment across the blood–brain barrier. As long as the blood–brain barrier is intact, mannitol is effective in decreasing the water content of the brain, thereby reducing intracranial pressure (see Table 1). When the integrity of the blood–brain barrier is disrupted, however, the effectiveness of mannitol declines. In this setting, mannitol diffuses into the brain parenchyma, thereby preventing the establishment of an osmotic gradient favoring water movement into the vascular compartment. The ability of mannitol to decrease intracranial pressure is independent of its diuretic effect as a fall in cerebrospinal fluid pressure can be demonstrated even in the absence of urine flow.

The maximal reduction in brain water content achieved with mannitol is with doses of 1–2 g/kg/24 hr. At higher doses, brain water content may actually begin to increase. In this setting, severe hyperosmolality leads to a disruption in the integrity of the blood–brain barrier such that mannitol and water begin to enter the brain parenchyma. This modification of the blood–brain barrier with high doses of mannitol is used clinically as a means to reversibly enhance the entry of chemotherapeutic agents into the brain parenchyma during the treatment of central nervous system tumors.

Acetazolamide has been shown to affect the central nervous system in several ways which are independent of its diuretic effect (see Table 2). Inhibition of carbonic anhydrase with acetazolamide increases cell pH in the choroid plexus. The increase in cell pH leads to a slowdown in uptake of Na and Cl which normally occurs by parallel Na–H and Cl–HCO_3 exchangers located on the blood side of the membrane. Acetazolamide may also block anion channels located on the apical membrane which are responsible for the extrusion of Cl and HCO_3. The net effect is decreased vectorial transport of NaCl from the blood to cerebral spinal fluid (CSF). As a result, CSF formation is markedly inhibited since transport of Na and Cl across the choroid plexus into the ventricles is the major determinant of fluid formation. Clinically, acetazolamide

TABLE 1 Extrarenal Effects of Mannitol

↓ Intracranial pressure
↑ Entry of chemotherapeutic agents into central nervous system across blood–brain barrier
↓ Intraocular pressure

TABLE 2 Extrarenal Effects of Acetazolamide

↓ Cerebral spinal fluid formation
↑ Cerebral blood flow
↓ Bronchoconstriction in response to cold-air hyperventilation
↓ Intraocular pressure
↓ Aqueous humor formation
↑ Absorption of vitreal fluid
↓ Basal and stimulated gastric acid production
↓ HCO_3 secretion in duodenum
↓ NaCl and water absorption in jejunum
↓ NaCl absorption in ileum
↓ Pancreatic fluid flow
↑ Biliary flow

has been used to lower the secretion of CSF in cases of increased intracerebral pressure and hydrocephalus.

In addition to inhibiting choroid plexus secretory activity, administration of acetazolamide leads to an increase in cerebral blow flow. The mechanism behind this vasodilatory effect is multifactorial. While there may be a direct effect of acetazolamide upon the cerebral vasculature, most evidence suggests that extracellular acidification is the primary mechanism behind the vasodilatory response. Administration of acetazolamide at doses which are sufficient to inhibit both blood and brain carbonic anhydrase results in acidification of the cerebral extracellular fluid. This decrease in pH results from increases in the extracellular fluid concentration of pCO_2 and carbonic acid (H_2CO_3). The increase in blood flow with acetazolamide has largely been attributed to an increased hydrogen ion concentration resulting from the elevated pCO_2 since cerebral blood flow is known to be directly related to arterial carbon dioxide concentration. More recently, the increase in carbonic acid concentration has also been shown to exert a vasodilatory response refuting the notion that increased acidity in brain tissue leads to vasodilation solely as a result of an elevated pCO_2. The independent effect of an increase in pCO_2 or carbonic acid concentration to increase cerebral blood flow may explain some of the benefit of acetazolamide on central nervous system function under conditions of high altitude. In this setting, the pCO_2 concentration is typically low as a result of hyperventilation. The low pCO_2 would tend to constrict cerebral blood vessels and lower oxygen delivery to the brain. Acetazolamide tends to counteract the vasoconstrictive effects of low pCO_2 by causing an elevated hydrogen ion con-

centration in cerebral tissue as a result of carbonic acid accumulation. The net effect is that cerebral perfusion is better maintained and brain oxygenation is improved.

In experimental animals acetazolamide has been shown to alter cardiovascular and respiratory function by altering central chemoreceptor activity. Application of acetazolamide to the ventral surface of the medulla oblongata in cats results in hypotension, bradycardia, and respiratory depression. This effect was not influenced by peripheral chemoreceptor or baroreceptor input. In a similar experimental design using a lower dose of acetazolamide, phrenic nerve activity was increased. These observations suggest that carbonic anhydrase is involved in the central chemoreceptor response to changes in acid–base balance. The clinical relevance of these observations with regards to the therapeutic use of acetazolamide is unknown.

Acetazolamide has been used therapeutically in several neurologic disorders of varying etiology. This agent has been found superior to a variety of antimyotonic drugs in the treatment of a variant form of myotonia congenita. In these patients painful muscle stiffness is provoked by potassium loading and fasting. A missense mutation has been described in the sodium channel in patients with this disease. Acetazolamide-induced hypokalemia results in an increase in muscle transmembrane potential. It has been suggested that this increased potential may be the basis of the clinical benefit observed in this patient population. Acetazolamide has also been reported effective in a patient with chronic paroxysmal hemicrania. This disease is characterized by unilateral headaches of short duration which are accompanied by ipsilateral changes in the function of the autonomic nervous system. The mechanism by which acetazolamide provides a beneficial effect in this disease is unknown.

The loop diuretics have been shown to decrease the formation of cerebral spinal fluid formation by inhibiting NaCl secretion in the choroid plexus. These agents block NaCl transport on both the ventricular (apical) and blood sides (basolateral) of the choroid plexus. The loop diuretics decrease the uptake of NaCl on the basolateral membrane by blocking a Na–K–2Cl cotransporter. On the apical membrane, these agents block a cotransport protein responsible for the extrusion of K and Cl. High dose furosemide but not ethacrynic acid or bumetanide can further limit NaCl secretion by acting as a carbonic anhydrase inhibitor.

The loop diuretics have been utilized in a variety of experimental models of brain injury as a means of reducing brain edema and intracranial pressure. In a recent model of vasogenic brain edema induced by a freezing lesion to the exposed brain, administration of torsamide either before or after the insult was found effective in reducing tissue water content as compared to that seen in control animals. There was no change in hematocrit or plasma osmolality, suggesting that the benefit was related to direct effects of the drug in the brain

rather than increased renal excretion of salt and water. The same drug was also found to lower intracranial pressure in a model of cerebral hypertension induced by distilled water administration in nephrectomized rats. The decrease in brain edema noted in these studies may be secondary to decreased secretion of CSF by the choroid plexus as discussed above. Alternatively, these agents may affect transport processes on glial and neuronal cells which serve to limit cellular swelling. For example, torsamide has been shown to attenuate glial swelling induced by lactic acidosis. Similarly, the same drug limits the swelling of brain slices and astrocytes induced by increased potassium levels. Finally, loop diuretics have been shown to inhibit NMDA receptors. Stimulation of these receptors by the massive release of excitotoxic amino acids such as glutamic acid may mediate a wave of secondary injury to the brain parenchyma after any given initial insult.

In experimental animals thiazide diuretics have been shown to decrease the formation of cerebral spinal fluid. Amiloride and triamterene also depress fluid formation. By contrast, spironolactone has been shown to increase CSF formation in cats.

PULMONARY SYSTEM

Acetazolamide has effects on pulmonary function that may be of clinical importance. Carbonic anhydrase is abundantly present in the lung, primarily located at the alveolar–capillary barrier. This location allows for the enzyme to cause the rapid dehydration of carbonic acid, thereby facilitating the excretion of pCO_2. Inhibition of this enzyme with acetazolamide leads to an increase in tissue pCO_2. In patients with chronic obstructive pulmonary disease in whom pulmonary reserve is limited, such an increase may be of clinical consequence. In patients with asthma, inhaled acetazolamide has been shown effective in limiting the bronchoconstrictive response to cold-air hyperventilation. The mechanism of this protective effect is unknown.

The loop diuretics have also been shown to have direct effects on the lung. In experimental animals furosemide has been shown to increase thoracic duct lymph flow, redistribute pulmonary blood flow, and decrease transvascular filtration of fluid in the lung. In a model of noncardiogenic pulmonary edema, administration of furosemide was associated with improved gas exchange, an effect thought to be mediated by these extrarenal processes.

A large number of studies have shown that furosemide is effective in preventing bronchoconstriction induced by a variety of stimuli. This protective effect is mostly seen when asthmatic subjects are challenged with stimuli that indirectly act to induce bronchoconstriction. Examples would include exercise, cold air, and allergens. By contrast, little to no protection is afforded against

agents which directly constrict the bronchial smooth muscle such as histamine and methacholine. The mechanism by which furosemide produces its salutary response is unclear. Most, but not all, studies have found that furosemide has no effect on baseline lung function and therefore the drug is not considered to be a bronchodilator. It has been postulated that furosemide's effect on the lung is mediated by blocking the Na–K–2Cl cotransporter which is known to be found in the airway epithelium. A number of observations, however, have questioned whether inhibition of this transporter is the sole mechanism which accounts for the protective effect. For example, bronchoprotection in exercise-induced asthma is found only with inhaled furosemide and not when the drug is given systemically. Since the Na–K–2Cl cotransporter is located on the serosal side of the airway epithelium, access of the drug to the transporter should be greater with systemic administration as opposed to application to the mucosal surface. Second, inhalation of bumetanide which is a more potent inhibitor of the cotransport mechanism has very little effect in preventing bronchoconstriction induced by stimuli that are effectively antagonized by furosemide.

While an effect on the serosal Na–K–2Cl cotransporter cannot be totally excluded from the foregoing observations, there are other potential mechanisms by which furosemide may prevent bronchoconstriction. One of these mechanisms may involve effects on airway nerves. In *in vitro* studies, furosemide and bumetanide have both been shown to inhibit both cholinergic and nonadrenergic, noncholinergic mediated contraction of bronchial smooth muscle devoid of airway epithelium (see Table 3). Another mechanism may involve anti-inflammatory effects of the drug. Furosemide has been shown to suppress neutrophil chemotactic activity in serum following bronchial challenge with inhaled distilled water. This drug has also been shown to reduce production of histamine and leukotrienes in lung tissue and decrease superoxide anion release in alveolar macrophages. In addition, furosemide may exert an inhibitory

TABLE 3 **Extrarenal Effects of Furosemide**

↓ Cerebral spinal fluid formation
↓ Cerebral edema
↑ Thoracic duct lymph flow
↓ Transvascular fluid filtration in lung
↓ Bronchoconstriction induced by exercise, cold air, allergens
↑ Nasal airway resistance
↓ Volume of nasal cavity
↓ Intraocular pressure by facilitating outflow of fluid
↑ Biliary flow rates
↑ Venous capacitance

TABLE 4 Mechanisms by Which Furosemide Prevents Bronchoconstriction

Inhibit the serosal Na/K/2Cl cotransporter
Inhibition of cholinergic and noncholinergic nonadrenergic mediated bronchoconstriction
Suppression of neutrophil chemotactic activity
Reduce production of histamine and leukotrienes from lung tissue
Decrease release of superoxide anion from alveolar macrophages
Inhibit mast cell function

effect on mast cells. Finally, furosemide may alter pulmonary eicosonoid metabolism such that production of bronchodilator prostaglandins is increased.

Aerosolized furosemide has been used in the treatment of mechanically ventilated preterm infants with bronchopulmonary dysplasia (see Table 4). In one study there was a significant improvement in lung compliance, pulmonary resistance, and tidal volume, all of which occurred in the absence of diuresis or renal side-effects. Loop diuretics also have effects in the nasal airways. Nebulized furosemide causes a significant increase in nasal airway resistance and decreases the volume of the nasal cavities. It has been postulated that both of these effects are the result of vasodilation of the nasal vasculature possibly mediated by increased production of vasodilatory prostaglandins. Furosemide topically applied to the nasal mucosa has also been shown to decrease the resting membrane potential.

Amiloride is known to inhibit the Na channel located on the mucosal side of the airway epithelium (see Table 5). In clinical studies, inhaled amiloride has been shown to attenuate the bronchconstrictive effect of nebulized distilled water in asthmatic children. As with furosemide, the drug does not protect against inhaled stimuli that directly act as brochoconstrictors such as histamine and

TABLE 5 Extrarenal Effects of Potassium Sparing Diuretics

Amiloride
↓ Cerebral spinal fluid formation
↓ Bronchoconstriction to external stimuli
↑ Mucociliary clearance in patients with cystic fibrosis
↓ Luminal electronegativity in rectum
↑ Left ventricular function in setting of stunned myocardium
↓ Reperfusion arrhythmias
Spironolactone
↑ Biliary flow rates
↓ Myocardial fibrosis in animal models of hypertension

methacholine. Nebulized amiloride has also proven to be of clinical benefit in cystic fibrosis. In this disease there is defective cyclic-AMP-mediated Cl secretion and excessive Na reabsorption. Amiloride aerosol inhibits the excessive Na reabsorption. Preliminary studies in adults with cystic fibrosis using this therapy show improved mucociliary clearance and a slowing of the decline in lung function.

Eye

One of the most common extrarenal indications for the use of diuretics is the treatment of glaucoma. The osmotic agents are extremely effective in lowering intraocular pressure. These agents create an osmotic gradient for movement of water from the anterior and posterior chambers and the vitreous cavity of the eye to the blood. The osmotic agents are most useful when immediate intraocular pressure reduction is necessary, such as in the patient with acute angle-closure glaucoma. The ocular hypotensive effect occurs in 30–60 min and lasts for approximately 6 hr.

Acetazolamide and related drugs are commonly used in the chronic management of patients with increased intraocular pressure. The intraocular pressure is determined by the balance between aqueous humor production in the ciliary body and its drainage from the anterior chamber. The carbonic anhydrase inhibitors reduce this pressure by decreasing the production of aqueous humor. Aqueous humor is secreted into the posterior chamber by the nonpigmented epithelium which covers the ciliary body. The formation of fluid is critically dependent upon the active secretion of Na on the aqueous side of this epithelium. This secretory step has been attributed to the Na–K–ATPase which is known to be densely distributed on the highly invaginated basolateral surface of the secretory cell. In order to maintain electroneutrality HCO_3, and to a much lesser extent Cl, follows Na into the intercellular space. The movement of HCO_3 is critical for the ongoing production of fluid. The precise mechanism by which HCO_3 secretion is coupled to Na is unclear. Transport mechanisms which have been reported to exist in this epithelium include an electrogenic Na–HCO_3 cotransporter, Na–K–2Cl cotransporter, and a Cl–HCO_3 exchanger. The increase in Na concentration creates an osmotic gradient which draws fluid into the invaginated spaces and subsequently into the posterior chamber.

A decrease in bicarbonate production in the ciliary body is thought to be the primary mechanism by which the carbonic anhydrase inhibitors decrease aqueous humor production. These drugs may also lower pressure by increasing the rate of absorption of vitreal fluid by the retinal pigment epithelium. This absorptive effect may account for the observation that topically administered carbonic anhydrase inhibitors are less effective than when given systemically. Lo-

cal administration of the drug may not reach a high enough concentration to affect the retinal pigment epithelium. If the drug is given systemically in doses sufficient enough to induce a systemic acidosis, there may be a further lowering of the intraocular pressure. A direct effect of metabolic and respiratory acidosis in inhibiting aqueous humor production accounts for this additive effect.

The loop diuretics have been shown to decrease intraocular pressure in experimental animals. Rather than decrease fluid production these agents increase the outflow of fluid from the anterior chamber. The mechanism by which this occurs is unknown. This effect has been demonstrated only when the drug is either applied topically or injected directly into the anterior chamber. Systemic use of loop diuretics in humans has not been associated with any consistent effect on intraocular pressure.

Stomach

Carbonic anhydrase is present in high concentrations in the gastric epithelium, where it plays a major role in gastric acid secretion. Inhibition of this enzyme has been shown to inhibit basal and stimulated gastric acid secretion in both experimental animals and in humans. In fact, acetazolamide has been used in the treatment of patients with peptic ulcer with a reported response rate of greater than 90%. In parietal cells, protons derived from water molecules are secreted into the gastric lumen via the H–K ATPase, while the corresponding hydroxyl ions, via carbonic anhydrase, are converted to HCO_3. The bicarbonate ions exit the basolateral surface of the cell in exchange for chloride. Chloride is secreted into the lumen by way of a KCL symporter. Potassium ions secreted on the symporter are largely recycled across the apical membrane in exchange for protons via the apical H–K ATPase.

Carbonic anhydrase is also found in non-acid-secreting cells of the stomach. These cells secrete bicarbonate into the unstirred mucous gel layer which overlies the gastric epithelium. As a result, an alkaline pH is maintained near the surface of the epithelium which protects against the backdiffusion of hydrogen ions. The secretion of bicarbonate is either coupled to Na or is secreted in exchange for Cl such that its movement into the lumen is electroneutral. The role that carbonic anhydrase plays in bicarbonate secretion is unclear. In experimental animals, acetazolamide has been reported to either inhibit or have no effect on bicarbonate secretion. In humans, doses of acetazolamide that inhibit acid secretion have no effect on gastric bicarbonate secretion. The ability to inhibit acid secretion and yet preserve bicarbonate secretion may explain the therapeutic benefit of acetazolamide in the treatment of peptic ulcer disease.

Acetazolamide has also been shown to exert a cytoprotective effect on the gastric mucosa which is independent of the drug's effect on acid secretion. Gas-

tric injury induced by ethanol or stress is reduced in experimental animals treated with acetazolamide. In these models the protective effect is reduced in the presence of indomethacin, suggesting that the drug increases the production of prostaglandins. In addition, the sulfhydryl content of the drug, rather than the drug's ability to inhibit carbonic anhydrase, may be playing a role in this cytoprotective effect.

Furosemide has been shown to decrease gastric acid secretion in dogs. When applied to the serosal side of isolated guinea pig fundic mucosa, furosemide decreases electrogenic transport of Cl, suggesting that the drug blocks Na and Cl cotransport on the basolateral side of the epithelium. There is no clinically apparent effect of loop diuretics on gastric acidification which has been reported in humans.

INTESTINE

On a daily basis the small and large intestine absorbs a large quantity of salt and water as well as dietary nutrients. Many of the transport mechanisms involved in this absorptive process are similar, if not identical, to ones present in the kidney. Several diuretics have been shown to interact with these transport processes in the intestine. For the most part, diuretic therapy is not associated with clinically evident gastrointestinal manifestations; however, administration of diuretics have on occasion been associated with the onset of diarrhea.

In the duodenum bicarbonate secretion serves to alkalinize the acidic fluid which emerges from the stomach, thereby protecting the duodenal mucosa against acid and peptic damage. This secretion is stimulated directly by luminal acidity as well as by a variety of secretagogues. Unlike the stomach where bicarbonate secretion is resistant to inhibition of carbonic anhydrase, acetazolamide decreases bicarbonate secretion in the duodenum. In normal human volunteers, acetazolamide was found to inhibit both basal and prostaglandin-stimulated bicarbonate secretion but not acid-stimulated secretion. Similar results have been reported in experimental animals.

In the human jejunum, acetazolamide given intravenously or added directly to the perfusate results in decreased NaCl and water absorption. With regard to bicarbonate transport, no effect was found with intravenous administration while intraluminal acetazolamide decreased baseline bicarbonate absorption. In the human ileum, intraluminal acetazolamide also decreases NaCl absorption but has no effect on net bicarbonate movement. The ability of acetazolamide to inhibit NaCl absorption lends support to the existence of parallel Na–H and Cl–HCO3 exchangers in which H^+ and HCO_3 are derived from CO_2 and H_2O under the influence of carbonic anhydrase.

The loop diuretics have also been shown to effect salt and water transport in the human intestine. A 40-mg dose of intravenous furosemide has been shown to decrease jejunal absorption of NaCl and water in some subjects. No effect on transport was seen following a 20-mg dose. Intraluminal application of loop diuretics has produced conflicting results. Ethacrynic acid infused into the jejunal lumen of normal human volunteers induced net secretion of Na and water and inhibited glucose absorption. In contrast to its stimulatory effect of basal secretion, ethacrynic acid markedly inhibited the secretion of salt and water which was induced by prostaglandin E_1. Intraluminal furosemide had no effect on basal absorption or prostaglandin-induced secretion rates in this segment. In the human ileum, intravenous administration of furosemide has been shown to enhance bicarbonate secretion and induce chloride absorption.

The potassium sparing diuretics do not have major effects on the intestinal transport of salt and water or other nutrients. These agents have been used as a tool to study ionic transport mechanisms in the large intestine. In the colon, a lumen negative potential is normally present which is thought to be generated by the active transport of sodium from the lumen to the blood. Mineralocorticoids stimulate sodium absorption in the large intestine and increase the potential difference across the colonic mucosa. Infusion of amiloride into the rectum of normal human volunteers has been shown to decrease the electronegativity of the rectum.

Pancreas

Diuretics have been shown to alter the composition of pancreatic juice in both experimental animals and humans. The pancreatic acinar cells secrete a bicarbonate rich solution which is transported by way of the pancreatic ductal system into the duodenum. Within this solution are secreted pancreatic enzymes which become activated in the lumen of the duodenum in the setting of an alkaline pH. A Cl–HCO_3 exchange mechanism is present along the length of the pancreatic ducts such that the Cl and HCO_3 concentrations vary inversely according to pancreatic flow rates. During low flow states, the Cl concentration progressively increases, while high flow rates are characterized by a high HCO_3 concentration.

Acetazolamide has been shown to decrease the volume of pancreatic fluid flow in normal human volunteers. Accompanying the reduced flow rate was the usual association of decreasing HCO_3 concentration and increasing Cl concentration. The concentration of total protein in the fluid increased, suggesting that enzyme secretion was not inhibited. Studies examining the effect of loop diuretics on pancreatic fluid flow have produced conflicting results. In

dogs, both furosemide and ethacrynic acid were found to decrease secretin-stimulated pancreatic fluid flow. By contrast, furosemide increases secretin-stimulated pancreatic fluid flow in normal humans. The composition of the fluid changes as expected in that the HCO_3 concentration increases while the concentration of Cl falls. It has been suggested that furosemide increases pancreatic fluid flow by inhibiting ductal absorption of sodium. Alternatively, furosemide may stimulate fluid secretion by increasing pancreatic blood flow. The relationship, if any, between the effects of diuretics on pancreatic secretion of electrolytes and water and diuretic-induced pancreatitis is unknown.

Hepatobiliary System

Formation of bile involves the movement of water and electrolytes and other solutes from the sinusoidal blood or intracellular compartment into the canaliculus. Canalicular secretion of bile is made up of two major components. Active transport of bile acids into the bile canaliculus provides the osmotic driving force for movement of water and smaller solutes, giving rise to the bile acid-dependent component of canalicular bile. The osmotic drive for a second bile acid-independent component of canalicular bile is mediated by the transport of inorganic electrolytes which includes a mechanism for the active transport of HCO_3. A third component of total bile flow involves ductular secretion of a HCO_3 rich fluid. A large component of formed bile is stored in the gallbladder where it is concentrated and later discharged into the intestine after the ingestion of a meal. In the gallbladder, up to 90% of water in hepatic bile is resorbed as an isotonic solution composed of sodium, chloride, and bicarbonate. This reabsorptive process appears to be the result of electroneutral sodium-coupled chloride transport.

Each of the major classes of diuretics have been shown to increase bile flow and output of sodium, potassium, and chloride in bile. The exact mechanism by which these drugs increase flow remains undetermined. It has been suggested that diuretics such as ethacrynic acid and chlorothiazide exert a choleretic response in a manner similar to bile acid-dependent increased flow. Since these drugs are secreted into the bile, an osmotic gradient would be created favoring osmotic water flow, thereby increasing total bile flow. Alternatively, some diuretics may increase HCO_3 secretion in the biliary ducts. Finally, some diuretics may inhibit isotonic fluid reabsorption in the gallbladder since fluid reabsorption is dependent upon sodium-coupled chloride transport. In this regard, acetazolamide has been shown to inhibit NaCl transport in the rabbit gallbladder. The significance of diuretic-induced alterations in biliary flow appear to be of little clinical significance. The relationship, if any, of diuretic-

induced increases in biliary flow rates to the increased incidence of cholelithiasis reported in infants receiving furosemide is unknown.

CARDIOVASCULAR

Diuretics affect the cardiovascular system in several ways. The effects of diuretics on the peripheral vasculature are reviewed in detail elsewhere in this book and will only be summarized here. Furosemide has been shown to decrease left ventricular filling pressure and increase venous capacitance within minutes of administration, well before a diuretic response is apparent. This venodilatory response has, in part, been attributed to the release of vasodilatory prostaglandins from the kidney. The importance of normal renal function in this response is highlighted by the observation that the venodilatory response is markedly attenuated in the anephric state. This increase in venous capacitance provides an immediate hemodynamic benefit to patients with increased left ventricular filling pressures that is later maintained by the reduction in plasma volume resulting from the drug's natriuretic effect.

Some diuretics have been shown to have direct cardiac effects which may eventually prove to be of clinical benefit. For example, amiloride has been shown to have favorable effects on ventricular function in the setting of ischemia. In particular, intracoronary amiloride prevents contractile dysfunction which typically accompanies a stunned myocardium. This drug has also shown efficacy in the prevention of reperfusion arrhythmias. The mechanism behind these beneficial effects may be related to the drug's ability to prevent large increases in the intracellular concentration of sodium and calcium during ischemia. Another observation that has potential clinical importance is the ability of spironolactone to limit myocardial fibrosis in a variety of animal models of hypertension.

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PART IV

Diuretic Use

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CHAPTER IVA

Diuretic Pharmacokinetics and Pharmacodynamics

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INTRODUCTION

Much work over the past decade has allowed a better understanding of the response to loop diuretics [1, 3, 4, 6, 12], and, in turn, mechanisms of diuretic resistance. It is presumed that most of the concepts relevant to these drugs can be extrapolated to other classes of diuretics. Determinants of diuretic effect can be grouped into pharmacokinetic and pharmacodynamic factors. Pharmacokinetic factors influencing response are the total amount of drug reaching the site of action and the time course of its delivery to the active site. For example, decreased bioavailability of a diuretic could diminish total amounts of diuretic reaching the active site and thereby response. An example of the importance of the time course of delivery occurs in renal transplant patients in whom diminished response appeared to be caused by a change in the time course of drug delivery, though the same total amount of drug reached the site of action as in those patients responsive to the drug. The pharmacodynamic factor affecting overall diuretic response is the "sensitivity" of the active site to the diuretic as assessed by the concentration vs response relationship [3]. The sensitivity of the nephron can change because of diseases, as has been observed in congestive heart failure, cirrhosis, and nephrotic syndrome, with development of tolerance

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(both acute, so called "braking," and chronic), and with administration of nonsteroidal anti-inflammatory drugs [4, 6].

INHIBITORS OF CARBONIC ANHYDRASE

PHARMACOKINETICS AND PHARMACODYNAMICS

These agents are now most frequently used for glaucoma, but they represent a milestone in the development of diuretics. Modern diuretic therapy was launched when it was noted that sulfanilamide caused a diuresis rich in sodium bicarbonate. Chemical modification of this compound resulted in current carbonic anhydrase inhibitors such as acetazolamide, and subsequently thiazide, and loop diuretics. Little is known of the pharmacokinetics or pharmacodynamics of carbonic anhydrase inhibitors. The only study examining the pharmacokinetics of acetazolamide did so in five healthy volunteers. Peak concentrations occurred in 1 to 3 hr after an oral dose and the elimination half-life averaged 13 hr [14]. This half-life means acetazolamide can be used on a once or twice daily basis with chronic therapy. The most frequent use of acetazolamide as a diuretic is to induce an alkaline diuresis to facilitate renal elimination of drugs such as salicylates or phenobarbital in overdose settings.

Another diuretic use of acetazolamide is in combination with loop diuretics in patients refractory to the latter. The presumed mechanism of this strategy is that many clinical conditions (e.g., congestive heart failure) are associated with avid proximal tubular reabsorption of sodium. Hypothetically then, lack of response to a loop diuretic could occur because so much sodium is reabsorbed proximally that only small amounts reach the loop of Henle. In turn, if acetazolamide decreased proximal sodium reabsorption in this setting, so doing would allow the effect of the loop diuretic to manifest itself. It is important to emphasize that this putative mechanism has never been verified nor have formal clinical trials assessing combinations of acetazolamide and loop diuretics been performed. This cautionary note notwithstanding, there is theoretical rationale for using the combination and anecdotal reports support efficacy. If this strategy is employed, it should be considered after combined loop and thiazide diuretic therapy has failed. Usually, 500 mg of intravenous acetazolamide is followed in 30 to 60 min by a loop diuretic. If acetazolamide is administered by mouth, 2 hr should probably ensue before giving the loop diuretic. A predictable consequence of acetazolamide use will be development of a metabolic acidosis.

Effects of Disease

Since inhibitors of carbonic anhydrase are eliminated by the kidney, decrements in renal function should result in their accumulation in serum. Similarly, since these drugs presumably inhibit solute transport from the luminal side of the nephron, decreased renal function should cause decreased delivery of absolute amounts, and an altered time course of delivery of drug to the site of action. No studies have confirmed these hypotheses or assessed the impact of concomitant disease on response.

OSMOTIC AGENTS

Mannitol as a diuretic is most often used in patients with acute oliguria to prevent acute renal failure and/or convert oliguric to nonoliguric renal failure. When used to treat conditions such as cerebral edema, a predictable diuresis ensues.

In patients with normal renal function, mannitol is eliminated quickly by glomerular filtration (half-life = 1.2 hr) (Table 1). Patients with decreased renal function have a diminished ability to eliminate mannitol (Table 1), which can cause adverse effects. The osmotic effect of mannitol retained in the vascular space draws water into this compartment and can expand volume sufficient to precipitate congestive heart failure. In addition, profound hyponatremia can ensue.

A study in eight subjects summarized in Table 1 demonstrates the retention of mannitol in patients with end-stage renal disease [5]. Mannitol was measured indirectly by osmolal gap and had an elimination half-life of 1.5 days. Elimination was enhanced considerably by hemodialysis, indicating that this modality might prove useful for removing mannitol if deemed necessary; peritoneal dialysis did not remove enough mannitol to be clinically relevant. It

TABLE 1 Pharmacokinetics of Mannitol

	Half-life (hr)
Normal renal function	1.2
End-stage renal disease	36
Hemodialysis	6
Peritoneal dialysis	21

would appear that the potential risks of mannitol administration considerably outweigh any potential benefits in most patients with renal dysfunction.

LOOP DIURETICS

The first loop diuretics were the mercurial agents, which are of historic interest only. The discovery of furosemide opened a new dimension to diuretic therapy, providing an effective agent in many conditions unresponsive to other available diuretics. Additional loop diuretics have since been developed with little if any difference from furosemide in terms of pharmacology. The tangible differences among loop diuretics are in their pharmacokinetics.

Numerous studies have assessed the pharmacokinetics of loop diuretics, the majority of which have been conducted in healthy subjects (Table 2) [8]. Most of the studies in healthy volunteers assessed a young age group; importantly, healthy elderly subjects appear to differ from their young counterparts only insofar as would be predicted by their mildly diminished renal function.

Many studies have assessed concentrations of diuretic in only serum or plasma. Loop diuretics act from the lumen side of the nephron [3]. hence, urinary rather than serum amounts of these diuretics are the major determinants of response [3]. Since these diuretics are highly bound to serum proteins (namely, albumin), they cannot enter the tubular lumen by glomerular filtration and reach this site by active secretion by the organic acid transport pump at the straight segment of the proximal tubule. The relationship between amounts of diuretic at the site of action (urinary loop diuretic excretion rate) and response is shown in Fig. 1. This relationship is defined by a sigmoidally shaped curve. This relationship implies that a threshold concentration must be reached at the site of action before any response occurs. The relationship also allows definition of a maximal response (FE_{Na^+} = 20–25%) and a dose that causes this response.

TABLE 2 Pharmacokinetics of Loop Diuretics in Healthy Volunteers

	Furosemide	Bumetanide	Torsemide
Bioavailability (%)	50 (wide range)	80+	80+
Volume of distribution (liters/kg)	0.16	0.17	0.16
Clearance (ml/min/kg)	2.2	2.6	0.8
Fraction of dose excreted in urine (%)	60	65	20
Half-life (hr)	1.5	1	3–4

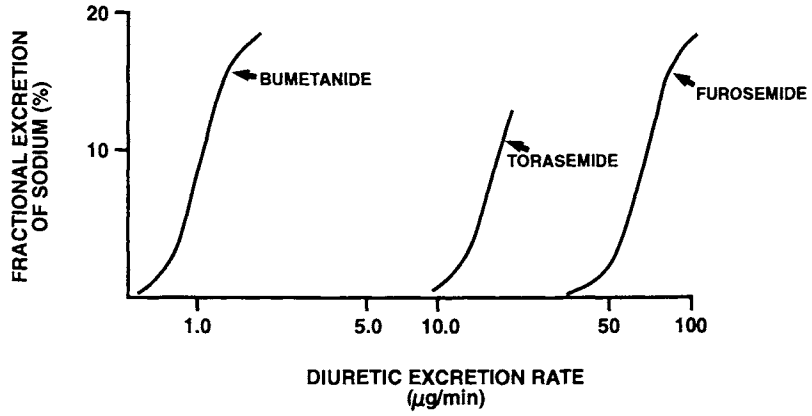

FIGURE 1. Relationship between urinary excretion rate of loop diuretics and diuretic response.

Pharmacokinetics and Pharmacodynamics

Table 2 summarizes pharmacokinetic data in healthy subjects for the most commonly used loop diuretics. These drugs are absorbed quickly with peak serum concentrations attained within 0.5–2 hr. Furosemide exhibits what are called absorption-limited kinetics wherein its rate of absorption is slower than the rate of elimination. This feature manifests clinically as a delay in the peak time at which furosemide appears in blood or urine. In turn, the onset of effect of furosemide after oral dosing is slower than that of other loop diuretics.

The bioavailabilities of loop diuretics differ, with that for azosemide being only 10%, bumetanide and torsemide 80–100%, and furosemide intermediate at 40–60%. These differences are important in switching from an intravenous (iv) to an oral formulation in that those with lesser bioavailability require a proportionally higher oral compared to iv dose. Another feature of the bioavailability of loop diuretics is the variability in their absorption. Those diuretics with essentially complete bioavailability (bumetanide and torsemide) have low variability in this parameter. In other words, with these diuretics it is predictable that all of the drug will be absorbed in virtually all patients. This contrasts with furosemide wherein the range of bioavailability is great (10–100%) even in healthy volunteers. Clinicians should appreciate this fact. In switching a patient from intravenous to oral furosemide, it is common practice to administer an oral dose twice that of the intravenous dose, since furosemide's bioavailability averages about 50%. However, for the substantial number of patients absorbing less than 50% of furosemide, this dosage calculation results in their receiving less furosemide than needed. The converse is also true, in that

some patients may receive too great an oral dose. This variability in furosemide absorption is statistically significantly greater than that of torsemide (and likely bumetanide). It likely has clinical ramifications that have not been examined through appropriately designed clinical trials.

Clearance, volume of distribution, and elimination half-life of azosemide, bumetanide, furosemide, and piretanide are similar. Their half-lives are approximately 1–2 hr. These drugs act very quickly if given either orally or iv. By the former route, one can expect an onset of effect within 30–60 min, peaking at 30–120 min with return to baseline within another 2–3 hr. After an intravenous dose, the onset of effect is within minutes, peaking at approximately 30 min and reaching baseline within 2–3 hr. Torsemide is somewhat longer acting with a half-life of 3 to 4 hr and a duration of effect of about 6 hr.

The loop diuretics that are used most frequently differ in their routes of elimination. About half of an intravenous dose of furosemide is excreted into the urine as unchanged drug. Most of the remainder is glucuronidated; it appears that this conjugation occurs in the kidney itself. In contrast, the nonrenal route of elimination of both bumetanide and torsemide is the liver. It has recently been shown that the cytochrome p450 2C9 isoenzyme is responsible for hepatic metabolism of torsemide. The specific isoenzyme responsible for bumetanide metabolism has not been identified.

Muzolimine, xipamide, and ozolinone (the active metabolite of etozolin), none of which are available in the United States, all have longer half-lives of 6 to 15 hr. Because of the longer half-life, these drugs (and torsemide) may be able to be administered less frequently. The short duration of action of the classical loop diuretics means that after a short-lived intense diuresis, there is no pharmacologic effect until the next dose. During this time the nephron can be sufficiently sodium avid to restore sodium balance back to the level before the dose of diuretic (so-called "braking") [9]. A longer-acting diuretic could theoretically obviate this problem. Whether muzolimine, ozolinone, xipamide, or torsemide will have such a benefit awaits clinical trails.

Muzolimine, ozolinone, and xipamide are intriguing drugs. They not only have long elimination half-lives but, additionally, elimination is unchanged in patients with renal insufficiency and congestive heart failure. Numerous questions remain with these drugs. Only negligible amounts of unchanged drug appear in the urine, raising several possibilities: (i) the diuretic is extremely potent so that only trivial amounts are necessary to cause an effect; (ii) the parent drug is not active; or (iii) the diuretic is unique in causing its effect from the blood or peritubular side of the nephron rather than the lumen. If the latter of these possibilities holds, this represents a unique property that could be important clinically. In a condition such as azotemia in which resistance to diuretics is due to insufficient delivery of drug to the urinary site of action (*vide infra*), a diuretic reaching its active site from the peritubular side of the

nephron should still be able to cause a response. Alternatively, the finding of negligible amounts of these drugs in urine might simply mean that an as yet unidentified metabolite is the active species, and it behaves like the other loop diuretics with a lumen site of action, albeit with a more prolonged duration of effect. This appears to be the case with muzolimine. This drug has been withdrawn from study because of severe adverse neurologic effects.

Effects of Disease

In most edematous disorders a degree of resistance to loop diuretics occurs. In other words, most patients do not respond as vigorously to a dose of loop diuretic as does a healthy subject. As noted previously, resistance can occur via pharmacokinetic or pharmacodynamic mechanisms. Since the loop diuretics are active from the lumen side of the nephron, one pharmacokinetic mechanism accounting for diminished response is a disease-induced decrease in diuretic reaching the urine, as occurs in patients with renal insufficiency.

Renal Insufficiency (Table 3)

Renal insufficiency affects the pharmacokinetics of loop diuretics in several ways. All of these drugs but muzolimine, ozolinone, and xipamide are highly bound (>95%) to albumin, thereby preventing filtration at the glomerulus. In azotemic patients, accumulated endogenous organic acids displace these drugs from albumin, increasing the fraction unbound. This effect results in increased amounts of drug reaching the urine by filtration, but the amount is quantitatively negligible compared to that reaching the urine by active secretion.

The accumulated endogenous organic acids have an additional effect on the pharmacokinetics of these drugs. They compete for transport at the organic acid secretory pump of the proximal tubule, diminishing renal clearance, and thereby the amount of drug that reaches the site of action. The effect on total clearance differs among the loop diuretics. Those diuretics with nonrenal clearance via hepatic cytochrome P450 (e.g., bumetanide, torsemide, and xipamide) have preserved nonrenal clearance in patients with renal insufficiency, so that total clearance is minimally changed (Tables 2 and 3). As a consequence, elimination half-life in patients with renal disease is similar to that in healthy subjects. In contrast, the total clearance of furosemide is decreased and half-life prolonged in patients with renal insufficiency, because not only is there a decrease in renal clearance, but also in metabolic clearance. A substantial component of the metabolic clearance of furosemide occurs by glucuronidation; this process appears to occur in the kidney itself. Therefore, decreased renal

TABLE 3 Pharmacokinetics of Loop Diuretics in Edematous Disorders

	Furosemide	Bumetanide	Torsemide
Severe renal insufficiency			
Half-life (hr)	2.6	1.6	4–5
Clearance (ml/min/kg)	0.8	1.6	1.0
Fraction excreted unchanged (%)	9	5	2–3
Cirrhosis			
Half-life (hr)	2.8	2.3	8.4
Clearance (ml/min/kg)	1.5	0.6	0.5
Fraction excreted unchanged (%)	50	70	27
Congestive heart failure			
Half-life (hr)	2.7	1.3	6
Clearance (ml/min/kg)	1.6	2.2	0.5
Fraction excreted unchanged (%)	60	60	17

function impairs both elimination pathways for furosemide. In turn, decreases in both renal and metabolic clearances cause total clearance to decline substantially with a concomitant increase in elimination half-life. There is no evidence that absorption or volume of distribution of loop diuretics changes in uremia.

These pharmacokinetic changes result in decreased total amount of drug reaching the site of action (Table 3). In addition, for furosemide, but not bumetanide or torsemide, appearance in the urine is delayed over time. The clinical ramifications of these changes are a less intense effect of all loop diuretics and a more prolonged effect of furosemide in patients with uremia as compared to healthy volunteers.

In patients with renal insufficiency, obtaining a diuretic effect requires administering a large enough dose of drug to deliver effective amounts of the diuretic into the urine even with a greatly diminished renal clearance. The urinary excretion rate of a drug is equal to the product of its serum concentration and renal clearance. Thus, any decrease in renal clearance of a loop diuretic will require a proportional increase in serum concentration (and dose) to cause the same amount of diuretic to reach the urine.

Several studies have explored the dose of furosemide, bumetanide, or torsemide needed to deliver effective amounts of diuretic into the urine of patients with severe renal insufficiency [4]. Single intravenous doses of 120–160 mg of furosemide, 6 to 8 mg of bumetanide, and 50 to 100 mg of torsemide were sufficient to reach the upper plateau of the concentration–response curve. These data mean that such doses are capable of causing the maximally attainable response in patients with severe renal insufficiency. In turn, larger single doses would be unwarranted in such patients.

These studies also documented that remnant nephrons responded normally in patients with endstage renal disease; i.e., the pharmacodynamic component

of response [4]. Since this component of response to bumetanide, furosemide, and torsemide was normal, diuretic resistance in patients with decreased renal function occurs by a pharmacokinetic mechanism.

Nephrotic Syndrome

Patients with nephrotic syndrome often require large doses of loop diuretics despite having essentially normal glomerular filtration rate and renal clearance of diuretic similar to healthy volunteers. This normal renal clearance means that there is no deficit in drug delivery to the site of action in such patients. The hypoalbuminemia in this disorder is associated with decreased protein binding that results in a slight increase in volume of distribution and clearance of total drug. Pharmacokinetics of the unbound drug, however, are unchanged [1, 3, 4, 12].

The most extreme example of the effects of hypoalbuminemia is the analbuminemic rat. This strain of rat has no albumin whatsoever. If furosemide is administered to this strain of rat, its volume of distribution is 10 times higher than in control animals, because there is no binding to circulating albumin, which in control animals restricts the diuretic to the intravascular space. In turn, less drug is delivered to proximal tubular secretory sites, and thereby less diuretic reaches intratubular sites of action in these rats. Diuretic response is concomitantly decreased. In these animals, administration of furosemide mixed with albumin predictably results in retention of the diuretic in the intravascular space, a return of volume of distribution toward normal, greater delivery of diuretic into the urine, and restoration of diuretic response. These findings, coupled with anecdotal reports, have raised the question as to whether administration of a mixture of loop diuretic and albumin is a logical therapeutic strategy in patients with nephrotic syndrome or other causes of hypoalbuminemia. Though no adequately controlled trials have addressed this question, it is important to stress that this strategy is predicated on the notion of enhancing delivery of diuretic into the urine. Three studies of the pharmacokinetics of loop diuretics in patients with nephrotic syndrome, however, indicate that delivery to the urinary site of action is not a problem in these patients, nor in those with cirrhosis (*vide infra*). These pharmacokinetic studies have, for the most part, studied patients with serum albumin concentrations of 2 g% or higher. As such, it seems safe to conclude that patients with albumin concentrations of 2 g% or greater are highly unlikely to benefit from loop diuretic–albumin mixtures. Whether patients with severe hypoalbuminemia might benefit is unknown; until conduct of a proper trial, such therapy should be considered experimental.

In animals rendered nephrotic and in man, furosemide (and presumably other loop diuretics) delivered into protein containing urine binds to albumin

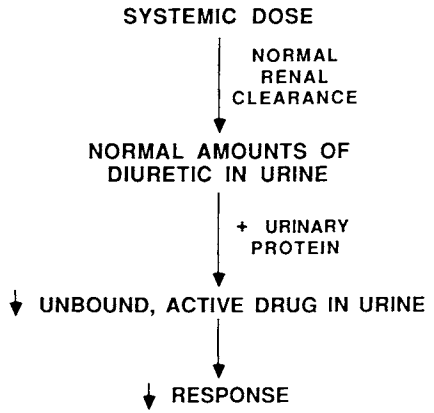

FIGURE 2. Schematic illustration of the role of albumin binding of loop diuretic to diminish diuretic response.

[11]. Theoretically, this binding to protein could prevent interaction of the diuretic with its active site and thereby cause a diminished response (Fig. 2). That this mechanism is operative is supported by studies in rats using the technique of *in vivo* microperfusion [11]. As would be expected, perfusion of the loop of Henle with a solution containing furosemide blocked solute reabsorption. When albumin was added to this solution, the response to furosemide was dramatically blunted [11]. In another set of experiments, it was shown that displacement of the furosemide from albumin restored efficacy of the diuretic. If these data can be extrapolated to man, binding of loop diuretic to luminal albumin accounts for a component of diuretic resistance in patients with nephrotic syndrome. Whether this mechanism explains all of the altered response that occurs is doubtful. If binding to urinary albumin were the sole mechanism, a normal response could be elicited by administering a sufficiently large dose to deliver normal amounts of unbound drug to the site of action. However, even with large doses of loop diuretics, there is still a diminished response, implying that other mechanisms also contribute to diuretic resistance in nephrotic syndrome. Possible additional mechanisms of altered pharmacodynamics include those which can be invoked in all the edematous disorders, namely, increased proximal and/or distal reabsorption of solute, the former preventing delivery of sodium to the site of action of the loop diuretic and the latter reclaiming sodium rejected from the loop of Henle [4]. A third putative mechanism is alteration of the receptor for the loop diuretic itself. Interestingly, the same technique of *in vivo* loop microperfusion in nephrotic animals showed that solute reabsorption at the loop of Henle is indeed altered, suggesting that at least a component of the altered pharmacodynamics occurs at the loop itself.

These findings can help design a rational therapeutic strategy for patients

with nephrotic syndrome. In a patient with nephrotic syndrome, one should first titrate the dose upward, either iv or oral (since absorption is normal), in order to find an effective dose. The maximum dose that should be used is speculative, but in a patient with normal renal function, even if 2/3 of drug in the urine is bound to albumin, the upper plateau of response to furosemide should be reached with 80 to 120 mg intravenous doses (or the equivalent of other loop diuretics). There seems little rationale for using larger single doses unless there is a concomitant decrease in glomerular filtration rate. Once this dose titration has occurred and an effective dose is ascertained, it then needs to be administered at a dosing frequency dictated by the needed cumulative natriuresis. For example, if the effective dose cause 50 mEq of sodium to be excreted and a total excretion of 150 mEq is needed in a 24-hr period, then the effective dose needs to be given on three occasions throughout the day.

Patients refractory to large doses of loop diuretics may require combination therapy with thiazide diuretics [6]. If these strategies do not attain an adequate response, more aggressive treatment of the primary disease may be required.

Cirrhosis (Table 3)

In patients with cirrhosis who are hypoalbuminemic, protein binding is decreased with consequent effects on volume of distribution and clearance. Bioavailability is normal, though the rate of absorption is slowed. Overall, unless renal function is compromised, diuretic delivery into urine is normal (Tables 2 and 3); as such, resistance is pharmacodynamic in nature. The possible mechanisms for such resistance include increased solute reabsorption at the proximal or distal tubule and/or alterations in the receptor for loop diuretics.

A few studies have shown that some patients with severe cirrhosis have impaired delivery of diuretic into urine, presumably due to mild decreases in renal function. In such patients larger doses will attain adequate amounts of diuretic in the urine. Even including such patients, however, there seems little rationale for administering single intravenous doses of furosemide greater than 40 mg (or the equivalent dose of other agents or formulations).

Congestive Heart Failure (CHF) (Table 3)

Bioavailability of loop diuretics is no different in patients with CHF compared to healthy controls [1, 3, 4, 12]. Consequently, delivery of total amounts of diuretic to the urinary site of action is normal in CHF and cannot be invoked as a mechanism of resistance to loop diuretics. Despite prior speculation to the contrary, it is unlikely that malabsorption occurs in any but unusual circumstances.

TABLE 4 Time of Peak Diuretic Concentration (mins) as a Reflection of Speed of Absorption in Healthy Subjects and in Patients with CHF

	Furosemide	Bumetanide	Torsemide
Healthy subjects	108 ± 20	72 ± 7	52 ± 11
Congestive heart failure			
Compensated	180 ± 30	180 ± 19	66 ± 54
	177 ± 21		
	144 ± 150		
Decompensated	242 ± 25		

Though bioavailability is not affected by CHF, the time course of absorption is altered (Table 4). Studies with bumetanide and furosemide show a delay in the time of peak concentration in both serum and urine compared to healthy subjects. Interestingly, torsemide may not have a similar delay. This delay could occur from a prolongation of the lag time for absorption, a slowed rate of absorption, or both. Since the delayed peak concentration is also approximately half of that which occurs in normal subjects, a component of slowed rate of absorption must occur. Slowed absorption is of the greatest degree in patients with decompensated heart failure. In decompensated CHF, the lag time for absorption has been shown to be markedly increased with a diminished peak concentration. Attainment of dry weight resulted in changes of these parameters toward, but not to, normal.

It is conceivable that the observed changes account in part for resistance to oral loop diuretics in CHF, particularly in the decompensated state. Simplistically, if a threshold concentration is needed to elicit a response, then the decrease in peak concentration caused by slowed absorption could be sufficient that the threshold is not reached and no response occurs despite absorption of the same amount of drug as occurs normally. In turn, response would occur only at increased oral doses that would be disproportionately large compared to effective intravenous doses.

It is important to reemphasize that even when an effective oral dose is administered, response to oral drug will be delayed in patients with CHF. If a rapid response is desired, one must administer the diuretic parenterally; otherwise the onset of effect may be delayed several hours and the time at which it occurs is unpredictable.

In general, total body and renal clearance tend to be lower and elimination half-life longer in patients with CHF (Tables 2 and 3); these differences are due to diminished renal function, either intrinsic or secondary to severe heart disease. In patients with CHF with relatively normal renal function, normal amounts of loop diuretic are delivered into the urine. Consequently, in such

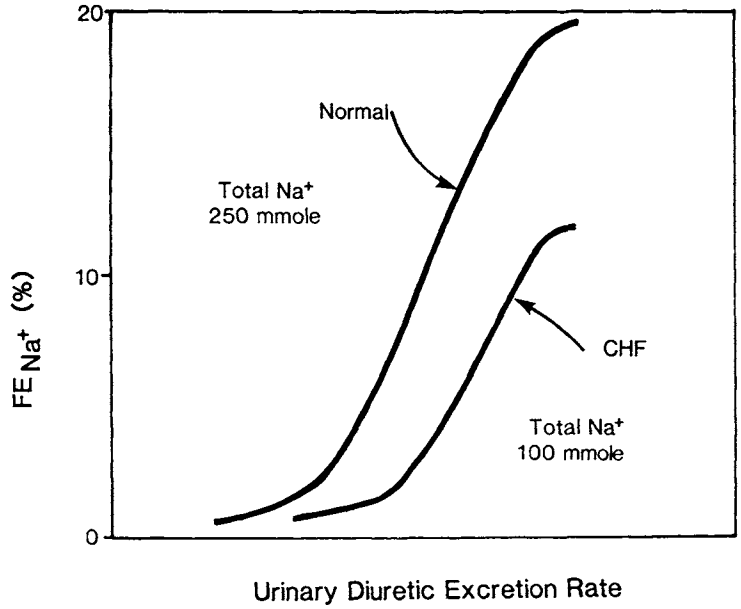

FIGURE 3. Schematic illustration of the changed pharmacodynamics of response to loop diuretics that occurs in patients with CHF.

patients resistance to intravenous diuretic cannot be accounted for by pharmacokinetic mechanisms.

Studies have shown dramatic changes from normal in pharmacodynamics in patients with CHF (Fig. 3). This undoubtedly is the major mechanism of resistance in these patients [4]. The mechanism(s) of this change is unknown, but the same possibilities can be invoked as discussed previously, namely, increased solute reabsorption at the proximal and/or distal nephron and changed dynamics of the receptor–diuretic interaction.

Since in most patients with CHF, normal amounts of diuretic are delivered to the site of action, little is to be gained by administering large doses. Single intravenous doses of 80 to 120 mg of furosemide or the equivalent of other loop diuretics should suffice even in patients with modest declines in renal function. If the patient does not respond adequately to such doses, combination of loop diuretics with thiazides should be attempted [6].

Children

The pharmacokinetics and pharmacodynamics of loop diuretics have not been rigorously assessed in healthy children. Neonates who received furosemide via

transplacental passage after their mothers received it for toxemia of pregnancy show prolonged elimination half-lives, which correlated inversely with gestational age. This observation probably represents the immaturity of the kidney at the various stages of development of the neonate.

Newborns have prolonged elimination half-lives of furosemide, which for the most part appear to be due to decreased clearance, with one study showing an increased volume of distribution. Prematurity or nephrotic syndrome does not seem to have an additional substantive influence on these parameters. Because of the longer half-life, newborns probably need dosing with loop diuretics less frequently. Presumably, the diseases for which loop diuretics are administered to children cause the same abnormalities in dynamics of response as in adults. Therapeutic strategies would then be similar.

Older children with nephrotic syndrome, and with hypertension reveal disposition of furosemide identical to adults when factored on a body weight basis.

SUMMARY

Both pharmacokinetic and pharmacodynamic changes that account for resistance to loop diuretics (Table 5). A pharmacokinetic mechanism is responsible

TABLE 5 Mechanisms of Resistance to Loop Diuretics

Disease	Pharmacokinetic Mechanism	Pharmacodynamic Mechanism
Renal insufficiency	Decreased amount and rate of delivery of drug into urine—competition for drug secretion by endogenous organic acids	None
Nephrotic syndrome	Binding of drug to urinary protein	Increased solute reabsorption at Proximal nephron Distal nephron Altered diuretic receptor?
Cirrhosis	None if renal function is normal	Increased solute reabsorption at Proximal nephron Distal nephron Altered diuretic receptor?
Congestive heart failure	Decreased rate of absorption; worse in decompensated state	Increased solute reabsorption at Proximal nephron Distal nephron Altered diuretic receptor?

for resistance in azotemia, while a pharmacodynamic mechanism is operative in cirrhosis and CHF (after iv dosing). If CHF and cirrhosis are associated with decrements in renal function, a pharmacokinetic component also plays a role. Last, oral dosing in CHF is associated with a minor pharmacokinetic abnormality (delayed absorption), which may also contribute to altered response.

THIAZIDE DIURETICS

Thiazide diuretics are available in many preparations both singly and in combination. This group of diuretics also includes chlorthalidone, indapamide, metolazone, and quinethazone; though not chemically benzothiadiazides, these drugs have sites of action identical to those of the classic thiazides. They are also used in the same clinical settings and can be used interchangeably. The only differences among all these drugs are potency (not efficacy) and duration of action.

Most studies of thiazide pharmacokinetics have been conducted in young healthy subjects. As with loop diuretics, thiazide diuretics reach their site of action from the urine rather than the blood side of the nephron. As such, measurement of amounts in urine is more meaningful than in blood; unfortunately, most pharmacokinetic studies focus on the latter. Far less is known of the pharmacokinetics of this group of drugs than the loop diuretics, even though they have been used clinically for a much longer period of time. Moreover, no studies have assessed the pharmacodynamics of response as has been attempted with the loop diuretics.

PHARMACOKINETICS AND PHARMACODYNAMICS (TABLE 6)

The onset of effect of thiazide diuretics is fairly rapid, and peak concentrations of drug are attained within 1.5–4 hr with no differences among the agents (Table 6) [10], with the possible exception of chlorthalidone, wherein a delayed peak effect has been reported (8–10 and 14 hr). These data disagree with an earlier report indicating peak effect in 1 to 3 hr; the reasons for the discrepant data are unclear.

After an oral dose, the amount of drug reaching the urine varies greatly among these agents with indapamide the lowest at approximately 5% ranging up to 40–70% for chlorthalidone, hydrochlorothiazide, hydroflumethiazide, and trichlormethiazide (Table 6). This variability among drugs could represent differences in absorption from the gastrointestinal tract, differences in renal clearance, or the combination. Differentiating these possibilities requires studies with both oral and intravenous administration. Since an intravenous prepa-

TABLE 6 Pharmacokinetics of Thiazide Diuretics

	Bioavailability (%)	% of dose excreted unchanged	Half-life (hr)
Bendroflumethiazide		20–50	2.5–9
Chlorthalidone	64	65	24–55
Chlorothiazide	30–50	10–20	15–27
Clopamide			8–12
Hydrochlorothiazide	65–75	40–80	3–29
Hydroflumethiazide	73	40–75	6–25
Indapamide	93	2–6	15–25
Mefruside		1	3–12
Polythiazide		3–32	26
Tizolemide			3–8
Trichlormethiazide		60–100	1–4

ration is available only for chlorothiazide, it is unlikely that definitive data are forthcoming.

The differences in duration of effect of the different thiazides as reflected by their elimination half-lives may be of most clinical relevance. Short-acting drugs, with half-lives of approximately 2 to 5 hr include bendroflumethiazide, hydrochlorothiazide, tizolemide, and trichlormethiazide. Medium-acting drugs include chlorothiazide, hydroflumethiazide, indapamide, and mefruside. Long-acting agents include chlorthalidone, metolazone, and polythiazide. Whether these differences are important clinically is unclear, for the biologic effect of these drugs, particularly as antihypertensives, may be prolonged compared to their elimination rates. In addition, though the longer-acting agents may have an advantage of less frequent administration, they allegedly cause more potassium loss.

Indapamide and mefruside are two agents with interesting features. Only minor amounts of indapamide appear in the urine. Consequently, it must either act from the peritubular side, be active at very low concentrations in urine, or be inactive as the parent drug but yield an active metabolite. The diuretic effect is delayed relative to urinary excretion of the parent drug, suggesting that an active metabolite may be formed.

Mefruside is also eliminated in minor amounts in the urine; it has a short elimination half-life, but the diuretic effect is prolonged. Both metabolites of this drug, a lactone and an hydroxycarboxylic analog, are delivered into the urine in substantial quantities, have longer half-lives than the parent drug, and are likely candidates as the active species of this diuretic.

Effects of Disease

Few studies have assessed the pharmacokinetics and pharmacodynamics of thiazide diuretics in the clinical conditions in which they are used. In general, changes seem to be similar to those discussed with loop diuretics. No studies have assessed pharmacodynamics. Patients with decreased renal function have slowed elimination of tizolemide and trichlormethiazide with an inverse correlation of elimination half-life with creatinine clearance. This effect would presumably result in a diminished peak diuresis and a prolonged response compared to healthy subjects. No studies have assessed this hypothesis, probably because thiazides are relatively ineffective in patients with decreased renal function. One study showed no difference from normal in the time at which the peak concentration of chlorothiazide occurred in patients with cirrhosis.

The influence of CHF on the disposition of chlorothiazide, hydrochlorothiazide, and hydroflumethiazide has been assessed. As with loop diuretics, patients with concomitant decreases in renal function had longer half-lives of elimination. In contrast to loop diuretics, CHF does not delay absorption of the thiazides. Consequently, patients with CHF with relatively normal renal function do not differ from healthy subjects in the pharmacokinetics of thiazide diuretics.

POTASSIUM-RETAINING DIURETICS

Spironolactone

The disposition of spironolactone is complex and not completely elucidated. In addition, it is not clear whether spironolactone itself or one or more metabolites is the predominant active compound. Spironolactone (half-life of about 1.5 hr) is rapidly converted to canrenone and other metabolites, including 7α-thiomethylspirolactone and a 6α-hydroxy-7α-thiomethylspirolactone [10], all of which have half-lives of about 15 hr. Early studies using combinations of radiolabeled drug and fluorimetric techniques concluded that approximately 80% of spironolactone was converted to canrenone, which was thought to be the active moiety. In 21 subjects, canrenone attained peak concentrations about 5 hr after an oral dose of spironolactone and was eliminated with a half-life of 17–72 hr. Neither hepatic ($n = 6$) nor renal disease influenced the pharmacokinetics of canrenone or the conversion of spironolactone to canrenone.

The development of more specific assays allowed discovery that spironolactone is rapidly converted to the 7α-thiol which then loses H_2S to form canrenone. However, this intermediate can undergo further metabolic degradation to the 6α-hydroxy-7α-thiol and other unidentified compounds that may be active and may account for the major portion of spironolactone's biologic effects. Studies in over 50 healthy subjects showed that canrenone accounted for ap-

proximately 1/10 of the antimineralocorticoid effect after acute dosing and at most 1/3 after chronic dosing. A more recent study in four healthy men concluded that activity resided in spironolactone itself and the 7α-thiol. In contrast, yet another study showed spironolactone to be a minor species compared to the 7α-thiol and the 6α-hydroxy-7α-thiol and concluded that activity resided predominantly in these metabolites. Hence, the identity of the active species has not been satisfactorily resolved, though it appears that neither spironolactone itself nor canrenone accounts for activity.

Interestingly, the heretofore determined pharmacokinetics of canrenone during dosing of spironolactone indicate that it is formation-rate limited. When canrenone itself was administered to five healthy subjects, an elimination half-life of 2.5–5.5 hr, and clearance of 3.0–7.3 ml/min/kg was found in contrast to a half-life of about 15 hr in studies where spironolactone was given.

Spironolactone must be titrated to a dose sufficient to block the effects of primary or secondary aldosteronism. This dose may vary widely among patients and can be determined only by titration in an individual. The prolonged half-lives of the active species fit well with clinical observations that it takes at least 3 to 4 days of dosing to reach peak effect.

Amiloride and Triamterene

In contrast to spironolactone, amiloride and triamterene inhibit distal nephron sodium reabsorption by non-aldosterone-dependent mechanisms. They block sodium entry from the luminal surface of distal nephrons.

Scant data are available concerning amiloride [13]. In six healthy subjects (age 35–56 years) peak concentrations occurred at 4 hr with elimination half-lives ranging from 7 to 11 hr. This study employed radiolabeled compound and therefore lacks specificity. Another study with better precision using thin layer chromatography (TLC) confirmed that peak concentrations occur at 3–4 hr but found an elimination half-life of 17–26 hr. Since 40–60% of an amiloride dose is eliminated unchanged in the urine, one would predict diminished clearance and a prolonged half-life in azotemic patients. In five subjects with varying degrees of azotemia, half-lives ranged from 8 to 144 hr with the most prolonged values in the patients with the lowest levels of renal function. A more accurate study using TLC in 9 patients found a half-life of about 100 hr in patients with endstage renal disease, and a study in elderly subjects with decreased renal function coincident with aging found renal clearance values 1/3 of those of young controls.

Amiloride reaches the urine by active secretion at the organic base transport pump of the proximal tubule. This contrasts with the organic acid secretory pathway for loop and thiazide diuretics. As such, amiloride transport is suscep-

tible to blockade by other organic bases such as trimethoprim, cimetidine, ranitidine, and procainamide.

Triamterene itself has low diuretic activity and approximately 80% of it is converted first to para-hydroxytriamterene and then to the sulfuric acid ester of the para-hydroxy metabolite, which accounts for diuretic activity [7]. In 6 healthy subjects after oral dosing, peak concentrations of the parent compound occurred within 0.8 to 2.3 hr and that of the active metabolite within 1.1 to 1.7 hr. Consequently, there is a rapid onset of diuretic effect. Bioavailability is 83%.

The elimination half-lives of the parent drug and metabolite are similar, ranging from 3.3 to 5.1 hr and from 2.1 to 5.3 hr, respectively. Clearance is 0.06 $\pm$ 0.02 ml/min/kg with a volume of distribution of 13.4 $\pm$ 4.9 liters/kg. Consequently, triamterene is both absorbed and eliminated quickly, which accounts for the need for multiple (2 to 3) daily doses.

Because of triamterene's complex pharmacokinetics, one would predict important influences of hepatic and renal disease. Liver disease results in impaired biotransformation to the active metabolite so that the half-life of the parent drug is prolonged to approximately 13 hr with no change in elimination of the metabolite. Since smaller amounts of active metabolite are formed, larger doses of triamterene would be required in such patients. This strategy, however, would result in elevated and potentially toxic concentrations of the parent drug. A better alternative would be to use a different agent.

In contrast, renal insufficiency does not affect excretion of the parent drug but dramatically prolongs elimination of the active metabolite and decreases its renal clearance. Since triamterene should be avoided in patients with decreased renal function, the consequence of these changed kinetics is moot.

As with amiloride, triamterene acts from the urine side of the nephron. Triamterene is also a basic compound and is secreted into the urine by the organic base pathway. Consequently, other basic drugs such as cimetidine, procainamide, and trimethoprim potentially interact. To this end, cimetidine has been shown to inhibit the renal secretion of triamterene. However, as indicated above, activity of this diuretic resides in a sulfate metabolite, the appearance in the urine and effects of which were not altered by cimetidine. Pharmacodynamic data are not available for triamterene.

Overall, amiloride and triamterene are similar in clinical use, both having considerably shorter half-lives than spironolactone and thereby requiring less time to achieve a steady-state effect. The elimination of amiloride is somewhat slower than that of triamterene and may require less frequent dosing. In patients with hepatic disease, amiloride seems preferable to triamterene to avoid the problems of conversion of the latter to its active metabolite. All of these drugs, including spironolactone, should be avoided in patients with renal disease.

These distally acting diuretics are usually used for their potassium-retaining properties. However, they can be useful for enhancing natriuresis, particularly in patients already receiving loop diuretics or combinations of loop and thiazide diuretics. Importantly, one can predict in which patients an additive natriuretic effect will occur by assessing the pattern of sodium and potassium excretion in a urine sample. If concentrations of both sodium and potassium are low, then insufficient amounts of sodium are being delivered distally for exchange with potassium. Hence, in this setting, distally acting diuretics will have no effect. In contrast, if concentrations of sodium are low, but potassium concentrations are high, then distal exchange is occurring and distally acting agents will have an effect.

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CHAPTER IVB1

Adaptation to Diuretic Drugs

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INTRODUCTION

When a diuretic drug is first administered to a normal individual or to a patient with an edematous disorder (see Fig. 1), rates of urinary sodium and chloride excretion usually increase above baseline, leading to a period of negative sodium and chloride balance. This natriuresis (and chloriuresis) is a hallmark of effective diuretic therapy of edema. Yet within several days to several weeks, net daily solute and water losses decline and eventually approach prediuretic levels despite continued drug administration. These changes in diuretic responsiveness result from adaptive processes that occur during diuretic therapy in every individual. When these processes become manifest once the desired extracellular fluid (ECF) volume has been attained, they are clinically useful and prevent progressive ECF volume contraction. When these same processes develop prior to achieving the desired ECF volume, they would be viewed as contributing to diuretic resistance. Because specific therapeutic approaches can be devised to overcome these adaptations, an understanding of renal adaptations to diuretic treatment is crucial for a rational approach to the diuretic resistant patient. This chapter will categorize adaptations to diuretic treatment according to the time at which they develop. *Immediate adaptations* limit the intrinsic potency of diuretic drugs; they occur during the initial diuretic-induced

Diuretic Agents: Clinical Physiology and Pharmacology

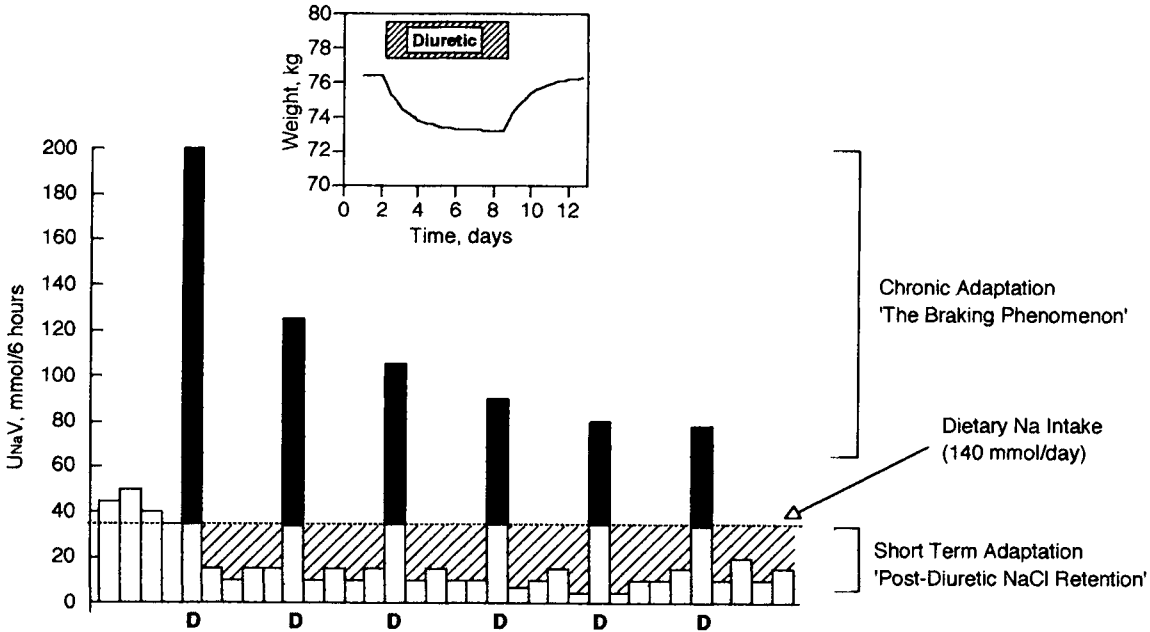


FIGURE 1. Effects of diuretics on urinary Na excretion and extracellular fluid volume. (Inset) Effect of diuretic on body weight, taken as an index of extracellular fluid volume. Note that steady state is reached within 6–8 days despite continued diuretic administration. (Main graph) Effects of loop diuretic on urinary Na excretion. Bars represent 6-hr periods before (in Na balance) and after doses loop diuretic (D). The dotted line indicates dietary Na intake. The solid portion of bars indicates the amount by which Na excretion exceeds intake during natriuresis. The hatched areas indicated the amount of positive Na balance after the diuretic effect has worn off. Net Na balance during 24 hr is the difference between the hatched area (postdiuretic NaCl retention) and the solid area (diuretic-induced natriuresis). Chronic adaptation is indicated by progressively smaller peak natriuretic effects (the braking phenomenon) and is mirrored by a return to neutral balance, as indicated in the inset. As discussed in the text, chronic adaptation requires ECF volume depletion.

natriuresis and generally result from intrinsic renal processes. *Short-term adaptations* occur after the initial effect of the diuretic drug has worn off and may result from both systemic and intrarenal processes. *Chronic adaptations* occur only when diuretic drugs have been administered during a long period of time (weeks to months). Because diuretic resistance is most commonly observed in patients who have received high doses of diuretic during a long period of time, these chronic adaptations may be especially relevant to the phenomenon of diuretic resistance in patients.

IMMEDIATE ADAPTATIONS

About 25 mol of sodium are filtered every day by the kidneys in a normal human. Because dietary salt intake on a Western diet is typically 130–260 mmol daily, approximately 3 pounds of salt (17 mol = 1 kg NaCl) must be reabsorbed every day by the renal tubules to maintain salt balance. All sodium chloride reabsorption along the mammalian nephron is driven by the action of Na/K ATPase, which is present along the basolateral cell membrane of most renal epithelial cells. Transepithelial sodium transport occurs because apical transport pathways permit Na to move down its electrochemical gradient from tubule lumen to cell, often coupled to the movement of other ions across the same membrane. Most diuretic drugs act by inhibiting apical Na transport pathways. Because apical Na transport pathways are nephron segment specific, each class of diuretic inhibits Na transport *predominantly* along a single segment of the nephron. As an example, loop diuretics inhibit Na/K/2Cl cotransport at the apical membrane of medullary and cortical thick ascending limb cells. Although loop diuretics have effects along other segments of the nephron (the proximal tubule and perhaps medullary collecting duct), these are relatively minor compared with their effect of inhibiting NaCl reabsorption along the loop of Henle. The axial organization of renal tubules and the nephron segment-specific inhibition of salt transport by diuretics means that diuretics have both direct effects and indirect effects on solute transport along the nephron.

When NaCl reabsorption along the thick ascending limb is inhibited by loop diuretics, the NaCl concentration in fluid that enters the distal tubule is greatly increased (see Fig. 2a). In one study, the Na concentration in fluid entering the distal tubule of rats rose from 42 to 140 mM during acute loop diuretic infusion [15]. The increased luminal NaCl concentration led to increased Na absorption along the distal tubule (from 148 to 361 pmol/min) [15] because NaCl transport varies directly with the luminal NaCl concentration and loop diuretics have little or no effect on ion transport along the distal tubule (see Fig. 2b). The bulk of the increased NaCl transport along the distal tubule appears to result from enhanced transcellular transport via the thiazide-sensitive Na/Cl

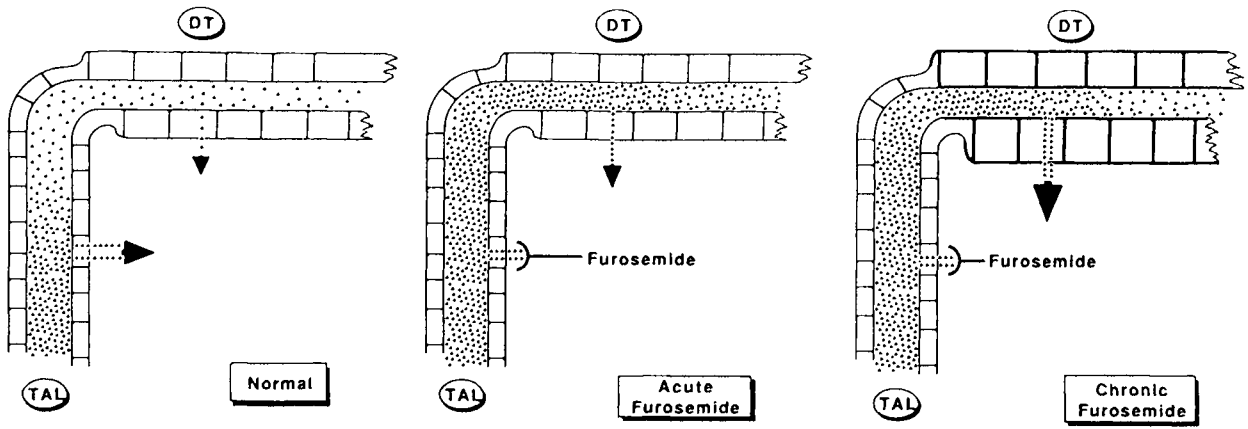


FIGURE 2. Effects of furosemide on ion transport along the thick ascending limb (TAL) and distal tubule (DT). Dots represent NaCl. Under normal conditions (left), the TAL dilutes tubule fluid and the NaCl concentration in fluid entering the DT is low. When furosemide (or other loop diuretic) is administered acutely (middle), NaCl reabsorption along the TAL declines and NaCl concentration in fluid entering the DT rises. When this process continues (right), cells in the DT enlarge and reabsorb more NaCl. Because more NaCl is now reabsorbed by the DT, the amount of NaCl leaving the DT declines back toward control values (compare the amounts leaving the DT in the left and the right panels). (From Ellison, D. H. in Diuretics IV. Exerpta Medica, Amsterdam 1993, with permission).

cotransporter. In microperfused rat distal tubules, raising the luminal NaCl concentration twofold increased transepithelial Na transport by a factor of 3; this increase could be blocked entirely by luminal chlorothiazide [9]. The dependence of transepithelial NaCl transport on luminal NaCl concentration probably results from a dependence of the thiazide-sensitive Na/Cl cotransporter on extracellular Na and Cl concentrations [11].

This first level of adaptation to diuretic drugs, exemplified in Fig. 2b, occurs *during* the period of diuretic-induced natriuresis [43]. The *net* effect of acute diuretic administration on urinary Na and Cl excretion, therefore, reflects the sum of effects in the diuretic-sensitive segment (inhibition of NaCl reabsorption) and in diuretic-insensitive segments (secondary stimulation of NaCl reabsorption). Although the most clinically important example of this form of adaptation involves loop diuretics, these compensatory processes occur during administration of most classes of diuretics. The importance of compensatory processes to blunt the acute effects of diuretics is exemplified by carbonic anhydrase inhibitors which inhibit Na transport across cells of the proximal tubule. The proximal tubule reabsorbs approximately 2/3 of the filtered Na load, suggesting that proximal diuretics might be very potent. Instead, because a large portion of the Na that is rejected by the proximal tubule during carbonic anhydrase inhibitor administration is reabsorbed along the loop of Henle and distal tubule, only a fraction escapes into the urine. Carbonic anhydrase inhibitors, therefore, are drugs of only modest potency. As is discussed in Chapter X on Intensive Diuretic Treatment, blockade of immediate adaptive processes enhances the effects of the administered diuretic.

SHORT-TERM ADAPTATIONS

POSTDIURETIC NACL RETENTION

The half-life of most diuretics (especially the loop diuretics; see Chapter IVA) is relatively short. Thus, serum diuretic concentrations are often below the natriuretic threshold during a portion of each day, except when the drugs are infused constantly. Even during continuous diuretic infusion, however, water and solute losses will decline as ECF volume falls [7]. This second type of adaptive response to diuretic administration occurs after the peak natriuresis has occurred and is most prominent when the drug concentration in plasma and tubular fluid declines below the diuretic threshold. In this situation, diuretic is no longer present in tubule fluid to inhibit renal Na reabsorption and a period of NaCl retention, often termed "postdiuretic NaCl retention" begins (see Fig. 1). The net effect of the diuretic drug during 24 hr, therefore, results from a period of natriuresis (when NaCl transport is inhibited by the diuretic)

and a period of anti-natriuresis (when the drug concentration is low, before the next dose is given).

Mechanisms that contribute to postdiuretic NaCl retention have been investigated intensively and may be grouped into three classes: *first,* factors that result from changes in extracellular fluid volume; *second,* factors that result from diuretic-induced increases in distal sodium, chloride, and fluid delivery; and *third,* factors that result from direct effects of diuretic drugs on tubule transport processes. One signal initiating NaCl retention in the postdiuretic period is the change in extracellular fluid volume and the change in "effective" arterial blood volume. Evidence indicating a central role for changes in ECF volume includes the observation that postdiuretic NaCl retention can be prevented by administering Na, K, and Cl at rates sufficient to equal diuretic induced losses [2]. This observation does not, however, exclude a contributory role for mechanisms that occur independent of changes in ECF volume, as will be discussed below.

Diuretic drugs have effects on vascular and ECF volume within minutes of administration, both because of their ability to increase renal Na and Cl excretion and because they have direct vascular effects. These changes activate a number of physiological control systems which tend to favor NaCl retention and act to attenuate further NaCl loss. Important contributors to ECF volume dependent NaCl retention include changes in the glomerular filtration rate, activation of the renin/angiotensin/aldosterone system, stimulation of efferent renal sympathetic nerves, suppression of atrial natriuretic peptide secretion, and suppression of renal prostaglandin secretion. Postdiuretic NaCl retention has been shown to occur in humans whether dietary NaCl intake is high or low, suggesting that true ECF volume depletion may not be essential, but a decline in ECF volume was shown to be necessary for secondary NaCl retention during furosemide-induced natriuresis in rats. In rats given furosemide continuously, the secondary decline in NaCl excretion was associated with a 25% decline in glomerular filtration rate, suggesting that decreases in filtered NaCl load contribute to the short-term adaptation to diuretic treatment [7]. On the other hand, changes in glomerular filtration rate were reported to be statistically insignificant during postdiuretic NaCl retention in normal humans [42]. When the data from all groups studied in this paper are combined, a significant decline in glomerular filtration rate (GFR) is apparent in the postdiuretic period [42], even in normal humans; yet the magnitude of this effect is small and increases in NaCl reabsorption probably play a larger role.

One mechanism that may mediate a decline in GFR after loop diuretic drug concentrations decline may be activation of the tubuloglomerular feedback system. This control system operates at the single nephron level to reduce GFR when the delivery of Na and Cl to the macula densa increases. Loop diuretics block this system directly by interfering with Na and Cl uptake by macula densa cells. Thus loop diuretics tend to maintain the GFR higher than would

be expected in the absence of diuretic action. When the diuretic concentration declines and the inhibitory effects at the macula densa wane, the tubuloglomerular feedback system is poised to respond again to NaCl delivery and to suppress the GFR, thus contributing to postdiuretic NaCl retention.

Diuretic drugs stimulate the renin–angiotensin–aldosterone axis via several mechanisms. Diuretic-induced volume depletion can enhance renin secretion, but loop diuretics also stimulate renin secretion by blocking Na and Cl uptake by macula densa cells. The renin–angiotensin–aldosterone axis contributes importantly to renal NaCl homeostasis, but evidence for an important role of these hormones in postdiuretic NaCl retention has been mixed. In normal volunteers, postdiuretic NaCl retention was unaffected by the angiotensin converting enzyme inhibitor captopril [21] given in doses sufficient to block furosemide-induced changes in angiotensin II and aldosterone levels. Further, in those studies, diuretic-induced changes in blood pressure were similar with or without captopril, suggesting that hypotension did not mediate the NaCl retention in the angiotensin-converting enzyme (ACE) inhibitor group. These data indicate that postdiuretic NaCl retention *can* occur without activation of the renin/angiotensin/aldosterone system; they do not indicate, however, that stimulation of the renin/angiotensin/aldosterone axis has no role in postdiuretic NaCl retention when it occurs. Recently, the effects of volume removal via loop diuretics and hemofiltration were compared in patients with congestive heart failure [1]. Despite nearly identical ECF volume reductions during pharmacological and mechanical volume removal, ECF volume rose during the ensuing 3 days only in the loop diuretic group. The patients who received loop diuretics also had a dramatic rise in plasma renin activity, compared with the hemofiltration group, suggesting that stimulation of the renin/angiotensin/aldosterone axis contributed to the postdiuretic rebound, under these conditions.

Stimulation of alpha adrenergic renal nerves enhances NaCl reabsorption. Petersen *et al.* show that systemic α-1 blockade attenuated the secondary reduction in NaCl excretion that occurs during short-term furosemide-induced volume depletion in rats [32]. They concluded that stimulation of α-1 adrenoceptors on proximal tubules contributed to the compensatory response to short-term furosemide infusion. In humans, however, administration of prazosin in doses that block the pressor response to α adrenergic agonists does not prevent postdiuretic NaCl retention; even when both prazosin and captopril are administered concurrently, to block both the renin/angiotensin/aldosterone axis and the effects of renal nerve activity, normal postdiuretic NaCl retention may occur ([41]; although in this case, furosemide resulted in a significant decline in mean arterial pressure, which may have contributed to the postdiuretic NaCl retention). Thus, ECF volume dependent stimulation of α-1 adrenergic receptors, especially along the proximal tubule, may contribute to postdiuretic NaCl retention.

Diuretic induced decrements in ECF volume have been shown to be associated with suppression of atrial natriuretic peptide secretion. These changes occur following diuretic administration in both normal individuals and in patients with nephrotic syndrome [16], chronic glomerulonephritis, and essential hypertension. In some studies, atrial natriuretic peptide concentrations have declined before significant changes in extracellular or blood volume occur; in these cases it has been suggested that furosemide-induced changes in venous capacitance may underlie the effect.

The studies discussed above in which blockade of several effector mechanisms does not abrogate postdiuretic NaCl retention raised the possibility that changes in ECF volume were not required for postdiuretic NaCl retention to occur. Wilcox and colleagues [2] investigated acute effects of the loop diuretic bumetanide in the absence of extracellular fluid volume depletion. Na, K, Cl, and water were administered to volunteers during loop diuretic administration to balance electrolyte losses completely. When changes in ECF volume were prevented, postdiuretic NaCl retention did not occur, indicating that decrements in ECF volume do play a critical role in postdiuretic NaCl retention. Despite the central role of ECF volume contraction to postdiuretic NaCl retention, a volume independent component of adaptation *also* contributes to the tendency toward NaCl retention that occurs after loop diuretic administration. Volunteers received a bolus of loop diuretic accompanied by volume replacement (as above) or placebo; they were then challenged with a 100-mmol NaCl load. The NaCl load was excreted fully within 2 days in the absence of prior diuretic administration; when volunteers had been pretreated with bumetanide, however, they excreted less than 10 mmol during 2 days [2]. These results suggest that there are subtle but physiologically significant effects of diuretic administration even in the short term that favor NaCl retention in the absence of changes in ECF volume status (see below).

In normal individuals, diuretic administration strongly activates extracellular fluid volume control systems; in edematous individuals, however, one or more of these control systems may be active at baseline, having contributed to the pathological accumulation of extracellular volume. The role of these control systems in the adaptive response to diuretic may, therefore, be different in normal and edematous individuals.

One mechanism by which diuretic drugs may increase the tendency for NaCl retention directly, without participation of changes in ECF volume involves diuretic-induced *activation* of ion transporters within the diuretic sensitive nephron segment. Both the absorptive and the secretory isoforms of the loop diuretic-sensitive Na/K/2Cl cotransporter (NKCC) are activated allosterically by decreases in intracellular chloride concentration; because loop diuretics reduce the Cl concentration in cells of the thick ascending limb, preexisting transporters should be activated, leading to an increased NaCl transport capac-

ity of thick ascending limb cells that is unmasked once the luminal concentration of loop diuretic declines. Recently, Knepper and colleagues reported evidence that furosemide administration activates Na/K/2Cl cotransport via more than one mechanism. Five days of furosemide infusion led to a 50–100% increase in expression of the Na/K/2Cl cotransporter protein, detected using a polyclonal antibody to the cloned protein; this treatment also led to an upward mobility shift of 9 kDa in apparent molecular mass of the Na/K/2Cl cotransporter protein, as detected by Western blot. These results were interpreted as suggesting that furosemide blockade of apical NaCl uptake led to both increased expression and "modification" of the Na/K/2Cl cotransporter. As phosphorylation of the Na/K/2Cl cotransporter has been shown to regulate its activity, one possibility is that loop diuretic blockade of the Na/K/2Cl cotransporter activates the transporter via phosphorylation.

A similar mechanism has been reported to occur along the distal tubule during short-term administration of thiazide diuretics. Within 60 min of thiazide administration the number of thiazide-sensitive Na/Cl cotransporters in kidney cortex (measured as the number of [^{3}H]metolazone binding sites) increases substantially [6]. The techniques used to estimate the number of transporters in these experiments do not permit one to determine whether the increased number reflects insertion of preexisting transporters from a subapical storage pool or activation of transporters that are present but inactive in the apical membrane. Recent immunocytochemical studies show that a subapical compartment contains thiazide-sensitive Na/Cl cotransporters in distal convoluted tubules cells of rats, suggesting that a shuttle system, similar to that proposed to mediate vasopressin induced water permeability in principal cells of the collecting duct, may regulate functional activity of the thiazide-sensitive Na/Cl cotransporter in the distal tubule. An increase in the number of activated ion transporters at the apical membrane would be expected to increase the transport capacity so that when diuretic concentrations decline, increased Na and Cl transport would result.

A second mechanism by which diuretic drugs may enhance the tendency to NaCl retention directly involves stimulation of transport pathways in nephron segments that lie *distal* to the target of diuretic action (segments that are insensitive to the diuretic drug). For example, the number of thiazide-sensitive Na/Cl transporters in the kidney (and presumably in the distal convoluted tubule) increases within 60 min after a loop diuretic has been administered. Because thiazide-sensitive transporters are expressed only by nephron segments that *do not* express loop diuretic sensitive pathways, the increased number of thiazide-sensitive Na/Cl cotransporters is believed to result from increases in salt and water delivery to distal convoluted tubule cells (discussed in more detail below).

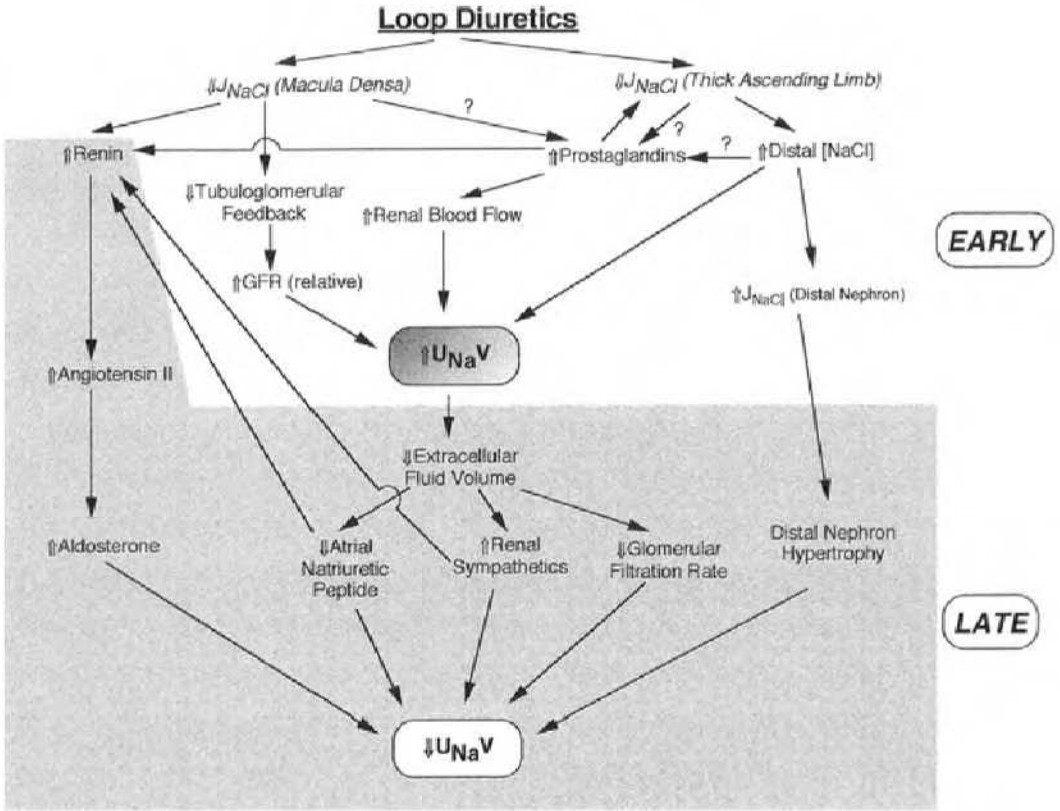
Postdiuretic NaCl retention can have major effects on the clinical efficacy of

diuretic drugs. The half-life of most loop diuretics is short, so that NaCl retention can occur during 18 hr per day, if the drug is administered once daily. If dietary NaCl intake is low, then postdiuretic NaCl retention does not compensate for the drug induced NaCl losses and NaCl balance becomes negative (the desired therapeutic response). If, on the other hand, dietary NaCl intake is high, then postdiuretic NaCl retention *can* compensate entirely for the initial NaCl losses during the period of drug action. When dietary NaCl intake is high, therefore, salt balance may be neutral, even from the first day of diuretic therapy [4, 42], despite impressive increases in urine volume after each dose of diuretic. This is one reason that dietary NaCl intake is a key determinant of diuretic efficacy, especially for the short acting loop diuretics.

Chronic Adaptations

When diuretics reduce ECF volume effectively, NaCl balance gradually returns to neutral despite continued diuretic administration (see Fig. 1 [13, 42]). This "braking phenomenon" occurs when the magnitude of natriuresis following each diuretic dose declines. Several factors, acting in concert, may participate in chronic adaptation (see Fig. 3). A critical factor that is necessary for the braking phenomenon to occur is a decline in the ECF volume. Wilcox and coworkers showed that the magnitude of each diuretic-induced natriuresis declined during ECF volume depletion induced by once daily furosemide treatment of humans consuming a low NaCl diet. In contrast, when dietary NaCl intake was high, ECF volume depletion did not occur, and the magnitude of diuretic-induced natriuresis did not decline [42]. Relative or absolute ECF volume contraction limits NaCl excretion by reducing the amount of NaCl that is filtered and by increasing the amount of NaCl that is reabsorbed. In experimental animals, declines in renal blood flow occur during chronic diuretic

FIGURE 3. Physiological control mechanisms affecting natriuresis following loop diuretic administration. Factors tending to increase NaCl excretion are shown on white background. Factors tending to retard NaCl excretion are shown on a shaded background. Effects are arbitrarily classified as "early" and "late," although overlap of these effects does occur. Early effects of loop diuretic administration primarily predispose to natriuresis. In addition to direct blockade of tubular NaCl transport along the thick ascending limb ($\Downarrow J_{NaCl}$), both increased secretion of prostaglandins and suppression of the tubuloglomerular feedback mechanism tend to increase Na excretion. Later effects of loop diuretic predominate once loop diuretic concentrations in tubule fluid decline. These effects include increases in renin, angiotensin, and aldosterone, decreases in atrial natriuretic peptide, increased renal sympathetic activity, declines in glomerular filtration rate, and distal nephron hypertrophy. These changes predispose to increases in renal Na reabsorption.


Loop Diuretics
⇓J_{NaCl} (Macula Densa)
⇓J_{NaCl} (Thick Ascending Limb)
?
?
?
⇑Renin
⇑Prostaglandins
⇑Distal [NaCl]
⇓Tubuloglomerular Feedback
⇑Renal Blood Flow
EARLY
⇑GFR (relative)
⇑J_{NaCl} (Distal Nephron)
⇑$U_{Na}V$
⇑Angiotensin II
⇓Extracellular Fluid Volume
⇑Aldosterone
⇓Atrial Natriuretic Peptide
⇑Renal Sympathetics
⇓Glomerular Filtration Rate
Distal Nephron Hypertrophy
LATE
⇓$U_{Na}V$

treatment, but declines in glomerular filtration rate are usually modest, unless volume depletion is extreme or renal perfusion is otherwise compromised by drugs or physical factors, such as renal artery stenosis. The effects of diuretics on glomerular filtration and renal blood flow (RBF) are not caused primarily by changes in mean arterial pressure, as the renal autoregulatory response tends to maintain glomerular filtration rate and renal blood flow relatively constant when arterial pressure changes. Instead, ECF volume contraction itself leads to decrements in renal blood flow and glomerular filtration rate; because renal blood flow declines proportionately more than glomerular filtration rate, ECF volume contraction increases the filtration fraction (GFR/RBF).

The role of the proximal tubule in diuretic adaptation has been documented clearly in rats treated chronically with thiazide diuretics and in animals and humans treated with loop diuretics. In the case of thiazide treatment, micropuncture studies showed that hydrochlorothiazide initially inhibited Na and Cl absorption along both the proximal tubule (by inhibiting carbonic anhydrase) and the distal tubule (by inhibiting Na/Cl cotransport) of rats (see Fig. 4 [39]). After 7–10 days of treatment, however, ECF volume contraction led to increases in proximal solute reabsorption, thereby limiting delivery of Na and Cl to the distal sites of thiazide action. During the chronic phase of treatment, inhibition of NaCl transport along the distal nephron (the predominant site of thiazide action) counterbalanced the reduction in distal NaCl delivery; under

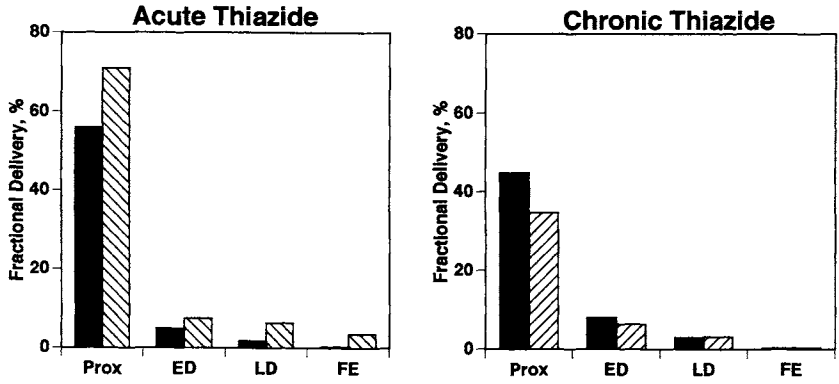


FIGURE 4. Comparison of effects of acute and chronic thiazide administration on fractional ion delivery along the nephron. Compared with control (■), acute thiazide administration ( ) increases ion delivery out of the proximal tubule (Prox) and into the early distal tubule (ED). Because distal ion reabsorption is inhibited, ion delivery to the late distal tubule (LD) is increased, leading to increased fractional excretion (FE) (data from [24]). In contrast, after 7–10 days of diuretic treatment ( ), ion delivery out of the proximal tubule is reduced, delivery to the early distal tubule is reduced, and, because transport along the distal tubule is inhibited, delivery to the late distal tubule is similar to control conditions (data from [39]).

these conditions, at steady state, urinary NaCl was equal to dietary NaCl intake because enhanced proximal NaCl absorption and inhibited distal NaCl absorption counterbalanced [39]. Loop diuretics such as furosemide have also been shown to inhibit Na and Cl absorption by the proximal tubule, although the mechanism is unclear. However, as with distal convoluted tubule (DCT) diuretics, chronic treatment with loop diuretics leads to ECF volume contraction and enhanced proximal NaCl reabsorption. That effects on proximal absorption require decrements in ECF volume was shown by comparing NaCl delivery out of the proximal tubule during furosemide administration with and without volume replacement. Only when the ECF volume was permitted to decline was proximal absorption stimulated [7].

Many of the same effector systems that participate in postdiuretic NaCl retention also may participate in chronic adaptations to diuretic drugs.

Physical Factors

A rise in filtration fraction increases the protein oncotic pressure in peritubular capillaries (more protein free filtrate is formed per milliliter of blood flow, thereby contracting the plasma volume around a constant amount of serum protein). The increased peritubular oncotic pressure increases solute and fluid reabsorption especially in the proximal tubule, where physical factors play a prominent role in regulating solute and fluid reabsorption. ECF volume contraction also enhances proximal solute and fluid reabsorption by decreasing the renal interstitial pressure during chronic diuretic treatment.

Sympathetic Renal Nerve Activity

Efferent sympathetic nerves innervate the renal vasculature, the macula densa, and essentially all segments of the nephron. Stimulation of sympathetic nerves reduces urinary NaCl excretion by reducing renal blood flow, by stimulating renin release at the macula densa, by stimulating tubule NaCl reabsorption along the nephron, and by interacting with hormonal modulators of NaCl transport. Renal nerves may contribute to NaCl retention in edematous disorders, and renal nerve activity is stimulated when furosemide is administered either to normal or to volume depleted animals [8]. Yet experimental models of chronic diuretic administration have failed to substantiate a central role for renal nerve activity in adaptive processes. Chronic sympathectomy or blockade of α-1 receptors inhibits the compensatory increase in proximal NaCl reabsorption that occurs during furosemide induced ECF volume depletion, but these maneuvers did not lead to an enhanced natriuretic response to furosemide [33]. This indicates that the inhibition of proximal solute reabsorption that occurs secondary to adrenergic blockade is compensated by increased reabsorption

distally. Use of systemic pharmacological sympathetic blockade to study the role of renal nerves in diuretic adaptation is limited because of drug-induced systemic hypotension, but Petersen and DiBona showed that even anatomical renal denervation in normal rats does not abrogate the compensatory response to chronic furosemide administration [31]. Although it seems clear that renal nerves do not play a critical role in mediating compensation to chronic diuretic use in normal humans and animals, the consistent observation that diuretics do stimulate renal nerve activity does suggest the renal nervous activity may contribute to diuretic adaptation in some patients. In patients suffering from edematous disorders, distal Na reabsorption may already be stimulated; denervation in this situation might lead to significant impairment in adaptation to diuretic drugs.

Renin/Angiotensin/Aldosterone

A third factor participating in chronic adaptation to diuretic drugs is the renin/angiotensin/aldosterone system. Diuretics stimulate renin secretion via several mechanisms. *First,* loop diuretics stimulate renin secretion by inhibiting NaCl uptake into macula densa cells. Sodium chloride uptake via the loop diuretic sensitive Na/K/2Cl cotransport system is a central component of the macula densa mediated pathway for renin secretion [36]. Macula dense cells express both the loop diuretic-sensitive Na/K/2Cl transport pathway and a constitutive isoform of nitric oxide synthase (NOS, type 1 [30]); blocking Na/K/2Cl uptake at the macula densa stimulates renin secretion directly leading to a volume independent increase in angiotensin II and aldosterone secretion. *Second,* loop diuretics stimulate renal production of prostacyclin. Cyclooxygenase inhibitors (nonsteroidal anti-inflammatory drugs) inhibit the increase in renin secretion that results from loop diuretic administration, suggesting that the increased secretion of prostaglandins plays a critical role in diuretic-induced renin release [10]. *Third,* ECF volume contraction stimulates renin secretion via vascular effects on juxtaglomerular cells; diminished stretch is believed to hyperpolarize juxtaglomerular cells, thereby closing calcium channels and reducing intracellular calcium concentrations. Reduced cellular calcium appears to stimulate renin secretion. *Fourth,* renal nerves (see above) directly stimulate renin secretion via interaction with β adrenergic receptors on juxtaglomerular cells that affect cellular production of cAMP. *Fifth,* extracellular fluid volume contraction inhibits secretion of atrial natriuretic peptide. Among its other effects, atrial natriuretic peptide inhibits renin release. Renin acts on angiotensinogen to generate angiotensin I, which is converted to angiotensin II by converting enzyme. Angiotensin II stimulates aldosterone secretion from the adrenal cortex; aldosterone stimulates salt reabsorption by the distal nephron. In addition, however, angiotensin II directly stimulates Na reabsorption along both the proximal and

the distal tubule by stimulating Na/H exchange activity [40]. Thus, diuretic drugs frequently result in stimulation of the renin/angiotensin/aldosterone system and the Na retention that occurs during diuretic treatment may result in part from this. As is the case with renal nerves, it has been difficult to show conclusively that the renin/angiotensin/aldosterone system plays a critical role in chronic adaptation to diuretic drugs. Yet as with renal nerves, the systemic effects of inhibition of the system, with either angiotensin I converting enzyme inhibitors, angiotensin II receptor blockers, or competitive aldosterone blockers, make it difficult to exclude a role for this hormonal system in the compensation to diuretic therapy.

Epithelial Hypertrophy and Hyperplasia

Other factors that can enhance renal NaCl reabsorptive capacity are structural and functional changes in the nephron itself. When a diuretic is administered, solute delivery to segments that lie distal to the site of diuretic action increases, leading to load dependent increases in solute reabsorption, as discussed above. When solute delivery and solute reabsorption increase chronically, epithelial cells undergo both hypertrophy and hyperplasia (see Fig. 5). Infusion of furosemide into rats continuously for 7 days increased the percentage of renal cortical volume occupied by distal nephron cells (see Fig. 5). Distal convoluted tubule cell volume increased by nearly 100% with accompanying increases in luminal membrane area per length of tubule, in basolateral membrane area per length of tubule, and in mitochondrial volume per cell (see Fig. 6 [9, 18, 19]). Biochemical and functional correlates of these structural changes are shown in Fig. 7. Chronic loop diuretic administration increases the Na/K ATPase activity in the distal convoluted and cortical collecting tubules [35, 38] and increases the number of thiazide-sensitive Na/Cl cotransporters, measured as the maximal number of binding sites for [^{3}H]metolazone [6, 29]. In one study, chronic furosemide treatment increased expression of mRNA encoding the thiazide-sensitive Na–Cl cotransporter, as detected by *in situ* hybridization (see Fig. 7) [29]. In another study, however, mRNA expression of the thiazide-sensitive Na/Cl cotransporter as well as the ouabain sensitive Na/K ATPase was not affected by chronic furosemide infusion, when detected by Northern analysis [27]. Distal tubule cells that express high levels of transport proteins and are hypertrophic have a higher Na and Cl transport capacity than normal tubules. Compared with tubules from normal animals, tubules of animals treated chronically with loop diuretics can absorb Na and Cl up to 3 times more rapidly than control animals, even salt and water delivery is fixed by microperfusion (Fig. 7). When distal tubules are presented with high NaCl loads, as occurs during loop diuretic administration *in vivo,* Na and Cl absorption rates approach those commonly observed only in the proximal tubule [9]. Recently, it has been observed

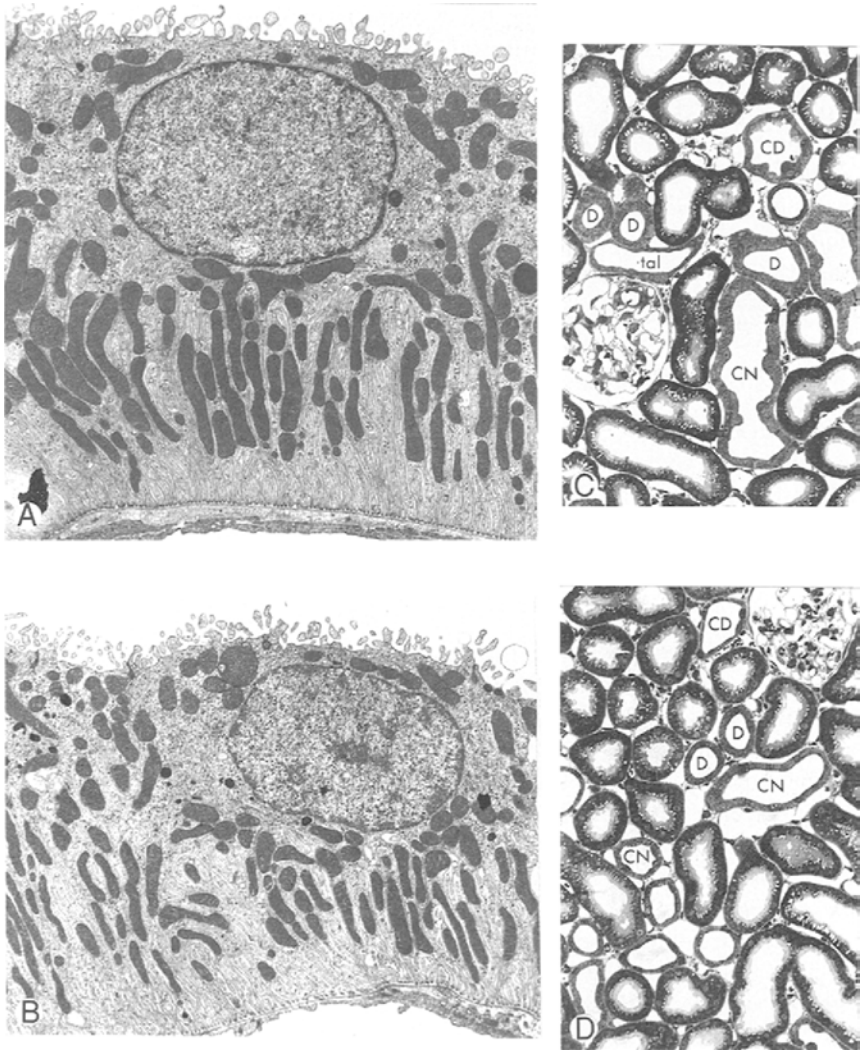


FIGURE 5. Effects of chronic loop diuretic administration on distal convoluted tubule cells of rats. Rats received furosemide continuously for 7 days. (A and B) Electron micrographs (×10,000) of distal convoluted tubule cells from control (B) and furosemide (A) infused animals. Note that furosemide increases the size of the cell, the size of the nucleus, the amount of mitochondrial volume, and the amount of basolateral membrane area. (C and D) Photomicrographs of kidney cortices from control (D) and furosemide (C) infused animals (×480). *D* indicates distal convoluted tubule, *CN* indicates connecting tubule, *CD* indicates cortical collecting duct, *tal* indicates thick ascending limb. Note thickening of the epithelium in all distal segments. Photomicrographs are used with permission from Ellison, D.H. et al., Journal of Clinical Investigation 83:113–126, 1989.

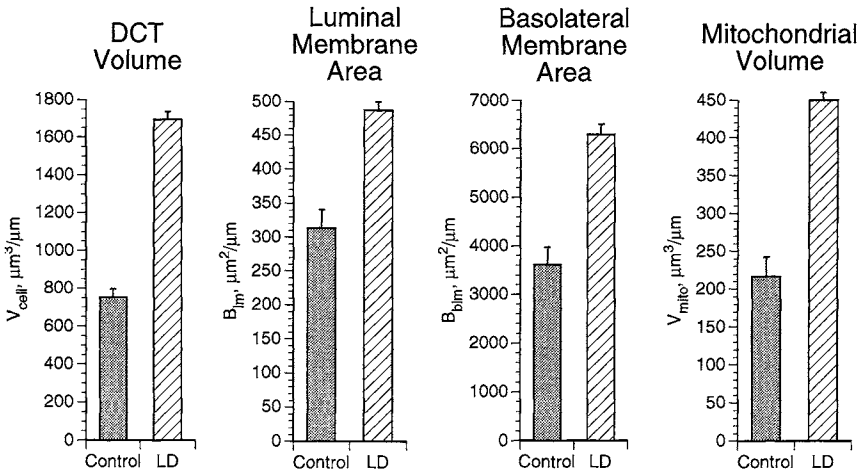


FIGURE 6. Effects of continuous loop diuretic infusion in rats on distal convoluted tubule cells. Diuretic treatment increased the fraction of cortical volume occupied by distal convoluted tubule cells (V_{cell}), the area of luminal membrane relative to cortical volume (B_{lm}), the area of basolateral membrane relative to cortical volume (B_{blm}), and the volume of mitochondria relative to cortical volume (V_{mito}). All changes were statistically significant. Drawn from Kaissling & Stanton, Am. J. Physiol. 255:F1256–F1288, 1988.

that chronic treatment of rats with loop diuretics also results in significant *hyperplasia* of cells along the distal nephron. Whereas mitoses of renal tubule epithelial cells are infrequent in adult kidneys, distal tubules from animals treated with furosemide chronically demonstrate prominent mitoses; increased synthesis of DNA in these cells was confirmed by showing increases in labeling of distal convoluted tubule cells with bromodeoxyurindine and proliferating cell nuclear antigen [25].

The diuretic-induced signals that initiate changes in distal nephron structure and function are poorly understood. Several factors, acting in concert, may contribute to these changes; these include diuretic induced increases in Na and Cl delivery to distal segments, effects of ECF volume depletion on systemic hormone secretion and renal nerve activity, and local effects of diuretics on autocrine and paracrine secretion. Increased production of angiotensin II or increased secretion of aldosterone resulting from increases in renin activity may contribute to hypertrophy and hyperplasia. Angiotensin is a potent mitogen; angiotensin II receptors have not been localized definitively to DCT cells but recent functional studies do suggest that DCT cells express angiotensin II receptors. Aldosterone also promotes growth of responsive tissues under some circumstances [20]: when salt delivery to the collecting duct is increased in the presence of high levels of circulating aldosterone, principal cell hypertrophy

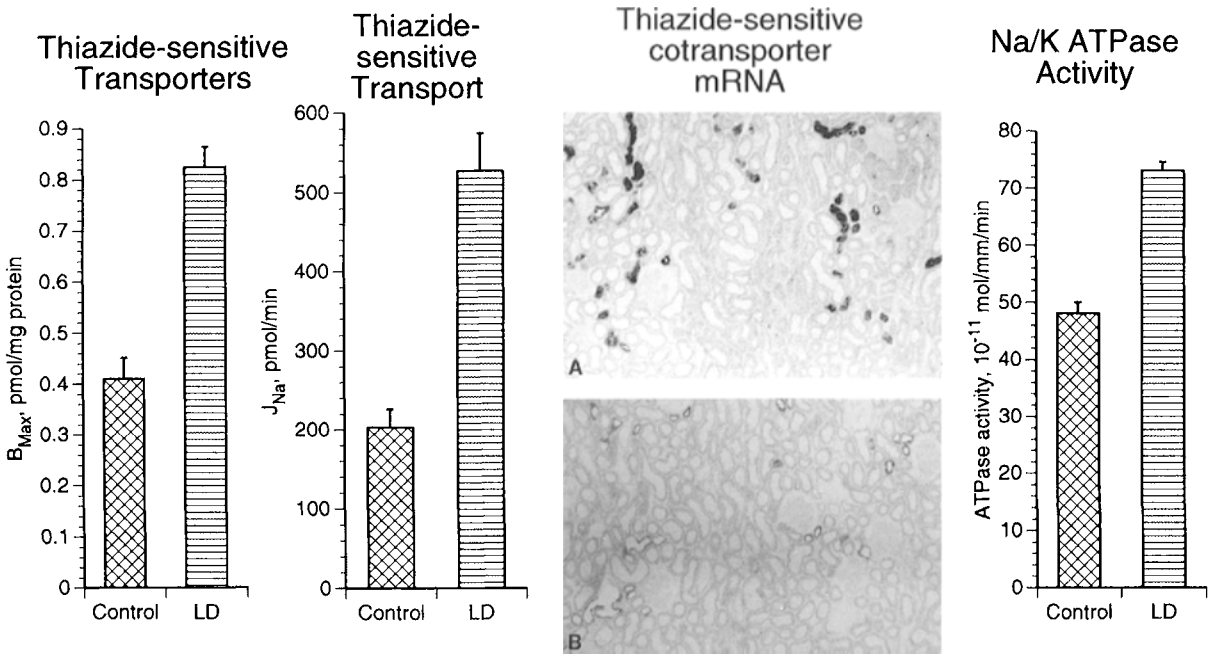


FIGURE 7. Effects of continuous loop diuretic infusion on rat kidney. Loop diuretic infusion increased the number of thiazide-sensitive Na/Cl cotransporters (data from J. Am. Soc. Nephrol. 1:91–98, 1990), the rate of thiazide-sensitive Na transport along the distal tubule (data from J. Clin. Invest. 83:113–126, 1989), the abundance of thiazide-sensitive Na–Cl cotransporter mRNA (A, furosemide-treated kidney cortex; B, control kidney cortex; Obermüller et al. Am. J. Physiol. 269:F900–F910, 1995, used with permission), and NaK ATPase activity along the distal convoluted tubule (data from Am. J. Physiol. 252:F910–F915, 1987).

develops; when salt delivery is high in the absence of aldosterone secretion, hypertrophy is absent. This indicates that aldosterone plays a permissive role in the development of cellular hypertrophy in this aldosterone responsive renal epithelium. Although recent experiments suggest that aldosterone does affect ion transport by cells of the DCT, and aldosterone almost certainly contributes to adaptations along the cortical collecting tubule, hypertrophy of DCT cells has been shown to occur during chronic loop diuretic infusion even when changes in circulating mineralocorticoid, glucocorticoid, and vasopressin levels are prevented [19].

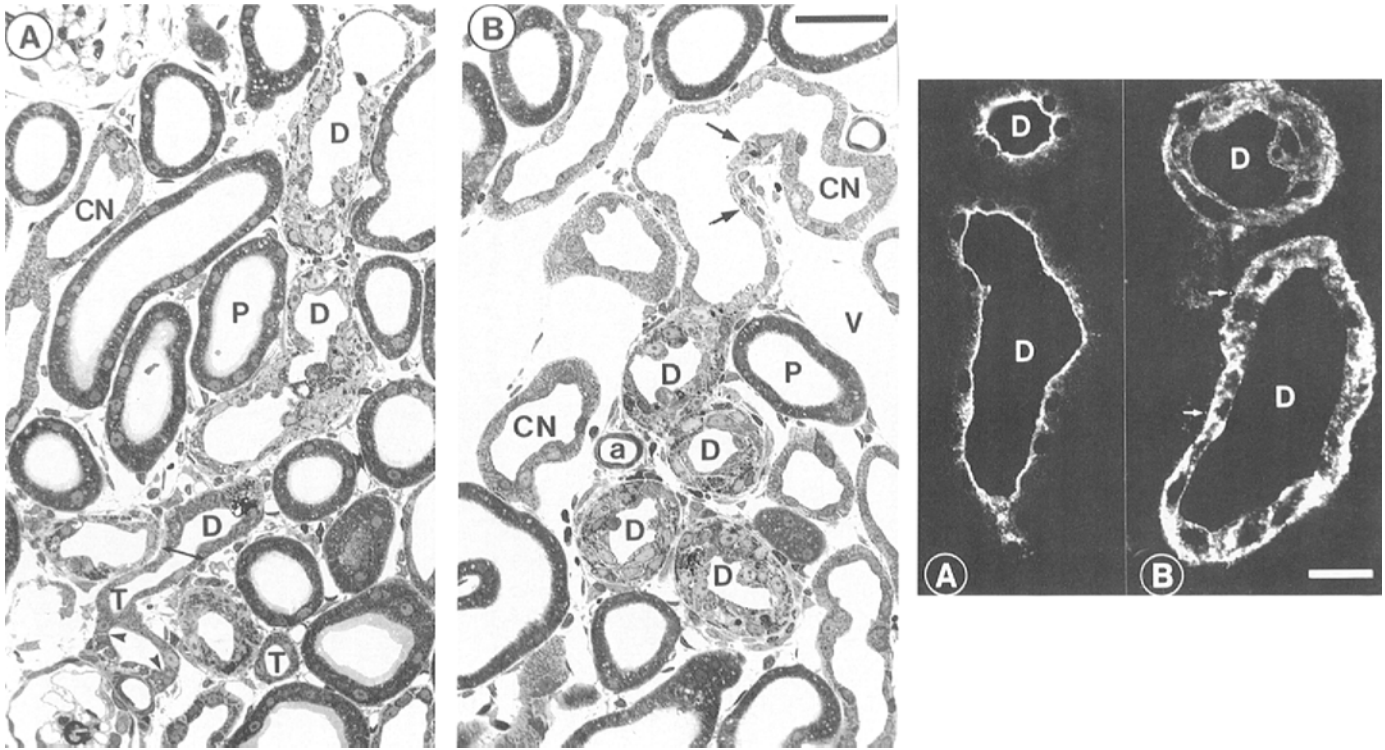
One intriguing hypothesis is that cellular ion concentrations regulate epithelial cell growth directly [37]. Increases in Na uptake across the apical plasma membrane precede cell growth in the thick ascending limb during treatment with ADH [5], in principal cells of the cortical collecting tubule during treatment with mineralocorticoid hormones [17, 34], and in the DCT during treatment with loop diuretics [9, 19]. Although the cause of the increased Na uptake varies, changes in the intracellular Na concentration appear to precede growth in each example. This hypothesis predicts that blockade of apical Na entry would lead to atrophy of epithelial cells. Chronic treatment of rats with DCT diuretics reduces activity of NaK ATPase and Na transport capacity of DCT segments [12, 28], but these experiments are complicated by other structural effects of chronic DCT diuretic treatment, discussed below. Regardless of the proximate stimulus for DCT cell growth, recent experiments have shown that immunoreactivity for insulin-like growth factor-1 (IGF-1) and for an IGF-binding protein (IGFBP-1) increases during chronic treatment of rats with loop diuretics [23]. The changes in IGF-1 expression appeared not to result from changes in IGF-1 mRNA expression, but rather appeared to reflect posttranscriptional events. IGFBP-1 mRNA was increased threefold 18 hr after loop diuretic treatment was initiated. IGF-1 has been shown to participate in regeneration of injured or ischemic renal tissue and promotes cell proliferation and differentiation *in vitro*. Whether these changes in IGF expression mediate the effects of diuretics on distal nephron structure remains to be established. Figure 2 summarizes the effects of chronic loop diuretic administration on distal nephron structure and function.

Morphological changes in the distal nephron during loop diuretic administration are not restricted to Na reabsorbing cells. Chronic diuretic infusion stimulates selective hypertrophy of type B intercalated cells [22]. Type B intercalated cells secrete bicarbonate and express apical Cl/HCO_3 exchangers and basolateral H-ATPase pumps; chronic bumetanide infusion increased the number of apical microvilli in type B cells, increased the basolateral cell membrane area and led to marked cytoplasmic and basolateral labeling for H-ATPase. Type A cells, which normally mediate acid secretion, were small; H-ATPase was distributed primarily within intracellular tubulovesicles in the tubules of

treated animals. The authors concluded that the structural changes in intercalated cells resulted from increased distal chloride delivery because serum pH and electrolyte concentrations were not affected by the diuretic treatment. Increased distal chloride delivery might be expected to enhance Cl/HCO_3 exchange, increasing transepithelial solute transport, stimulating cell growth via mechanisms similar to those discussed above.

Chronic diuretic administration has structural effects not only on nephron segments that lie distal to the site of diuretic action, but also on the nephron segments that are directly inhibited by the drugs themselves. Within hours of furosemide administration to rats, autophagocytic vacuoles develop in thick ascending limb cells [3]. Following 7 days of furosemide treatment of rats, the cell height of thick ascending limb cells was significantly reduced [9]. Chronic treatment of rabbits with loop diuretics decreased Na/K ATPase activity in medullary thick ascending limb cells by approximately one-third [14]. These results are consistent with an effect of transepithelial ion transport to stimulate "work hypertrophy" and blockade of transepithelial transport to stimulate "disuse atrophy." When DCT diuretics are administered chronically, Na/K ATPase activity in the distal convoluted tubule is reduced [12] and the capacity of distal convoluted tubule cells to reabsorb Na and Cl declines [28]. Yet chronic administration of DCT diuretics to rats leads to profound changes in cellular morphology; DCT cells undergo apoptosis and necrosis with resulting interstitial fibrosis (see Fig. 8). Chronic treatment also leads to the disappearance of normal polarization of thiazide-sensitive Na/Cl cotransporter proteins. Under normal conditions, immunoreactivity for the thiazide-sensitive Na/Cl cotransporter is restricted to the apical membrane and to a small subapical pool of vesicles. During chronic treatment with DCT diuretics, the protein is distributed uniformly throughout the cell. Surprisingly, based on the severe morphological degenerative changes in tubular morphology, chronic thiazide administration results in an *increase* in the density of [^{3}H]metolazone binding sites (functional thiazide-sensitive transporters) in kidney cortex [12] despite a decline in mRNA

FIGURE 8. Effects of continuous DCT diuretic treatment on the structure of distal convoluted tubules. (A and B, left) Photomicrographs of kidney cortex from animals treated chronically with thiazide diuretics; note extreme hyperplasia and dysmorphology of distal segments (compare normal distal convoluted tubules in Fig. 5). T is thick ascending limb, D is distal convoluted tubule, CN is connecting tubule, CD is collecting duct, P is proximal tubule, a is arteriole. Double arrow indicates transition from thick ascending limb to distal convoluted tubule; note normal morphology of the thick ascending limb. (A and B, right) Immunostaining for the thiazide-sensitive Na–Cl cotransporter from control rats (A) and rats infused with a thiazide continuously for 10 days (B). Note that the normal apical localization of the transporter immunoreactivity (A) is distributed throughout the cytoplasm in animals exposed to diuretics chronically (B). From Kidney Int. 1996. Used with permission.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expression for the transporter [25]; this may reflect an increased ability of diuretic to bind to degenerating receptors that have been internalized into cells during the diuretic treatment.

Although experimental data concerning structural and functional responses of the distal nephron to chronic treatment with diuretic drugs come predominantly from studies employing experimental animals, Loon *et al.* [26] reported that chronic treatment with loop diuretics in humans enhanced ion transport rates in the distal tubule. They estimated the transport capacity of the DCT as the portion of Na and Cl reabsorption that could be inhibited by thiazide diuretics. When furosemide was administered to volunteers for 1 month, the enhancement in sodium excretion resulting from dose of a thiazide diuretic was significantly larger than at baseline. Although these data are necessarily indirect, they are entirely consistent with the data derived from experimental animals given loop diuretics chronically.

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CHAPTER IVB2

Use of Diuretics in Chronic Renal Disease and Nephrotic Syndrome

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INTRODUCTION

Diuretics are important therapeutic tools in the management of chronic renal failure. Reductions in kidney function or nephrotic syndrome result in inability to excrete sodium appropriately, leading to increases in extracellular fluid volume, increases in blood pressure, and edema. All of these conditions can be improved with appropriate diuretic therapy. Although a variety of diuretics are available for use, patients with chronic renal insufficiency may not respond to diuretics appropriately, making achievement of an adequate natriuresis difficult. Additionally, some classes of diuretics are inappropriate for use in chronic renal failure. Osmotic diuretics are of limited value in chronic renal failure because they further expand extracellular fluid volume and require adequate glomerular filtration for their entry into the renal tubule. Mannitol is also extremely difficult to remove from the body in the absence of renal function. Thus symptomatic increases in vascular volume induced by this agent are difficult to correct. Mannitol has found some use in patients with end-stage renal disease on hemodialysis to prevent hypotension and alleviate muscle cramps. However, osmotic diuretics should probably be avoided in patients with chronic renal insufficiency in most circumstances. Carbonic anhydrase inhibitors which enhance water and salt excretion through inhibition of sodium bicarbonate

Diuretic Agents: Clinical Physiology and Pharmacology

transport in the proximal tubule are also of limited value in chronic renal insufficiency. First, these drugs are weak organic acids which enter the proximal tubule through the organic acid secretory pathway. This event is inhibited by the increase in endogenous organic acids which occur in uremia. Second, the metabolic acidosis which frequently accompanies chronic renal insufficiency reduces serum bicarbonate concentration, bicarbonate reabsorption, and thus diuretic efficacy. Finally these agents potentiate the metabolic acidosis associated with renal insufficiency. Thiazides which inhibit sodium reabsorption in the distal tubule are also of limited value in chronic renal failure because their natriuretic capacity is markedly reduced when glomerular filtration rates fall below 25–30 ml/min. Potassium sparing diuretics such as spironolactone, triamterene, and amiloride have limited natriuretic effects even in normal individuals and may induce potentially life threatening hyperkalemia in renal insufficiency. Thus, loop diuretics which may achieve natriuretic effect equivalent to 20–25% of the filtered sodium load are the agents of choice for treatment of symptoms of sodium excess in chronic renal failure.

DIURETIC PHARMACOKINETIC AND PHARMACODYNAMICS IN RENAL INSUFFICIENCY

Both pharmacokinetic and pharmacodynamic mechanisms contribute to the reduced efficacy of loop diuretics in chronic renal disease. Several pharmacokinetic mechanisms limit delivery of diuretic to its active site. First, as renal blood flow is reduced in parallel to glomerular filtration rate (GFR), delivery of diuretic to the organic acid transport system in the proximal tubule is delayed. Additionally some uremic toxins are organic anions and can competitively inhibit tubular diuretic secretion. Voelker and associates found that patients with severe renal insufficiency (creatinine clearance of 14 ± 2 ml/min/1.7 m^2) excrete only 10% of an intravenous (iv) dose of furosemide, 5% of an iv dose of bumetanide, and 2% of an iv dose of torasemide into their urine [14]. This compares with 50% of the dose of furosemide and bumetanide and 20% of the dose of torasemide usually found in the urine in individuals with normal renal function. The differences in excretion rate between these three loop diuretics can be accounted for by the fact that renal disease reduces the nonrenal clearance of furosemide but has no effect on nonrenal clearances of bumetanide or torasemide. This leads to increased plasma furosemide concentrations and eventually greater furosemide delivery into the tubule fluid. Consequently, the efficacy of furosemide relative to bumetanide and torasemide increases from 40/1 and 2/1 respectively in normal individuals to 20/1 and 1/1 in individuals with severe renal insufficiency. Nonetheless, larger amounts of these diuretics

TABLE 1 Suggested Initial Single Effective Doses and Theoretical Maximally Effective Doses of Common Loop Diuretics in Patients with Chronic Renal Insufficiency

Drug	Route of delivery	Creatinine clearance (ml/min)	Starting dose (mg)	Maximal effective dose (mg)
Bumetanide	iv or po	20–50	1	4–6
	iv or po	<20	4	8–10
Furosemide	iv	20–50	40	120–160
	iv	<20	80	160–200
	po	20–50	80	240–320
	po	<20	160	320–400
Torasimide	iv or po	30–60	20	50–100
	iv or po	<20	50	100–200

Note. iv, intravenously; po, by mouth. Adapted from Brater *et al.* and Rudy *et al.* (1,9) by permission.

must be administered to patients with chronic renal insufficiency to achieve adequate diuretic concentrations in the tubule fluid. Brater and associates have performed diuretic dose–response curves in patients with chronic renal disease and determined reasonable initial and maximally effective diuretic doses for the three loop diuretics most frequently used in the United States (1, 14; Table 1).

Once a loop diuretic gains entry to the tubule lumen, the remaining functional renal tubules in patients with chronic renal insufficiency respond no differently from tubules in patients with normal renal function. Thus following bolus diuretic administration, patients with chronic renal disease have a urinary dose–response curve, obtained by plotting urinary sodium excretion against urinary diuretic concentration, which is essentially identical to that obtained from individuals with normal renal function through the initial and steep parts of the sigmoid-shaped dose–response relationship (Fig. 1). Indeed, following a single bolus of furosemide, the urinary concentration of diuretic inducing half maximal inhibition of sodium excretion is identical in normal subjects and patients with creatinine clearances of less than 20 ml/min [1]. The upper plateau of the curve representing maximal diuretic response, however, is increased in individuals with renal insufficiency compared to that seen in normal subjects if sodium excretion is expressed as a fraction of filtered sodium load. The exaggerated maximal fractional excretion rate probably results from increased basal sodium excretion per nephron due to the osmotic effects of uremic solutes and from stimulation of physiologic natriuretic processes associated with reduced renal function. Knauf and Mutschler have shown that this phenomenon is also present in urinary dose–response curves obtained from individuals with chronic renal disease given thiazide diuretics and amiloride [7].

Changes in pharmacokinetics may also influence the rebound sodium reten-

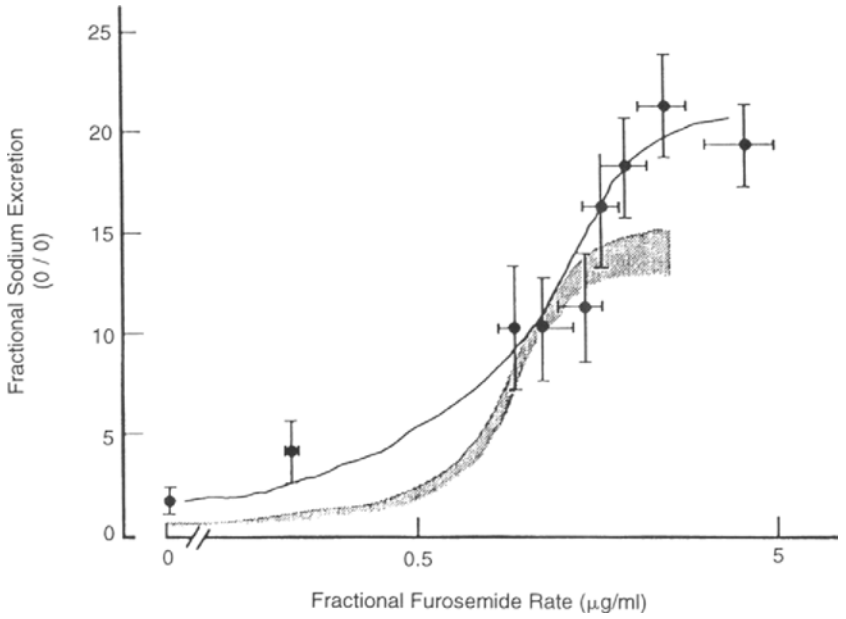

FIGURE 1. Relationship between fractional excretion of furosemide and fractional excretion of sodium after a bolus of furosemide in patients with chronic renal insufficiency. Shaded area represents the curve for subjects with normal renal function. Patients with chronic renal insufficiency have a greater maximal fractional sodium excretion in response to diuretics than individuals with normal renal function. From Brater (1986, Fig. 2, p. 137) with permission.

tion, which occurs following dissipation of the effects of loop diuretics in normal subjects. This diuretic-breaking phenomena is almost absent in individuals with chronic renal disease treated with torasemide and markedly attenuated following furosemide administration [8]. For furosemide this may be explained in part by the prolongation of diuretic effect seen in chronic renal insufficiency. However, as the duration of action of torasemide is independent of renal function, other factors must also play a role. Consistent with this is the finding that the efficacy of bumetanide is reduced by 30% in the 6th through 14th hr of a 12-hr bumetanide infusion in individuals with chronic renal failure [9]. The acute diuretic tolerance, however, was not as marked as that observed following bolus bumetanide infusion. Knauf and Mutschler have demonstrated that the intensity of the diuretic-breaking phenomena depends on the amount of sodium eliminated per unit time [7]. Thus, as the quantitative response to the diuretic is reduced so is the magnitude of the breaking effect.

Despite the changes in pharmacokinetics of loop diuretics present in chronic renal insufficiency it is the reduction in glomerular filtration rate, a pharmaco-

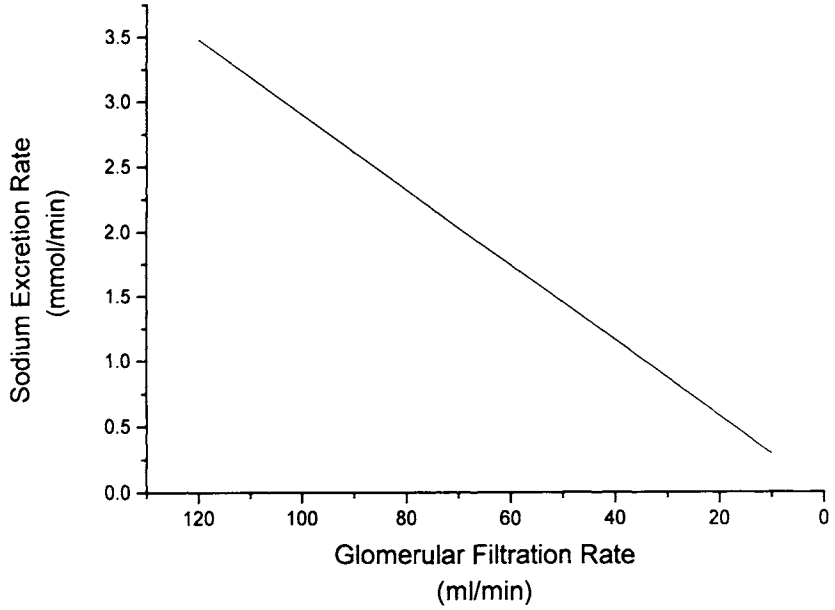

FIGURE 2. Correlation between sodium excretion rate and glomerular filtration rate following administration of furosemide. As GFR decreases, sodium excretion rate is significantly reduced.

dynamic mechanism, which most profoundly influences diuretic efficacy. The effect of a reduction in GFR on the quantitative response to a loop diuretic is shown in Fig. 2. A dose of diuretic which inhibits 20% of the filtered sodium load produces a net excretion of 3.5 meq/min in someone with a glomerular filtration rate of 120 ml/min but only 0.29 meq/min in an individual with chronic renal disease and a GFR of 10 ml/min. Similar quantitative reductions in sodium excretion with decreasing GFR are also observed with weaker thiazide diuretics and late distal tubule diuretics and accounts for the frequently found statement that these diuretics are ineffective when used alone in patients with creatinine clearances of less than 25–30 ml/min.

STRATEGIES FOR DIURETIC THERAPY IN CHRONIC RENAL INSUFFICIENCY

From the above considerations it is apparent that the first step toward effective diuretic therapy for patients with chronic renal disease is to define the single effective dose of diuretic which induces natriuresis. If there is an inadequate or no response, the single dose should be increased until the ceiling dose of that

diuretic agent is reached. While increasing the dose of a diuretic above its ceiling may produce some additional increase in cumulative daily sodium excretion, this occurs primarily through prolongation of drug delivery into the tubule fluid and places patients at risk for dose-related drug toxicities. Repeating the ceiling dose at frequent intervals results in more efficient drug utilization. For long-term management of sodium overload even this strategy is limited by poor patient compliance and the development of diuretic refractoriness. As a result, coadministration of a loop diuretic with a thiazide type diuretic has been suggested to attempt to induce segmental blockade of the nephron and an overall increase in sodium excretion. The rationale for this approach is the observation that inhibition of tubular reabsorption in the loop is offset by increased tubular reabsorption in more distal nephron sites which attenuates net urinary sodium excretion. In normal individuals, both acute and chronic increases in distal tubule sodium delivery lead to functional and structural changes in the distal convoluted tubule and cortical collecting duct which blunt the natriuretic effect of loop diuretics. On the other hand, chronic renal disease is associated with an increased extracellular fluid volume and distal sodium delivery per residual nephron, events which may limit adaptive responses to diuretic induced increases in distal delivery. Nonetheless, coadministration of loop diuretics with thiazide-type diuretics, especially metolazone, has been reported to increase sodium excretion to a greater extent than that produced by a loop diuretic alone in patients with chronic renal insufficiency. Results from some of these studies are difficult to interpret as a few of them have documented that patients were receiving maximally effective doses of the loop diuretic prior to addition of the thiazide or metolazone. Wollam and associates noted that the addition 25–50 mg of hydrochlorothiazide per day to individuals with chronic renal insufficiency (serum creatinine of 3.9 mg/dl) to 40–80 mg of furosemide three to four times a day increased average weight loss by 2.6 kg over 3 days [15]. Knauf and Mutschler have reported that patients with glomerular filtration rates ranging from 50 to 5 ml/min had significantly greater sodium excretion by combining twice daily administration of the loop diuretic piretanide with 25 mg of hydrochlorothiazide than they did by doubling the dose of either drug given alone (7; Fig. 3). Coadministration of torasemide with a thiazide has been reported to increase 24-hr sodium excretion by 25% and blunt diuretic braking [2]. In the United States most clinicians are now using metolazone in combination with loop diuretics as the former agent appears to have sites of action in both proximal and distal tubules, is effective at low GFR, and has less tendency to depress GFR than other thiazide diuretics.

Continuous infusion of a loop diuretic has also been proposed to overcome the poor diuretic response observed in chronic renal failure. In a small series of patients with an average creatinine clearance of 17 ml/min, 12 mg of bumetanide given by continuous infusion over a 12-hr period induced 25% greater

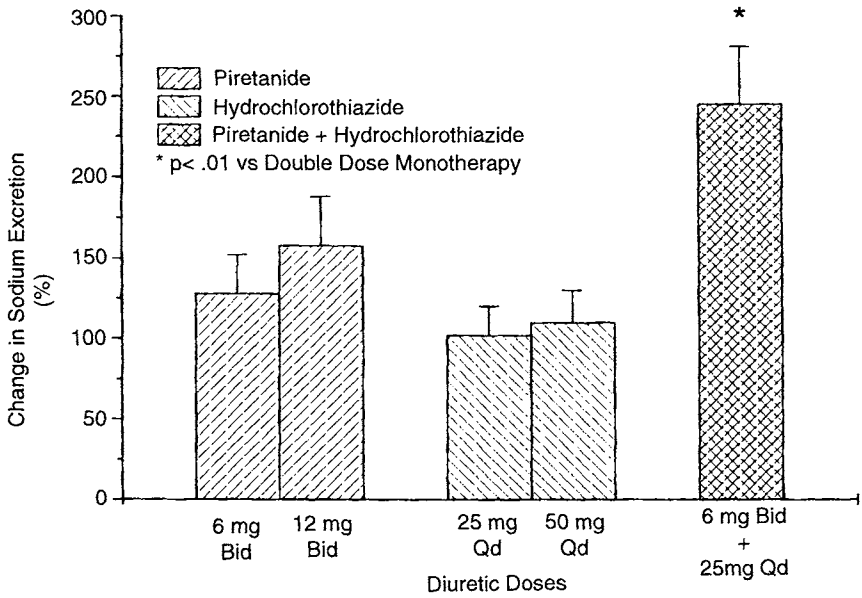

FIGURE 3. Percentage increase in urinary sodium excretion following twice daily loop diuretic, piretanide, or once daily hydrochlorothiazide and the combination of twice daily piretanide (6 mg) and once daily hydrochlorothiazide (25 mg) in patients with GFRs between 50 and 5 ml/min. The combination of a thiazide and loop diuretic increased sodium excretion to a degree greater than twice the dose of either agent used alone. Adapted from Knauf and Mutschler (1993, Fig. 7, p. 455).

sodium excretion than two 6-mg bolus infusions given 6 hr apart [9]. Diuretic tolerance occurred with both regimens but was less pronounced during the continuous infusion. Additionally, the continuous infusion resulted in fewer episodes of diuretic induced myalgia. As this approach requires continuous intravenous access, it is unlikely to find widespread use in the management of sodium excess in the majority of patients with chronic renal insufficiency.

USE OF DIURETICS AS AN ADJUNCT TO DIALYSIS

Loop diuretics have also been administered to patients with end-stage renal disease on maintenance dialysis in an attempt to reduce interdialytic weight gains, prevent heart failure or pulmonary congestion, and control blood pressure without unpalatable limitations in fluid or sodium intake. It has also been suggested that this strategy could reduce the number of hypotensive episodes which occurred during hemodialysis during removal of excess fluid. The ma-

jority of these studies have been performed in patients on chronic hemodialysis. Most individuals on dialysis who have residual renal function respond to loop diuretics, although very large doses are frequently required. However, the effect of diuretics on weight gain and blood pressure in this population have been inconsistent. In a double blind study of hemodialysis patients with residual creatinine clearances of less than 4 ml/min, 200 mg per day of torasemide or 250 mg of furosemide increased fractional sodium excretion compared to placebo, but only torasemide induced an improvement in interdialytic weight gain (−0.7 kg per day) [12]. In another double blind study comparing 200 mg of torasemide or 500 mg of furosemide with placebo in hemodialysis patients with residual renal functions of less than 4 ml/min, the torasemide group showed a 2-kg decrease in predialysis body weight and a 10 mm Hg reduction in systolic blood pressure after 12 weeks on the drugs [10]. Furosemide had no effect on either parameter. Whether these results are sustained over longer time intervals is unclear. Hemodialysis patients treated with 250–1000 mg of furosemide orally per day have been found to have a progressive decrease in diuretic response with time such that after 12 months of therapy, total 24-hr fluid and sodium excretion rates were no different than pretreatment values [13]. Diuretic side-effects are also frequent in this population especially with high dose furosemide. From the above considerations it is unclear that diuretic treatment in patients with end-stage renal disease on hemodialysis provides a significant improvement in their clinical condition or quality of life. The effects in patients on peritoneal dialysis remains to be determined.

USE OF DIURETICS IN NEPHROTIC SYNDROME

The subset of patients with chronic renal disease who have nephrotic syndrome provide an additional challenge to effective diuretic therapy. In patients with this condition blunted responses to diuretics are frequently observed early in the course of the disease when GFRs are normal or only modestly reduced. Both pharmacodynamic and pharmacokinetic mechanisms account for diuretic resistance in nephrotic syndrome. Most pharmacokinetic studies have focused on the effect of reductions in serum albumin on delivery of loop diuretic to the kidney. Because loop diuretics are so highly protein bound (>90%), reductions in serum albumin result in significant increases in the amount of free drug and the resultant increase in volume of drug distribution. Total plasma clearance of furosemide has also been reported to be increased in some studies but this may reflect the increase in nonrenal clearance of that agent reported with reduced renal function. Thus, as noted by Keller and associates, and confirmed by Smith and co-workers, urinary furosemide excretion in nephrotic patients is reduced along with the diuretic and natriuretic response [5, 11]. Pharmacokinetic pa-

rameters of other loop diuretics in nephrotic individuals have been less intensively examined but an increase in volume of distribution and decreased delivery into urine would be expected based on their extensive protein binding. Consistent with this supposition is the finding that there is greater impairment in diuretic and natriuretic response to torasemide in nephrotic than nonnephrotic patients with equivalent degrees of chronic renal insufficiency. The importance of albumin diuretic binding in the response to loop diuretics has been documented in patients with hypoalbuminemia from a number of causes in whom intravenous administration of equal molar amount of furosemide mixed with albumin produced a greater increase in urinary furosemide excretion and natriuretic response compared to either agent administered alone [4]. Keller and associates noted that the urinary dose–response curve is shifted to the right in nephrotics such that these individuals excrete less sodium than normal for any given concentration of furosemide found in voided urine [5]. Although this observation is usually considered the hallmark of a change in diuretic pharmacodynamics, Green and Merkin pointed out that the albumin present in tubule fluid from nephrotics could bind with secreted diuretic and limit the concentration of free drug available to inhibit sodium transport in the thick ascending limb of Henle's loop [3]. Attempts to evaluate the role of this interaction in the diuretic resistance associated with nephrotic syndrome has been difficult as the amount of furosemide bound to albumin is altered by changes in ionic strength which occur as tubule fluid transverse the loop and distal nephron. Thus, the amount of diuretic bound to albumin in voided urine may not be representative of the amount bound in fluid entering the thick ascending loop of Henle's loop. We, however, have shown that albumin added to artificial tubule fluid antagonizes furosemide's inhibition of chloride reabsorption during microperfusion of rat loop segments *in vivo* (Fig. 4). Competitive inhibitors of albumin furosemide binding in plasma such as warfarin or sulfasoxazole restore furosemide's ability to inhibit chloride reabsorption in tubule fluid which contains albumin. These studies suggest that albumin in tubule fluid can modify the response to loop diuretics through albumin diuretic binding. To what extent this contributes to the overall attenuated diuretic response in human nephrotic syndrome is unclear.

Alterations in the pharmacodynamic response to diuretics are also likely to contribute to diuretic resistance in nephrotic syndrome. The role of reduced glomerular filtration rate in diuretic response in nephrotic syndrome is similar to that described for chronic renal failure in general. Additionally, however, there is evidence to suggest that renal tubules are less responsive to diuretics in nephrotic syndrome. Rats with aminonucleoside induced nephrotic syndrome and a normal GFR excrete less sodium following intravenous furosemide than normal rats even though urinary furosemide excretion rates are equivalent in both groups [6]. Micropuncture studies in these animals demonstrate that sol-

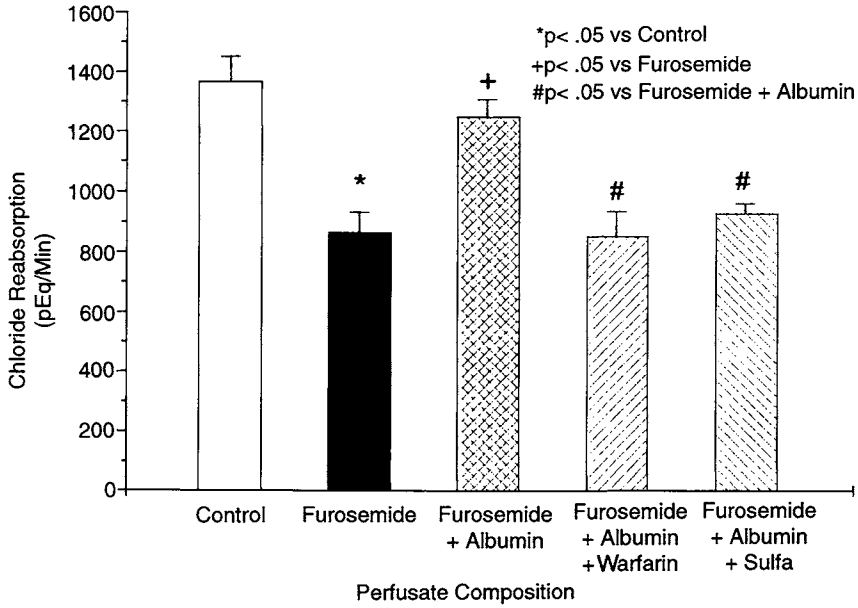

FIGURE 4. Absolute chloride reabsorption in the loop segment during microperfusion with furosemide alone, furosemide and albumin, and furosemide and albumin in the presence of agents which competitively inhibit furosemide albumin binding in plasma (warfarin and sulfazoxazole). Albumin blunted furosemide inhibition of loop chloride reabsorption and this effect was prevented by warfarin and sulfazoxazole. Neither inhibitor potentiated furosemide response in the absence of albumin (data not shown). Modified from Kirchner (Kidney Intern. 40,421. Fig. 1) with permission.

ute delivery out of the proximal tubule is not different between nephrotic and normal rats following furosemide administration but the ability of furosemide to inhibit loop chloride reabsorption is blunted in the nephrotic rats. A blunted loop response to furosemide is also demonstrated during *in vivo* loop microperfusion where perfusion of 6 or 60 μM furosemide directly into the loop segment resulted in 25–29% less inhibition of loop chloride reabsorption in nephrotic rats than normal rats (Fig. 5). Thus, the loop segment in nephrotic syndrome appears to be intrinsically less sensitive to loop diuretics. Whether increased sodium reabsorption is present in other nephron segments in nephrotic syndrome and contributes to attenuated diuretic response is unclear. Recent studies have shown that effective circulating volume is normal or increased in this condition in man, making increased proximal reabsorption unlikely. This would be consistent with animal data which find no changes in proximal reabsorption in any of the variety of models of nephrotic syndrome which have been examined by micropuncture. Increased sodium reabsorption in the collecting duct has been shown to account for the inability of nephrotic

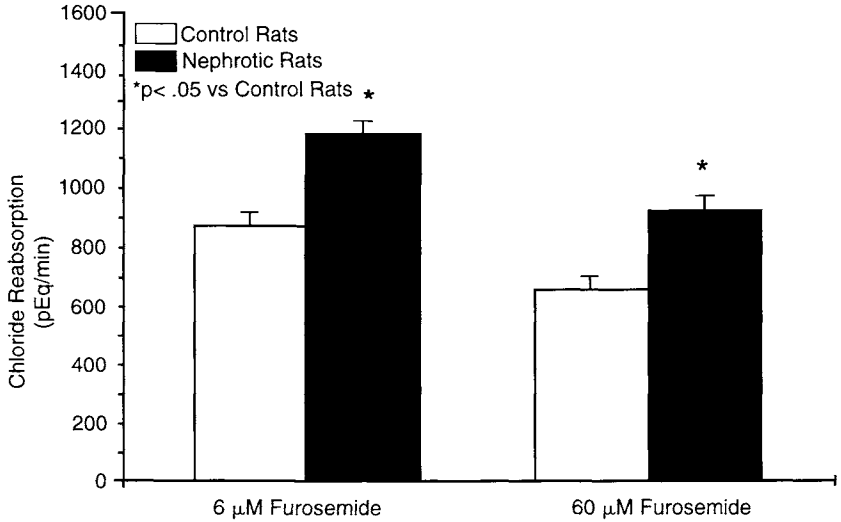

FIGURE 5. Loop chloride reabsorption in normal and nephrotic rats during *in vivo* loop segment microperfusion with perfusates containing either 6 or 60 μM furosemide. Chloride reabsorption in the loop segments of nephrotic rats was inhibited to a lesser extent than normal rats by furosemide delivered directly into that tubule segment. From Kirchner (1993, Fig. 5, p. 440).

animals to excrete a sodium load. This location could also participate in the attenuation of the response to loop diuretics.

Based on the above, strategies for improving diuretic response in nephrotic syndrome first include increasing the diuretic dose to maximize the amount of free drug entering the tubule fluid. There is as yet no effective method of limiting albumin diuretic binding in glomerular filtrate. Once an effective diuretic dose is established, administering the loop diuretic at more frequent intervals can be attempted to achieve the desired cumulative sodium loss. Some studies have suggested that torasemide may be more effective than furosemide in nephrotic syndrome. This may be due to differences in the bioavailability of these agents. Coadministration of loop diuretics with thiazides like diuretics to induce segmental blockade of the nephron have also been used with success. Despite these maneuvers, continued diuretic resistance is not uncommon.

COMPLICATIONS OF DIURETIC THERAPY IN RENAL INSUFFICIENCY

In general, the complications of diuretics in patients with chronic renal disease and nephrotic syndrome are similar to those seen in patients with normal renal function. Side-effects may be more common in these conditions as larger doses

of drug tend to be used. Renal blood flow and glomerular filtration rate are maintained or slightly increased during administration of loop diuretic, but worsening azotemia can develop during therapy in which the diuresis is excessive or blood pressure falls sharply. Increase in the blood urea nitrogen to creatinine ratio during diuretic therapy is a marker for extracellular fluid volume depletion. Increases in blood urea nitrogen and serum creatinine are especially common in individuals receiving combination therapy with loop and thiazide diuretics. The worsening azotemia appears to stabilize following several days of treatment and is reversible upon cessation of the combination therapy. Loop diuretics used alone and in combination can also induce hyponatremia, hypokalemia, hypomagnesemia, and metabolic alkalosis. Hypokalemia is a frequent problem and can develop rapidly. Increases in plasma concentrations of urate and cholesterol can occur as can carbohydrate intolerance. Important adverse effects of loop diuretics which occur predominantly in chronic renal failure include ototoxicity, interstitial nephritis, and bullous dermatitis.

Ototoxicity has been reported following administration of ethacrynic acid, furosemide, and bumetanide in man. Peritanide has been found to reduce endocochlear potentials in experimental studies. Ototoxicity is more frequent with high doses of diuretic given rapidly by intravenous infusion. Toxicity appears to be related to the amount of free drug entering the cochlea and is thus more likely to occur in patients with chronic renal failure and with nephrotic syndrome. Although deafness in most cases is acute and transient, permanent and profound hearing loss has been reported following administration of ethacrynic acid and furosemide. Permanent hearing loss has also been reported from large oral doses of furosemide.

An acute interstitial nephritis has been described in patients with chronic renal failure taking furosemide. While skin rash, fever, and eosinophilia may occur, most cases present with decreases in renal function not attributable to other causes and eosinophiluria. This syndrome can occur at any time after beginning therapy, but in our experience most patients have been on the drug for several months. Renal biopsy shows interstitial nephritis with eosinophils. In most cases renal function returns to baseline value after drug withdrawal. Most reported cases have occurred following furosemide therapy. Whether this problem occurs with other diuretics is unclear. We have substituted ethacrynic acid for furosemide in affected individuals without difficulty.

A sunlight-induced bullous dermatitis has also been described in patients with chronic renal failure treated with high daily doses of furosemide (500–2000 mg /day). The clinical and histologic picture looks identical to that of porphyria cutanea tarda. The lesions resolve after discontinuation of the drug.

Furosemide has also been reported to aggravate secondary hyperparathyroidism in patients with chronic renal disease by increasing serum parathyroid hormone levels. The clinical significance of this problem is uncertain.

Knauf and Mutschler have suggested that low dose combination therapy is associated with less side-effects than high dose monotherapy [7]. Clinical trials confirming this hypothesis have yet to be reported.

SUMMARY

Diuretics are often required to manage the complications of chronic renal insufficiency and nephrotic syndrome. However, altered pharmacokinetics and pharmacodynamics make achieving the desired response difficult. Loop diuretics used in high doses orally or by continuous intravenous infusion as monotherapy or in combination with thiazide-like agents are frequently required. In these settings diuretic complications are a significant risk.

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CHAPTER IVB3

Effect of Prostaglandin Inhibition on the Action of Diuretic Agents

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INTRODUCTION

Prostaglandins are synthesized throughout the kidney and play an important role in the modulation of many renal functions. It is therefore not surprising that inhibition of prostaglandin synthesis has consequences on renal function in normal individuals and on the action of diuretic agents [1]. Furthermore, nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin synthesis as their primary mode of action are the most widely prescribed therapeutic agents in use today. Thus the potential for their interference with diuretic efficacy is of considerable practical concern.

DETERMINANTS OF DIURETIC ANTAGONISM BY NSAIDS

In 1962 it was reported that the diuretic effect of spironolactone was attenuated during aspirin administration in humans. Although this interaction was first attributed to competitive inhibition for mineralocorticoid receptors, discovery of the prostaglandin system and the realization that many drugs which antagonize prostaglandin synthesis blunt the effect of diuretic agents has led to a reappraisal of this original report. Studies with the prototypic prostaglandin

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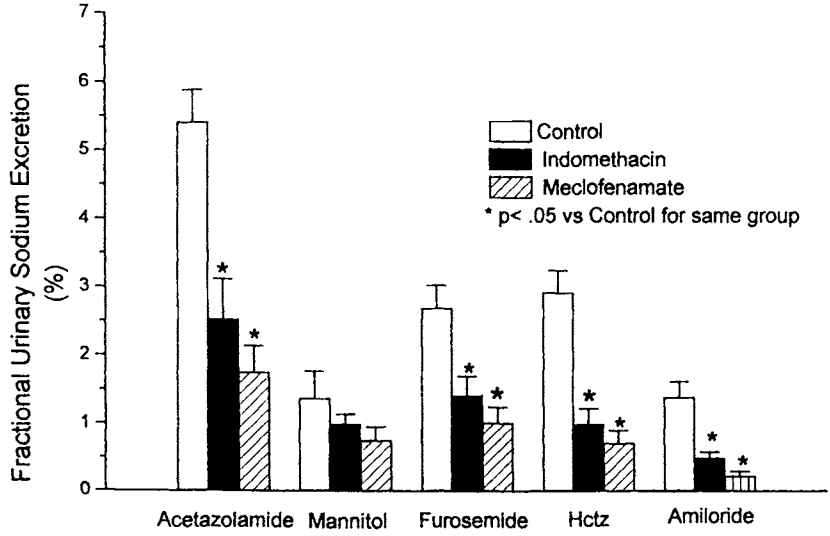

FIGURE 1. Effect of two structurally distinct prostaglandin synthesis inhibitors on the acute natriuretic response to different classes of diuretics in the rat. Only mannitol natriuresis was not significantly blunted by either indomethacin or meclofenamate.

inhibitor, indomethacin, have shown this drug antagonizes the natriuretic effect of loop diuretics in normal volunteers and causes weight gain and loss of blood pressure control in hypertensive individuals taking thiazide diuretics. In animals, inhibition of prostaglandin synthesis with a number of structurally different NSAIDS have shown attenuation of the diuretic response to acetazolamide, loop diuretics, thiazide diuretics, and potassium—sparing diuretics. Only the diuresis and natriuresis induced by mannitol appear to be unaffected by prostaglandin synthesis inhibition (Fig. 1). Inhibition of the response to thiazide, loop, and potassium sparing diuretics have also been reported in man.

The magnitude of the inhibitory effect of prostaglandin synthesis inhibitors on acute diuretic responses can be striking. A single 600-mg dose of aspirin has been reported to reduce the natriuretic response to 25 mg of spironolactone given four times a day by 33%. Indomethacin (50 mg) given the day before study and three times a day during the study interval inhibits the natriuretic response to twice daily furosemide (40 mg) by 36% and twice daily hydrochlorothiazide (25 mg) by 28% in man [10]. Indomethacin (100 mg) given orally has been reported to reduce the natriuretic response to 1 mg of intravenous bumetanide by 25% in volunteers. Indomethacin has also been reported to produce complete inhibition of the natriuretic response to furosemide, metolazone, and ticrynofen in conscious dogs [14]. Despite the intensity of the antagonism of acute diuretic responses reported in these studies, most patients

receiving diuretics and NSAIDs chronically do not manifest progressively worsening edema. Consequently, the intensity of antagonism between NSAIDs and diuretics must be modified by other factors when these drug combinations are found in clinical settings. Unfortunately, few studies have systematically examined the reasons for this discrepancy. Zawada and associates have demonstrated that the natriuretic effect of 0.57 mg/kg furosemide could be 50% inhibited by 0.1 mg/kg indomethacin and 100% inhibited by 0.25 mg/kg of indomethacin in conscious dogs [14]. Similar data were provided for metolazone and ticrynafen. Thus the dose of NSAID employed is one determinant of the magnitude of diuretic antagonism. There were also some initial suggestions that some classes of NSAIDs may preferentially spare renal prostaglandins; however, this has subsequently been shown to be incorrect [2]. The dose of diuretic used is also important. Brater has shown that the effect of a constant dose of indomethacin on the response to furosemide differed with the diuretic dose administered [2]. The underlying activity of the prostaglandin system appears to be an extremely important determinant of the interaction between NSAIDs and diuretics. Nies and colleagues have noted that indomethacin antagonizes furosemide response in salt depleted dogs but not in salt loaded dogs [11]. Others have correlated the antinatriuretic effect of indomethacin with the ability of indomethacin to abolish furosemide induced increases in urinary prostaglandin E_2 excretion. The extent to which antagonism between NSAIDs and diuretics dissipates with chronic administration of these agents remains to be determined. Normal volunteers on a fixed sodium intake, but not receiving diuretics, escape from indomethacin induced sodium retention after several days [3]. Chronic oral administration of indomethacin and hydrochlorothiazide to human volunteers over 4 weeks results in a weight gain of only 1 to 2 kg. This does not appear to result from escape from prostaglandin synthesis inhibition since antinatriuresis following acute furosemide administration can be demonstrated even after individuals have been maintained on indomethacin for 42 days. On the other hand, indomethacin and a thiazide diuretic given to conscious rabbits has been reported to induce continuous sodium retention over the entire 15-day study interval [14]. Thus, while it is clear that NSAIDs antagonize the natriuretic effect of diuretic agent and that this is more likely in conditions where the renal prostaglandin system is activated, additional studies are required to define the other factors important in determining the intensity of diuretic antagonism during inhibition of prostaglandin synthesis.

MECHANISMS FOR DIURETIC ANTAGONISM BY NSAIDS

Multiple mechanisms appear to play a role in the antagonism of diuretic action by NSAIDs. The contribution of each mechanism to the overall blunting of di-

uretic effect is likely to depend on the dose of drugs employed, the site of action of the diuretic agent in the nephron, and the activity of the prostaglandin system in the study group. From a conceptional standpoint potential mechanisms for NSAID antagonism of diuretic response can be divided into pharmacokinetic mechanisms and pharmacodynamic mechanisms.

Pharmacokinetic Mechanisms for Diuretic Antagonism

Most studies examining pharmacokinetic interactions between NSAIDs and diuretics have focused on indomethacin and furosemide. In these studies it has been noted that indomethacin induces an 18 to 40% reduction in plasma furosemide clearance [2]. In man, this results from a large reduction in furosemide's renal clearance and a smaller insignificant decrease in nonrenal clearance (primarily liver and intestine). In the dog, significant decreases in both renal and nonrenal clearances have been reported during administration furosemide and NSAIDs [4]. Total 24 hr urinary furosemide excretion and area under the urinary excretion curve are not altered in indomethacin pretreated humans, nor is the total amount of furosemide reaching the urine altered by indomethacin in the dog. The mechanism(s) for the change in time course of renal furosemide clearance by indomethacin is unclear. However, both furosemide and indomethacin are secreted by the renal organic acid secretory system and may competitively inhibit each other's transport into the proximal tubule lumen. Consequently the increasing plasma furosemide concentrations would eventually displace indomethacin from the transporter, resulting in a delay in furosemide appearance in the urine but leaving 24-hr furosemide excretion constant. The extent of pharmacokinetic interactions between NSAIDs and other classes of diuretics are less clear. In man, hydrochlorothiazide plasma concentrations and urinary excretion rates have been reported to the unaltered following administration of 25 mg of indomethacin 3 times a day, even though this combination produced significant increases in body weight and decreases in plasma renin activity [9]. Sulindac, on the other hand, reportedly reduced mean 24-hr renal hydrochlorothiazide clearance by 23% in the same study. These findings not withstanding, most investigators feel that the marked effects of the NSAIDs on diuretic response results from pharmacodynamic mechanisms.

Pharmacodynamic Mechanisms for Diuretic Antagonism

Since the clinically important diuretics work from the luminal side of the renal tubule, pharmacodynamic interactions between NSAIDs and diuretics can be

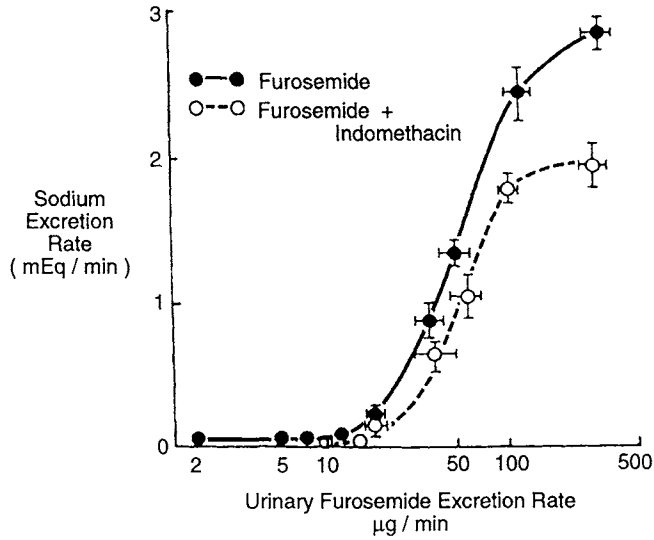

FIGURE 2. Dose–response curve depicting the relationship between urinary sodium excretion and urinary furosemide excretion rates in volunteers before and after indomethacin administration. After indomethacin treatment subjects required greater rates of furosemide excretion to achieve any desired rate of sodium excretion. (From Chennavasin P., Seiwell, R., Bater D, (1980) Pharmacokinetic-dynamic analysis of the indomethacin-furosemide interaction in man. J. Pharm. Exp. Ther. 215; Fig. 2, p. 66. with permission).

determined by examination of the relationship between urinary diuretic concentration and urinary sodium excretion. Pharmacodynamic interactions shift this dose–response curve to the right so that in the presence of the interaction a higher concentration of diuretic is required in the urine to achieve any given level of sodium excretion. The effect of indomethacin on the relationship between urinary furosemide concentration and urinary sodium excretion is shown in Fig. 2. Qualitatively similar curve shifts have been reported for the effect of salicyates, ibuprofen, naproxen, or sulindac on furosemide induced natriuresis and for effects of indomethacin on bumetanide and hydrochlorothiazide response in man. Curve shifts have also been reported for effects of indomethacin or meclofenamate on furosemide, acetazolamide, amiloride, and bumetanide natriuresis in experimental animals.

Multiple pharmacodynamic mechanisms could account for the ability of NSAIDs to decrease diuretic responses. Recognition that these are based on inhibition of prostaglandin synthesis does not allow identification of a specific mechanism because of the variety of prostaglandin mediated processes present in the kidney [1]. Additionally, administration of NSAIDs rarely inhibit renal prostaglandin synthesis by greater than 80%. Thus, it is possible that the amount of prostaglandin production remaining may be sufficient to support

prostaglandin dependent processes in some renal locations but not others. This makes assessment of the contribution of specific pharmacodynamic mechanisms to the overall antagonism of diuretic response difficult to quantify. NSAIDs could induce pharmacodynamic antagonism of diuretic response through two general categories of mechanisms: hemodynamic mechanisms and direct antagonism of the diuretic's tubule effect. These mechanisms need not be mutually exclusive.

Hemodynamic Mechanisms

Hemodynamic mechanisms potentially important in the attenuation of diuretic response by NSAIDs include reductions in glomerular filtration rate (GFR) and alterations in total renal blood flow or in intrarenal blood flow distribution. The first limits solute delivery to the tubule, while the second alters peritubular physical factors to favor sodium reabsorption. Reductions in GFR and, thus, reductions in filtered sodium load have been inconsistently reported in NSAID treated animals and humans during administration of loop and thiazide diuretics. Because of the magnitude of the daily filtered sodium load (approximately 20,000 mEq/day), a reduction in GFR undoubtedly plays a major role in attenuating the natriuretic response to diuretics in circumstances where it occurs. Although decreases in GFR are inconsistently observed in normal individuals during NSAID administration, reductions in GFR following prostaglandin synthesis inhibition are not infrequent in conditions associated with a decrease in effective extracellular fluid volume or an increase in plasma renin activity such as congestive heart failure, nephrotic syndrome, and cirrhosis. While this mechanism has not been considered a significant contributor to diuretic antagonism in most experimental studies, it is likely to play an important role in clinical settings where NSAIDs and diuretics are used. Even in these situations the contribution of this mechanism may not be fully appreciated because of the insensitivity of the techniques employed to estimate GFR.

Reductions in renal blood flow or changes in intrarenal blood flow distribution were some of the first mechanisms proposed to explain how NSAIDs alter diuretic action. The attractiveness of this hypothesis is enhanced by observations that furosemide increases urinary prostaglandin E_2 excretion by increasing availability of arachidonic acid, by decreasing prostaglandin degredative enzymes, and at high doses by directly stimulating prostaglandin E_2 synthesis. Furosemide stimulation of prostaglandin release induces vasodilation and increases venous capacitance. These events have been proposed to account for the observation that furosemide administered intravenously to patients in left heart failure produces a fall in pulmonary capillary wedge pressure prior to producing a significant natriuresis. The finding that this response is blocked by NSAIDs and does not occur in nephrectomized subjects suggests that these

events are mediated by furosemide stimulation of renal prostaglandin release. Stimulation of urinary prostaglandin excretion has also been reported following oral administration of loop, thiazide, and potassium-sparing diuretics in some human studies [10]. The intravenous administration of furosemide to anesthetized dogs increases total renal blood flow and redistributes this flow to the midcortical and away from juxtamedullary areas of the kidney [4, 12]. An increase in juxtamedullary flow has also been observed in some studies [4]. Indomethacin reduces basal total renal blood flow and blood flow to juxtamedullary areas and prevents the increase in blood flow induced by furosemide [4]. Increases in total renal blood flow have also been reported following intravenous administration of ethacrynic acid and bumetanide. Indomethacin blocks the increases in renal blood flow induced by these agents as well. Whether antagonism of the hemodynamic changes induced by loop diuretics is the primary mechanism accounting for the antinatriuretic effect of NSAIDs is not clear. In support of this hypothesis Nies and associates have found that indomethacin antagonized furosemide natriuresis only under conditions where it also antagonizes furosemide induced increases in renal blood flow [11]. On the other hand, attenuation of furosemide natriuresis by indomethacin and meclofenamate can occur in the absence of alterations in renal blood flow [5, 7]. NSAID induced reductions in renal blood flow have been reported in the absence of alterations in the natriuretic response to loop diuretics. Assessment of these studies is complicated because changes in intrarenal blood flow, especially in the medullary circulation, may not be reflected by changes in total renal blood flow. Indeed, there is evidence that blood flow in the medulla may be regulated independently of total renal blood flow largely due to the local influences of prostaglandins, angiotensin II, and perhaps nitric oxide. We have measured furosemide response in indomethacin treated rats in which the reduction in medullary plasma flow usually associated with NSAID administration was prevented by blocking angiotensin II mediated vasoconstriction [7]. Consistent with reports from other investigators the attenuated furosemide natriuresis found in indomethacin treated rats was associated with a significant reduction in medullary plasma flow. However, preventing the fall in medullary plasma flow associated with indomethacin administration did not alter indomethacin capacity to antagonize furosemide natruresis. In aggregate the available studies suggest that changes in renal hemodynamics are not a prerequisite for antagonism of loop diuretics by NSAIDs.

Tubular Mechanisms

Prostaglandin synthesis inhibition could also blunt natriuretic responses to diuretics by direct effects on tubule reabsorption. This could occur in the tubule segment directly inhibited by the diuretic or in tubule segments proximal or

distal to the diuretic's location of action. The magnitude of the reduction in sodium excretion observed during NSAID antagonism of loop and thiazide diuretics would favor more proximal tubule segments as the location for this event.

Whether prostaglandins play a direct role in the regulation of salt and water reabsorption in the anatomical proximal tubule is controversial. It is equally unclear whether inhibition of prostaglandin synthesis has direct effects on transport at this location. In micropuncture studies examining potential tubular locations for NSAID antagonism of diuretic response, we have shown that neither indomethacin nor meclofenamate alters chloride or fluid delivery to the late proximal convoluted tubule in rats receiving furosemide (Fig. 3). We have reported similar findings during indomethacin antagonism of hydrochlorothiazide natriuresis [8]. These findings are consistent with the observation of others that inhibition of prostaglandin synthesis does not alter proximal tubule function in the rat. However, micropuncture methodology examines only 60% of the proximal tubule. In humans there is also little objective evidence that major changes in proximal tubule reabsorption occur during antagonism of diuretic

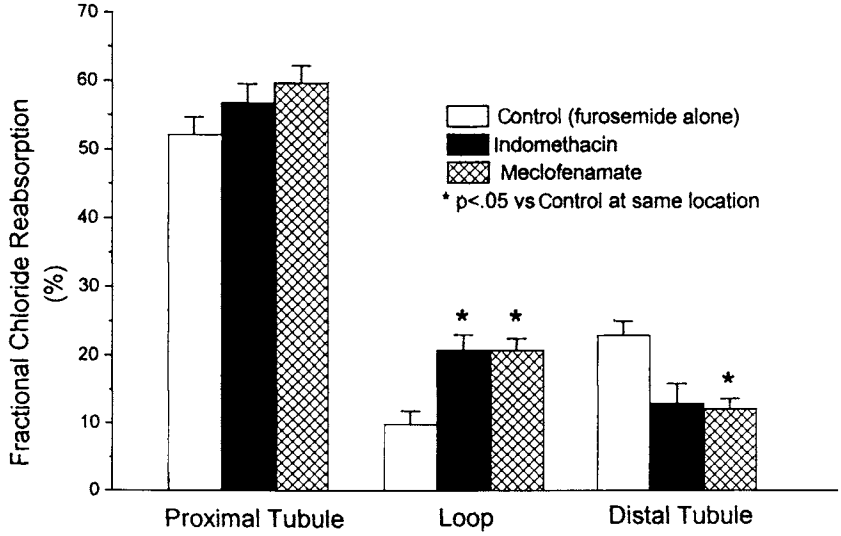

FIGURE 3. Fractional chloride reabsorption in proximal, loop, and distal tubule segments during furosemide natriuresis in control rats (open bars), indomethacin treated rats (hatched bars), and meclofenamate treated rats (solid bars). Indomethacin and meclofenamate had no effect on proximal tubule reabsorption but significantly blunted furosemide inhibition of loop reabsorption. Reabsorption in the distal tubule was lower in indomethacin and meclofenamate treated rats. * $P<.05$ vs control at same tubule location. From Kirchner (1985, Fig. 1, p. F701.) with permission.

effects by NSAIDs. Some human studies on effects of prostaglandin synthesis inhibition on renal function have shown altered free water clearance, a finding interpreted as evidence of a role for prostaglandins in proximal tubule reabsorption. Interpretation of free water clearance data during inhibition of prostaglandin synthesis is complicated, however, by independent effects of prostaglandin inhibition on collecting duct water uptake. Thus, even though increased solute reabsorption in this location would be an attractive mechanism for explaining the finding that NSAIDs antagonize multiple diuretic agents, whether NSAIDs blunt diuretic responses through alterations in sodium and water transport in the proximal tubule remains unknown.

There is convincing evidence that the loop segment is an important location for the attenuation of diuretic response during prostaglandin synthesis inhibition. Micropuncture studies have shown that rats receiving intravenous furosemide and indomethacin or meclofenamate have twice the fractional and absolute chloride, and thus presumably sodium, reabsorption in the loop segment as do rats receiving furosemide alone (Fig. 3). We have also shown that indomethacin treated rats had 40% less inhibition of chloride reabsorption than control rats when furosemide was microperfused directly into isolated loop segments [6]. Furthermore, the inhibitory effect of indomethacin could be abolished by the systemic or intratubular administration of prostaglandin E_2. These observations categorically demonstrate that antagonism between NSAID and loop diuretics can result from direct antagonism of furosemide's effect on tubule transport and can occur independently of furosemide or NSAID induced alterations in renal blood flow or in renal blood flow distribution. How NSAIDs antagonize loop diuretics at this location is as yet undetermined. Indomethacin does not alter furosemide induced changes in short circuit current in frog skin, suggesting that indomethacin effect is not the result of interference with furosemide binding to the Na–K–2Cl cotransporter or to the transport process itself. We have shown that indomethacin does not blunt furosemide response in ADH deficient Brattleboro rats despite equivalent stimulation of urinary prostaglandin excretion by furosemide and suppression by indomethacin. Indomethacin antagonism of furosemide response could be restored by ADH replacement. In the rat ADH stimulates loop sodium chloride transport and this effect is inhibited by prostaglandin E_2. Thus NSAIDs may increase loop uptake by interfering with prostaglandin modulation of ADH stimulated sodium chloride transport. Whether this mechanism is important in diuretic antagonism in humans is unclear as ADH is not felt to modulate loop transport in man. The loop segment may be the location for NSAID induced antagonism of other classes of diuretics as well. We have shown that the loop segment is the only nephron segment demonstrating increased reabsorption during indomethacin's antagonism of hydrochlorothiazide response [8]. Brater has proposed that the

antagonism between NSAIDs and potassium-sparing diuretics occurs as a result of increased sodium uptake in the loop as well [2]. Whether increased sodium uptake in nephron segments beyond the loop of Henle contributes to diuretic antagonism by NSAIDs has not been extensively examined. Chloride reabsorption in the distal convoluted tubule was found to be suppressed by NSAIDs during furosemide administration and unchanged during hydrochlorothiazide administration in the rat [5, 8]. Others have reported that all of the reduction in sodium excretion in meclofenamate treated rats and two-thirds of the reduction in sodium excretion in indomethacin treated rats observed during furosemide administration occurred before the inner medullary collecting duct [13]. Thus most experimental evidence implicates the loop segment as the primary location for the diuretic antagonism observed during NSAID administration.

Another potential tubular mechanism for antagonism between NSAIDs and spironolactone is competition for mineralocorticoid receptors. Displacement studies have shown that the sequence of binding affinity for these receptors is aldosterone → spironolactone → phenylbutazone → aspirin → indomethacin. The concentration of indomethacin required to displace aldosterone from its receptor is greater than would occur clinically but aspirin and phenylbutazone concentrations are within concentrations which could occur clinically. The extent to which this mechanism contributes to antagonism of potassium-sparing diuretics is unclear.

NSAIDS EFFECTS ON DIURETIC EXCRETION OF OTHER SOLUTES

The effect of NSAIDs on diuretic stimulated excretion of other solutes has not been extensively examined. The kalurietic effects of loop diuretics during NSAID administration have been reported to be unaltered in some studies and reduced in others [2, 10, 11]. Even in the latter cases the reduction in potassium excretion is usually quite modest compared with the reduction in sodium excretion. Greater reductions in potassium excretion have been reported in association with significant reductions in GFR. Studies reporting the time course of changes in sodium and potassium excretion following administration of loop diuretics in NSAID treated subjects show that potassium excretion is maintained during the initial phase of attenuated natriuretic response then slowly decreases after 30 to 60 min [2, 11]. The mechanisms for this phenomenon remain to be defined. However, there is some evidence that loop diuretics may directly inhibit potassium transport by mechanisms independent of their natriuretic properties. Indomethacin has been noted to abolish the antikaluretic effect of spironolactone even without reducing urinary sodium excretion.

EFFECT OF NSAIDS ON DIURETIC STIMULATED RENIN RELEASE

Indomethacin has been shown to attenuate the increase in plasma renin activity which follows furosemide, hydrochlorothiazide and even spironolactone administration in man [10]. The time course of this inhibition is rapid and occurs independently of diuretic effects on sodium excretion or measurable change in vascular volume. Therefore it seems likely that the inhibition of renin release is due to direct effects on the juxtamedullary apparatus. As aldosterone levels following diuretic administration are related primarily to changes in angiotensin II, they parallel the changes in renin release.

ACUTE RENAL FAILURE FROM DIURETIC AND NSAID ADMINISTRATION

Acute renal failure has been reported in two healthy volunteers taking indomethacin and triamterene as part of a drug study, in one patient taking this combination, and recently in a man with mild hypertension taking ibuprofen and the combination of hydrochlorothiazide and triamterene who had been strenuously exercising. The latter individual underwent a renal biopsy which showed acute tubular necrosis (ATN). All patients subsequently recovered renal function in a time course consistent with ATN. Why these individuals developed ATN is unclear, but an idiosyncratic reaction to this combination of drugs or potentiation of physiologic reductions in renal blood flow induced by exercise has been proposed. Clinicians and patients should be aware of the potential risks from this drug combination.

SUMMARY

The action of most frequently used diuretic agents is altered by drugs which inhibit prostaglandin synthesis. The most frequent finding is a reduction in diuretic efficacy. The mechanism appears to be primarily pharmacodynamic in nature. With the widespread use of NSAIDs and the increased availability of these agents without a prescription, NSAID antagonism should be considered in cases where the response to diuretics is less than expected.

ACKNOWLEDGMENTS

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CHAPTER IVB4

Impairment of Diuretic Secretion

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INTRODUCTION

Acetazolamide, the thiazides, loop diuretics, and amiloride must reach the lumen of the renal tubule to exert their effect. However, these agents are extensively bound to serum proteins, primarily albumin, which effectively prevents their entry into the tubule through glomerular filtration. Thus these drugs reach the tubular lumen by secretion from blood into tubule fluid. The transport mechanisms responsible for tubular secretion are not unique to the kidney and occur in other organs as well. In the kidney, however, these processes have gained considerable attention because of their importance to the pharmacology of many drugs and drug metabolites. The most frequently used diuretic compounds, thiazide and loop diuretics, exist in the serum as organic anions, while the diuretics amiloride and triamterene are organic cations. Both classes of compounds are secreted by the charge selective secretory pathways located in the proximal renal tubule. The general characteristics of both of these secretory systems are that they can move substances uphill against a concentration gradient, can at times transport substrates bidirectionally, can be saturated by high substrate concentrations, and demonstrate competitive inhibition between compounds in the same class. Although the focus of this chapter will be the importance of this system to diuretic pharmacology, the physiologic relevance

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of these systems for the removal of endogenous substances such as urate and creatinine and for the delivery of endogenous modifiers of renal function such as the protaglandin to their sites of action in the tubule should not be forgotten.

RENAL TRANSPORT OF ANIONIC DIURETICS

Three steps are necessary to effect tubular secretion of organic anions. First, the anionic compound must be delivered to the basolateral surface of the proximal tubule cell; second, the anionic compound must be transported into the cell across the basolateral membrane; and third, the anionic compound must be transported across the brush border membrane into the tubule lumen. Most investigations of these processes relating to anionic diuretic secretion have used furosemide and chlorothiazide as the probes and it is assumed that other loop diuretics and acetazolamide are secreted in a similar manner.

The first step in the process of tubule secretion is the delivery of the diuretic to the interstitial space surrounding the basolateral portion of the proximal tubule cell. Binding between the diuretic and albumin is central to this process. Inoue and associates have shown that the attenuated furosemide response observed in analbuminemic rats results almost entirely from impaired delivery of furosemide to the tubule lumen [7]. In these rats urinary furosemide recovery and diuretic response are significantly lower than in normal rats, although sodium excretion plotted as a function of urinary furosemide concentration is normal (Fig. 1). The essential role of albumin as a carrier for furosemide in this setting is demonstrated by the finding that a mixture of equal molar amounts of albumin with furosemide prior to intravenous diuretic administration significantly increased diuretic response in analbuminemic rats but had no additional effect in normal rats. The effects of this mixture was not due to the oncotic effects of the albumin since administration of the same amount of albumin prior to diuretic infusion resulted in no improvement in natriuretic response in either animal group. Thus diuretic albumin binding is a necessary step for diuretic secretion in the kidney. Albumin may also play an important role in the regulation of anionic diuretic secretion [2]. Albumin stimulates renal organic anion transport in a dose-dependent manner up to a concentration of 1.0 g/dl. This effect is independent of peritubular oncotic pressure and independent extent of anion–albumin binding. High concentration of albumin may also inhibit anion transport. The mechanism for the regulatory effect of albumin on renal anion secretion and whether this is important the regulation of diuretic secretion is yet to be determined. Nonetheless, albumin is an important component for the initial steps of renal secretion of anionic diuretics.

The transport of anionic compounds from the interstitial space across the basolateral cell membrane has been extensively examined. Early studies used

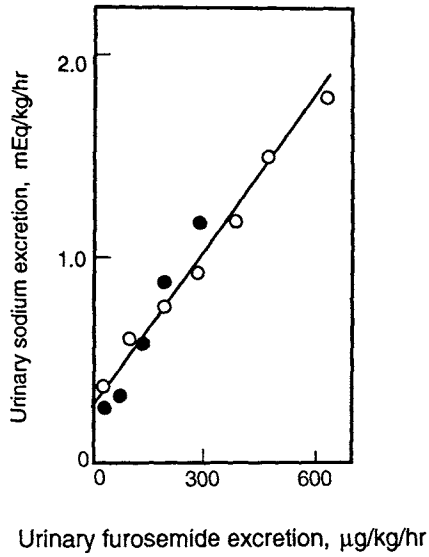

FIGURE 1. One-hour urinary sodium and furosemide excretion rates following intramuscular administration of various doses of furosemide to normal (open circles) and analbuminemic (closed circles) rats. Urinary furosemide recovery was low in analbuminemic rats compared with normal rats but sodium excretion as a function of urinary furosemide excretion was not different between groups. Adapted from Inoue et al (1987, Fig. 3, p. 199) with permission.

para-aminohippurate (PAH) as the probe for this process because PAH is as avidly secreted as hippurate, the principal endogenous anion secreted by the dog, PAH is not metabolized, and PAH is easily measured. These studies demonstrated that in the kidney anionic transport was localized to the proximal tubule with greater activity in juxtamedullary than cortical nephrons. Within individual proximal tubules the density of transporters seem to be greatest in the S_2 segment although there may be some species heterogeneity. Kinetic evaluation of PAH transport in the rabbit juxtamedullary and cortical proximal tubules suggests that there is unequal distribution of transporters with a common substrate affinity along the proximal tubule subsegments. The S_2 segment has a maximal transport rate five- to sevenfold greater than the S_1 or S_3 segment and this difference is due to differences in basolateral membrane transport [5, 6, 10]. However, more recent studies suggest that there are multiple renal anion transport systems which can operate exchanging organic for organic substrates, organic for inorganic substrates, or inorganic for inorganic substrates depending on the intra- and extracellular availability of the anionic substrates themselves (Fig. 2). Fortunately for our understanding of renal diuretic secretion the anionic transport system which transports PAH is also the one primar-

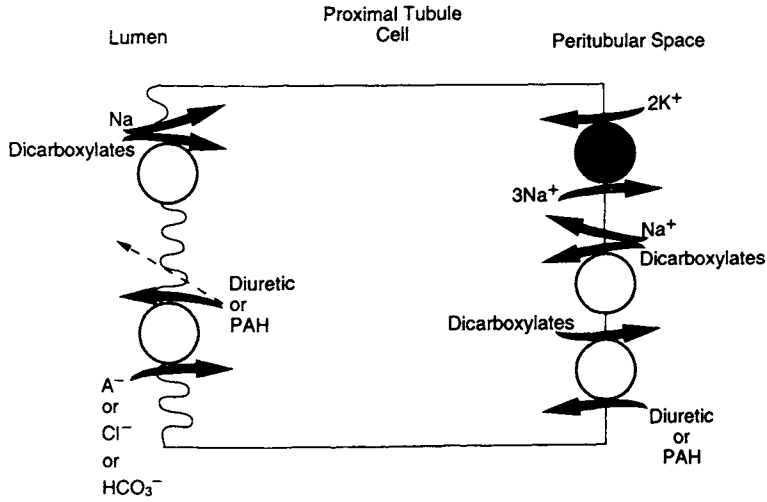

FIGURE 2. Tertiary active transport system for anionic diuretics. At the basolateral border of proximal tubule cells organic anions such as PAH or diuretic are transported across the cell membrane in exchange for dicarboxylate intermediates of the Kreb's cycle. Dicarboxylate intermediate enters by cotransport with sodium at either cell surface. Energy for both transport processes is provided by the NaK ATPase pump (solid circle). At the brush border membrane the diuretic exits the cell in exchange for tubular anion including chloride or bicarbonate or by passive diffusion.

ily responsible for the transport of acetazolamide, the loop diuretics, and the thiazide diuretics.

Transport across the proximal tubule basolateral membrane occurs in the form of bidirectional anion exchange between the pericellular and intracellular compartments. Specific anions can be moved in either direction based on their affinity for the transporter and concentration in each compartment. For the proximal tubule transporter it appears that *in vivo* the usual intracellular anionic substrates exchanged for the interstitial anions are dicarboxylate components of the Krebs cycle, usually alpha ketoglutarate or glutarate. These dicarboxylates can either be manufactured in the cell or more frequently added to the cytoplasm from tubule fluid or blood by cotransport with sodium. The tight association of these two distinct transport systems led to the initial consideration that PAH transport may be sodium dependent. However, in rat renal basolateral membrane vesicles inwardly directed gradients of lithium, potassium, and rubidium are as effective as sodium in stimulating PAH uptake in the presence of glutarate [9], while sodium in the absence of glutarate was ineffective in stimulating PAH transport. PAH uptake is also accelerated in vesicles preloaded with glutarate compared to glutarate-free vesicles. Therefore it appears that glutarate cotransported into the cell with sodium is then exchanged with

extracellular PAH, leading to accumulation of PAH in the vesicle. Subsequent studies have shown that in spite of the sharing of dicarboxylate substrates between the two transport systems, the affinity for other anionic compounds is not identical. It seems that while all substrates for the sodium dicarboxylate cotransporter are accepted by the dicarboxylate PAH exchanger, the latter transporter handles a number of organic and inorganic anions not accepted by the sodium dicarboxylate cotransporter. Probenecid and thiazide diuretics are examples of such compounds which compete with PAH for uptake by the basolateral PAH dicarboxylate exchanger but do not interact with the sodium dicarboxylate cotransporter. The energy for these exchanges is provided by Na/K ATPase and possibly other ATPases located in the basolateral membrane. These produce an outside-in transmembrane electrochemical cation gradient which powers the sodium dicarboxylate cotransporter. The entire basolateral membrane transport process has been referred to as tertiary active transport.

The mechanism for the exit of anionic compounds from the cell into the tubular lumen have also been intensively studied. Studies have demonstrated that this last step across the luminal brush border membrane is in part due to an electroneutral anion exchanger which can operate in organic–organic, organic–inorganic, inorganic–inorganic substrate exchange modes using a variety of substrates including even HCO^- and Cl^- from the tubule lumen in exchange for intracellular substrates [11]. The structural specificity for this transporter is diverse. Furosemide, bumetanide, probenecid, and penicillin show higher affinity for the brush border transporter than does PAH. Additionally, the capacity for transport is greater along the brush border than the basolateral membrane at least in the dog. Transport at this location is also less sensitive to inhibition by probenecid than is transport at the basolateral membrane. Transport across the brush border membrane also occurs by simple diffusion down an electrochemical gradient determined by both the pH and the flow rate of the tubule fluid.

Determinants of Diuretic Interaction with the Anionic Transport System

Examination of the interaction between thiazide or loop diuretics and the basolateral PAH transporter in isolated rabbit S_2 segments have shown that the affinity of a specific diuretic for the transporter is based on the diuretic's electrical charge and hydrophobic properties. Diuretics with a lower pK^a have greater affinity for the transporter. This accounts for the general observation that loop diuretics which have pK^as in the 3.6 to 4.1 range bind to the basolateral PAH transporter with greater affinity than thiazide diuretics which have pK^as in the range of 9.0 and greater. Using *in vivo* stop-flow capillary microperfusion tech-

TABLE 1 Substrate Specificities for Some Diuretics and Antibiotics Transported by the Organic Anion Transport System in the Renal Basolateral Membrane

Drugs	*Para*-aminohippurate (K_i (mM ± SE))	Dicarboxylate (K_i (mM ± SE))	Sulfate (K_i (mM ± SE))
Probenecid	0.03 ± 0.005	>10	7.9 ± 2.2
Acetazolamide	1.3 ± 0.47	>10	6.4 ± 7.7
Furosemide	0.04 ± 0.001	5.1 ± 8.9	0.87 ± 0.3
Piretanide	0.07 ± 0.02	>10	2.9 ± 1.9
Ethacrynic Acid	0.12 ± 0.04	>10	4.7 ± 4.8
Hydrochlorothiazide	0.72 ± 0.19	>10	4.4 ± 4.3
Benzylpenicillin	0.81 ± 0.24	>10	>25
Phenoxymethyl-penicillin	0.7 ± 0.18	>10	>25
Ticarcillin	0.84 ± 0.24	>10	8.2 ± 13.2
Cephalexin	2.3 ± 1.25	>10	>25

Note. Starting capillary perfusate concentration was 0.1 mM/liter for PAH and 0.15 mM/liter for dicarboxylate (succinate) and 0.01 mM/liter for sulfate. Concentrations of drugs were 1 mM for probenicid and ethacrynic acid and 10 mM for all other drugs against PAH and 10 mM against succinate and 5 mM against sulfate (probenicid was 50 mM). The apparent inhibitory constant K_i was calculated by computer program. From Ulrich 12, Tables 1 and 2, pp. 80–81) with permission.

niques loop diuretics were found to have almost a 5-fold greater affinity for the PAH transporter than either hydrochlorothiazide or acetazolamide in the rat proximal tubule [12]. Among the loop diuretics piretanide had greater affinity than furosemide or ethacrynic acid for the PAH transporter (Table 1). Acetazolamide, hydrochlorothiazide, and the loop diuretics also showed some affinity for the anionic sulfate transporter but at concentrations 6- to 10-fold higher than for the PAH transporter. Interestingly, furosemide in high concentrations but none of the other diuretics bound to the sodium dicarboxylate cotransporter. A similar order of diuretic interaction (bumetanide > piretanide > furosemide >> hydrochlorothiazide) with the basolateral PAH transporter system was also reported in studies using isolated S_2 segments from rabbit proximal tubules [1]. Among the group of loop diuretics, the affinity for the PAH transporter is identical with the order of affinity for the Na/K/2Cl transporter in the thick ascending limb of Henle's loop. As anion transport in the brush border membrane is less specific, of high capacity, and may be augmented by simple diffusion, the entry of diuretics into the tubule lumen depends primarily on uptake at the basolateral membrane. These transporters allow concentration of diuretics within the proximal tubule. With subsequent water removal, diuretic concentration in the lumen may be 10 to 20 times higher than that in the systemic circulation. Consequently, diuretics are able to inhibit sodium chloride transporters in the kidney preferentially over similar transporters located in the organs.

Significance of Competition for Diuretic Secretion

Competitive inhibition between diuretics and other substances transported by the basolateral anion transporter has a number of clinical ramifications. Probenecid, the prototypic competitive inhibitor of basolateral anion transport, has been used by many investigators to determine the mode of entry of diuretics into the renal tubule lumen. Probenecid has been found to decrease the intensity of the natriuretic activity of chlorothiazide, hydrochlorothiazide, furosemide, and piretanide, confirming that these diuretics require tubular secretion for their natriuretic action. Some confusion on the role of tubular secretion in the response to bumetanide occurred initially because several studies demonstrated no or partial attenuation of bumetanide diuresis during probenecid administration. Thus it was hypothesized that in man a significant amount of bumetanide entered the proximal tubule lumen through passive diffusion. However, subsequent animal studies have shown that bumetanide has greater affinity than most other diuretics for the basolateral anion transporter. Consequently the failure to observe antagonism between bumetanide and probenecid in humans may have been due administration of inadequate doses of probenecid to competitively inhibit bumetanide secretion.

Competitive inhibitor studies have also suggested more effective strategies for diuretic administration in diseases associated with diuretic resistance. Since total natriuretic response depends both on the intensity of inhibition of tubule transport and the duration of transport inhibition, prolonging exposure of the tubule to lesser concentrations of a diuretic may result in a greater overall effect. Thus competitive inhibitors of diuretic secretion, while reducing the rate of diuretic entry into the tubule, may prolong the duration of secretion and consequently exposure of the tubule to the effects of the diuretic. Brater noted that a large dose of chlorothiazide induced a greater cumulative natriuretic effect when given to volunteers pretreated with probenecid than when given alone even though the amount of diuretic excreted in the urine was equivalent in both settings (3; Fig. 3). This provides the rationale for trials of continuous diuretic infusion to maximize inhibition of sodium reabsorption at a diuretic's active site as a strategy for overcoming diuretic antagonism.

The most clinically important effect of competition between diuretics and other compounds for transport by the basolateral anion transport system is limitation of diuretic access to the tubule lumen. A wide variety of both endogenous and exogenous compounds are secreted by the renal organic anion transport system and can potentially interfere with diuretic secretion. Fortunately, the usual plasma concentrations of most endogenous organic anions such as benzoate, cyclic AMP, long-chain fatty acids, urate, and the prostaglandins are too low to significantly impair diuretic secretion in most circum-

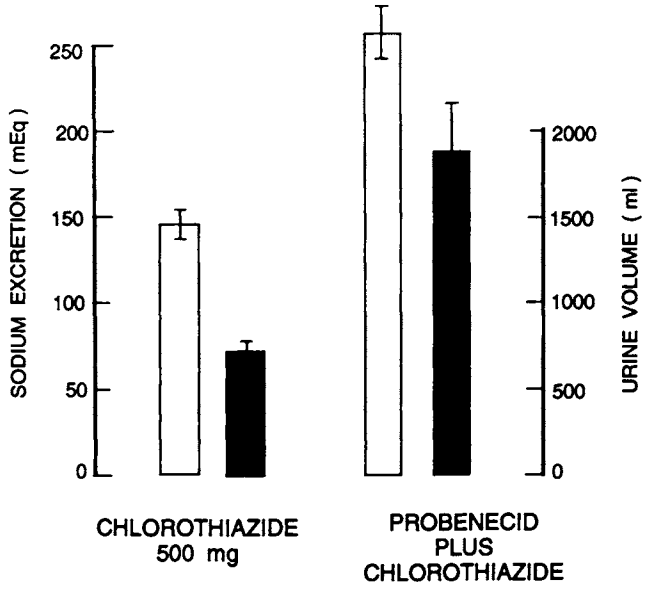

FIGURE 3. Cumulative 8-hr excretion of sodium (open columns) and fluid (solid columns) in subjects treated acutely with 500 mg of chlorothiazide before and after pretreatment with probenecid. Probenecid pretreatment resulted in a greater overall response by slowing diuretic secretion and increasing the duration of exposure of the tubule to the diuretic agent. Adapted from Brater (1978, Fig. 3, p. 262).

stances. However, in renal insufficiency anionic uremic toxins may increase to sufficient levels to significantly reduce diuretic secretion (Fig. 4). This occurs despite an adaptive increase in PAH secreting capacity in the remnant nephrons and an increase in the amount of free drug available to the tubule through glomerular filtration because of the interference of these compounds with the binding of diuretics to albumin [8]. Competition for basolateral anion transport may in part account for the finding that thiazides and acetazolamide, diuretics with low affinity for the anion transporter, have marginal natriuretic effects in advanced chronic renal insufficiency. However loop diuretics which have greater affinity for the anionic transporter are also affected. In azotemic dogs there is an inverse relationship between blood urea nitrogen and both urinary furosemide excretion rate and diuretic-induced natriuresis. The attenuated response could be partially overcome by increasing the plasma furosemide concentration. Bilirubin is also an organic anion. There are reports that chlorothiazide excretion and its natriuretic response are decreased in patients with jaundice. As thiazide is not cleared by the liver, this finding has been interpreted as evidence of competitive inhibition between bilirubin and diuretic for tubule secretion. Whether this is a clinically significant problem and the

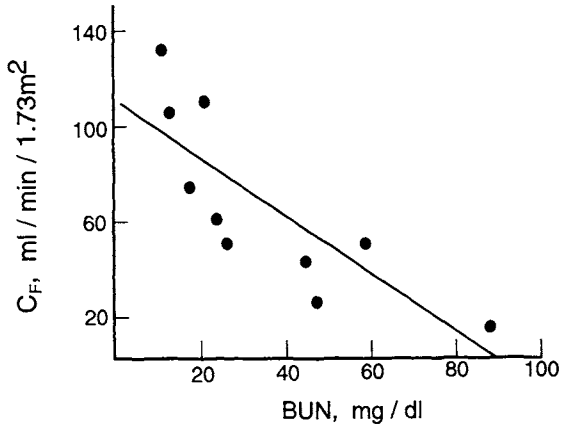

FIGURE 4. Urinary furosemide clearance (Cf) as a function of blood urea nitrogen concentration during continuous intravenous furosemide infusion in patients with varying degrees of renal function. From Rose (1976, Fig. 1, p. 144) with permission.

extent to which it occurs with the more potent loop diuretics remains to be determined.

A number of frequently used drugs are also present in serum as anions and thus could compete with diuretics for tubule secretion by the renal anion transport system. Commonly used drugs include aspirin, the nonsteroidal anti-inflammatory compounds (NSAIDs), antibiotics such as penicillin and its conjurers as well as cephalosporins, and some radiographic contrast agents. Competition for tubular secretion has been one mechanism proposed to explain the attenuated diuretic response observed in patients taking aspirin and other nonsteroidal anti-inflammatory compounds. While such competition does occur, most studies suggest that this is not a major contributor to antagonism of diuretic response during prostaglandin inhibition (see Chapter IVC3). Antagonism between antibiotics and diuretics has been infrequently reported as a clinical problem. This probably reflects the fact that antibiotics are used for only relatively short periods of time and that most antibiotics with the exception of benzyl- and phenoxymethyl penicillin and ticarcillin have very low affinity for anion transporters relative to that of the diuretics (Table 1). Nonetheless, competitive inhibition between diuretics and other drugs for entry into the renal tubule should be considered in evaluation of diuretic resistance.

RENAL TRANSPORT OF CATIONIC DIURETICS

The diuretics triamterene and amiloride exist in the blood as cations. These agents are secreted into the lumen of the renal tubule through an organic cation

transport system. The cation transport system is also located in the proximal tubule. Evidence in almost all species demonstrates that this system is separate from the systems used to transport anions. Quantitative cation transport capacity, however, differs significantly between species. From studies in rabbits it appears that the cation transporters are most abundant in the S_1 segment of superficial proximal tubules and decrease through the S_3 segment. Juxtamedullary proximal tubules have cation transporters in equal abundance in both the S_1 and S_2 segments. Tetraethyl-ammonium (TEA) and *N*-methylnicotinamide (NMN) have been the compounds used most frequently to delineate the renal cation transport systems. Many studies of these systems have used the chicken as the test animal since chicken kidneys have a portal blood supply which allows test compounds to be delivered directly into the kidney without entering the systemic circulation. This is desirable as many of these substances are toxic to other organs. Transport by the organic cation system can also be competitively inhibited. Interestingly, probenecid can also function as an inhibitor of this cation transport system. Endogenous compounds secreted by renal cation transporters include acetylcholine, choline, dopamine, epinephrine, norepinephrine, serotonin, and creatinine, while drugs removed by this system include trimethoprim, quinidine, quinine, atropine, cimetidine, morphine, and the insecticide paraquat as well as the diuretics amiloride and triamterene. The sequence of steps for renal organic cation transport is similar to that described for organic anion transport. However, albumin does not appear to have a regulatory influence on the renal transport of cations. Transport across the basolateral membrane is carrier mediated (Fig. 5). While this was originally thought to occur through facilitated diffusion, recent studies have shown that electroneutral increases in intracellular organic cation concentration stimulate basolateral TEA transport. This finding is most consistent with transport at the basolateral membrane occurring through a cation exchanger [4]. At the brush border membrane, movement of organic cations into the lumen occurs in parallel with sodium hydrogen exchange. The increase in luminal hydrogen ion concentration is then linked to a luminal brush border hydrogen ion cation exchanger powered by the inward hydrogen ion gradient. Energy for all these processes is supplied by the sodium potassium ATPase pump on the basolateral membrane which establishes an inward electrochemical gradient for the basolateral cation transporter. It appears that transport at the luminal membrane is the rate limiting step for organic cation transport and that this transporter has wide range of potential substrates.

Amiloride appears to have an extremely high affinity for the luminal transporter compared with that seen with either TEA or NMN. Thus, antagonism of diuretic action by competitive inhibition for transport into the tubule lumen is an infrequent clinical problem. Although amiloride has been found to inhibit the renal sodium hydrogen exchanger in high concentrations, it does not actu-

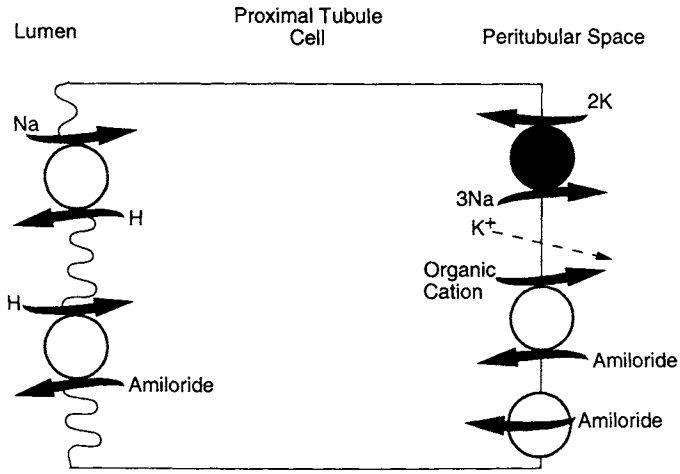

FIGURE 5. Transport system for cationic diuretics. At the basolateral border of proximal tubule cells organic cations are transported across cell membrane either by cation exchange for a reabsorbed cation or by facilitated diffusion down an electrical and chemical gradient. The former is created by passive K exit down a concentration gradient. At the luminal membrane secretion of the diuretic occurs in parallel with Na–H exchange, which allows secretion of the diuretic to be coupled to inward H+ gradient through a second antiporter. Energy for these processes is provided by the NaK ATPase pump (solid circle).

ally bind to the transporter. Additionally the concentration of amiloride required to inhibit sodium hydrogen exchange is higher than concentrations usually achieved in the proximal tubule. Finally, while triamtene is transported by the renal cationic transport system, most of this drug appears to reach the lumen through glomerular filtration. Few studies have examined the contribution of the tubule secretion of triamterene to its overall effect.

SUMMARY

In summary, secretion of diuretics into the lumen of the proximal tubule is an essential step for the action of these agents. It is this event that allows loop diuretics to maintain potency in the setting of reductions in glomerular filtration rate. Competitive inhibition for transport between diuretics and other endogenous and exogenous compounds is an important component of diuretic resistance in a number of circumstances, especially in chronic renal failure. For diuretics with a high affinity for the transporters, increasing the diuretic dose may improve tubule secretion and efficacy.

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CHAPTER IVB5

Albumin as an Adjunct to Diuretics for the Treatment of Edema

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INTRODUCTION

Albumin infusions have been used in conjunction with diuretics to increase natriuresis and diuresis for years. This combination has been usually employed in diseases associated with hypoproteinemia such as nephrotic syndrome, cirrhosis, and occasionally malnutrition. In these conditions diuretic resistance is often encountered. Albumin is most frequently combined with loop diuretics as they are the most potent diuretics in our armamentarium and because both agents can be administered intravenously, thus assuring optimal timing for the potential synergistic effect. The indications for the use of albumin with loop diuretics are the subject of controversy. Some authorities recommend temporary trials of hyperoncotic albumin for resistant edema, while other authoritative sources feel that the use of this combination should be discouraged. Evaluation of the role of diuretic–albumin combinations in the treatment of resistant edema is hampered by a lack of large carefully conducted clinical trials. Nonetheless, the current chapter will attempt to review the data available in this area.

Diuretic Agents: Clinical Physiology and Pharmacology

THEORETICAL MECHANISMS FOR COMBINING ALBUMIN AND LOOP DIURETICS

The rationale for combining albumin with loop diuretics in hypoproteinemic states is based on two potential benefits of albumin on diuretic action: first, improvement in solute delivery to the site of diuretic action; and second, improvement in diuretic delivery into the tubule fluid. These effects are not mutually exclusive.

Improvement in Solute Delivery

For many years hypoproteinemic states have been assumed to be associated with reductions in effective intravascular volume. This event has been postulated to play a seminal role in the intense renal sodium retention associated with nephrotic syndrome and cirrhosis through activation of a number of volume sensitive neurohumoral mechanisms stimulating sodium reabsorption. Additionally changes in vascular volume could induce direct increases in peritubular physical forces favoring sodium uptake in the renal proximal tubule. Intravenous infusions of albumin could therefore increase vascular volume, increase filtered sodium load, blunt neurohumoral mechanisms stimulating sodium reabsorption, and directly decrease the fraction of filtered sodium reabsorbed in the proximal tubule. In the presence of a diuretic, the resultant increase in distal delivery would be more effectively excreted. Data from a number of investigators, however, now suggest that most patients with hypoproteinemia from nephrotic syndrome and many patients with cirrhosis are not intravascularly volume depleted. Defects in the intrarenal regulation of sodium reabsorption are now felt to account for much of the sodium retention occurring in those disorders. A 1979 review of data obtained from 217 nephrotic patients in 10 published series found that plasma volume was reduced in one-third, normal in one-half, and increased in the remainder of untreated nephrotics with hypoproteinemia [2]. A more recent study of 88 patients with nephrotic syndrome has found normal or increased vascular volume in all of those individuals [4]. Plasma volume in animals with experimental nephrotic syndrome is also reported to be normal or increased. There have been some suggestions that patients with minimal change disease, especially children, may be more likely to present with a decreased effective intravascular volume, although this is not uniformly accepted. The finding that intravascular volume is not decreased in most patients with nephrotic syndrome is also supported by findings that hormones sensitive to changes in effective circulating volume such as

renin and aldosterone are decreased in the majority of nephrotics [2, 4, 5, 9]. It also seems unlikely that albumin has any direct effects on the renal mechanisms for sodium retention in nephrotic syndrome. Albumin infusion given without diuretics induce little or no increase in sodium excretion in the majority of nephrotics [9]. Furthermore, albumin had no effect on proximal sodium reabsorption as determined from maximal free water clearance studies. Normal proximal tubule function is also found in the majority of animal models of nephrotic syndrome examined by micropuncture techniques. Thus, most evidence does not support a specific role for albumin in the correction of the antinatriuretic defect associated with nephrotic syndrome. Such a conclusion is consistent with other observations that natriuresis occurs prior to an increase in plasma protein concentration during the recovery phase of minimal change disease [5].

Similar evaluations in the hypoproteinemia associated with cirrhosis suggest that a decreased intravascular volume does not uniformly account for reduced renal sodium excretion in that condition as well [12]. Measurements of plasma volume suggest that this parameter is not reduced in the majority of cirrhotics. However, the increase in vascular capacitance associated with severe liver disease complicates determination of plasma volume in this condition. Plasma norepinephrine levels and plasma renin levels are frequently elevated in cirrhotics and have been interpreted as evidence for intravascular volume depletion in these patients. However a recent longitudinal evaluation of patients with alcoholic liver disease has shown no change in blood volume, plasma norepinephrine, plasma renin levels, atrial natriuretic factor, or several other parameters during episodes of ascites formation and spontaneous recovery in individual patients [12]. Thus the role of these factors as markers for volume depletion as well as the role of volume depletion in the pathogenesis of sodium retention in liver disease remains unclear. Finally, while vascular volume expansion with saline or albumin increases sodium excretion in many cirrhotics, it does not do so in all. Epstein using head-out water immersion to increase central vascular volume in cirrhotics has suggested that increased sodium reabsorption in the distal nephron may account for decreased sodium excretion in some cirrhotics [4].

Albumin infusion could function as a nonspecific volume expander in hypoproteinemic conditions. However, any increase in plasma volume is transient. In nephrotic syndrome 10% of the initial increase in plasma volume and none of the initial increase in plasma albumin concentration or oncotic pressure remain 24 hr after albumin infusion [10]. Exudation of albumin from the vascular space may occur even more rapidly in cirrhosis as a result of the elevated portal pressure. Thus, multiple doses of albumin must be administered for any sustained effect on vascular volume.

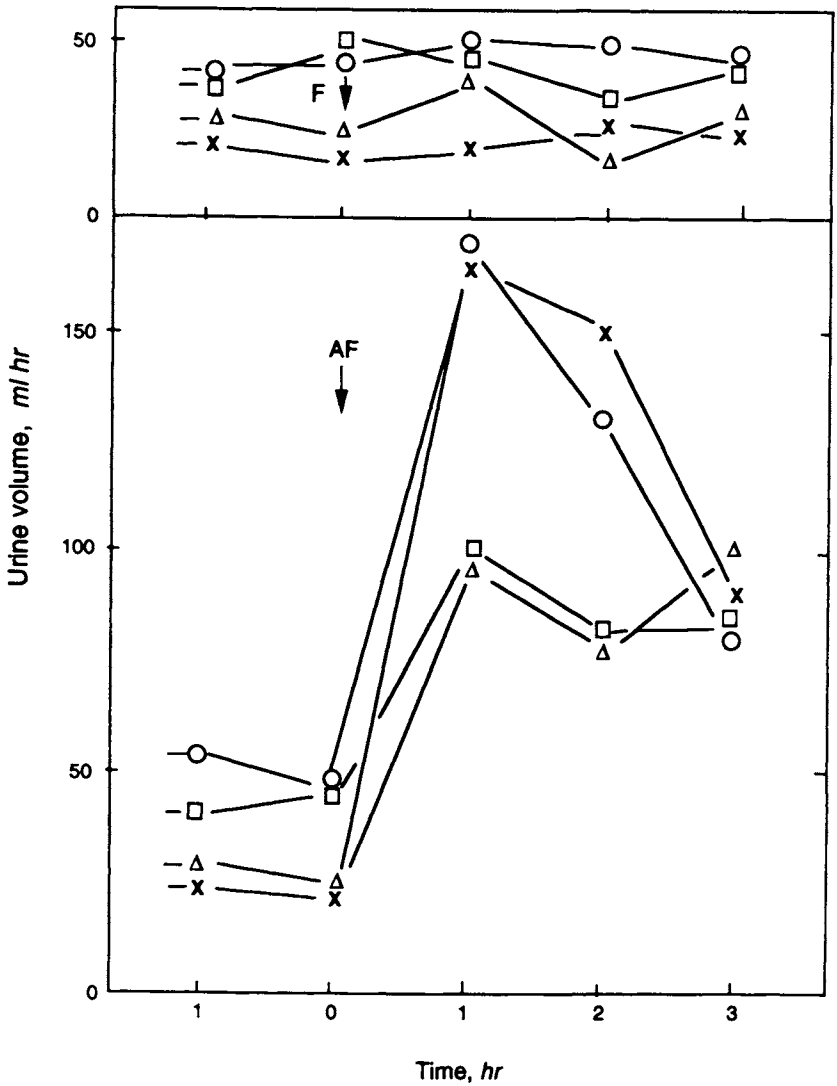

FIGURE 1. Effect of 30 mg of furosemide administered intravenously alone (point "F" top) or premixed with 6 g of albumin (point "AF", bottom) on urine flow rate in four hypoalbuminemic patients with serum albumin concentrations of less than 2.2 g/dl. Patients were resistant to furosemide administered alone but had significant increases in urine flow rate following administration of the albumin–furosemide complex. From Inoue (1987, Fig. 7, p. 201) with permission.

IMPROVEMENT IN DIURETIC DELIVERY

Loop diuretics as well as thiazides are highly bound to albumin in the plasma. This binding confines the drug to the vascular space and facilitates diuretic delivery to the peritubular space surrounding the proximal tubule. From this location the diuretics are secreted into the proximal tubule lumen. Albumin also plays a role in regulating the rate of secretion of anionic loop diuretics into the proximal tubule. This effect is independent of its function as a carrier molecule. Thus albumin is essential in determining the concentration of loop diuretic reaching its active site. The importance of these events in determining diuretic response has been shown by Inoue and associates using an analbuminemic rat model [7]. Thirty minutes following furosemide administration, these rats had a ninefold greater increase in the volume of furosemide distribution and a urinary furosemide excretion that was 74% less than that found in normal rats. Mixing furosemide with an equimolar concentration in albumin prior to administration reduced furosemide volume of distribution in analbuminic rats to twofold that of normal rats while increasing urinary furosemide excretion to 69% of that seen in normal animals. These changes were associated with significant increases in diuretic response. Likewise, patients with hypoalbuminemia from a variety of causes demonstrated a significantly greater diuretic response following administration of 30 mg of furosemide bound to 6 g of albumin than to 30 mg of furosemide alone (see Fig. 1). This effect could not be attributed to increases in plasma albumin concentration or oncotic pressure. The extent to which this mechanism contributes to attenuated diuretic response in nephrotic syndrome or cirrhosis is unclear. Several investigators have noted that nephrotic patients with well preserved glomerular filtration rates have renal clearances of loop diuretics and total amount of diuretic reaching the urine that are not different from normal subjects when examined over long time intervals. However, as diuretic response depends on both duration of exposure of the tubule to the diurectic and tubule fluid diuretic concentration, the observations of Inoue and associates and the findings from pharmacokinetic studies of others need not be contradictory. In fact several investigators have attributed part of the impaired diuretic or natriuretic response to loop diuretics observed in nephrotics to alterations in diuretic secretion.

USE OF ALBUMIN AND DIURETICS FOR EDEMA TREATMENT

Although the combination of albumin and diuretics has been used in the treatment of nephrotic edema for over 25 years, few studies have critically examined

the response to this therapy. Most studies report using 0.5–1.0 g/kg body weight of 20–25% albumin administered over 30–60 min followed by a 30-min infusion of 1–2 mg/kg furosemide. This therapy is then repeated daily or every other day as needed to achieve the desired degree of weight loss. Average weight losses of 1.2 to 2.5% of the initial pretreatment body weight have been reported in children responding to this regimen. Unfortunately, not all nephrotics respond to this treatment and it is not possible to predict who will respond based on renal histology, initial serum albumin concentrations, or other parameters. Additionally, it is difficult to ascertain how much greater a response will be obtained using the combination of albumin and loop diuretic compared to the diuretic alone. McLigeyo reported an average increase in urine volume of 874 ml/24 hr in 11 nephrotics following addition of 200 ml of 25% albumin solution to a regimen of furosemide and spironolactone [11]. A 59% improvement in sodium excretion rate and an 87% increase in total urinary furosemide excretion rate has been reported following addition of 20–25 g of albumin to 1 mg/kg body weight dose of furosemide injected into nephrotics with initial serum albumin values of less than 2.0 g/dl [9]. On the other hand, Akcicek and associates in a randomized cross-over study of eight nephrotics with average serum albumin concentration of 1.73 mg/dl found no potentiation of diuretic or natriuretic response with the combination of 0.5 g/kg albumin and furosemide compared to furosemide alone [1]. The albumin infusion did, however, produce a 30% increase in plasma volume (see Fig. 2). Combining several diuretics with different sites of action and albumin has been reported to induce no greater sodium excretion than administration of albumin with a loop diuretic. Even in those responding to diuretic and albumin therapy, intense sodium retention occurs rapidly after therapy is discontinued unless remission of the underlying glomerular disease is achieved.

Very little information is available on the use of albumin and diuretics for the edema associated with cirrhosis and other hypoproteinemic conditions. In cirrhosis this undoubtedly reflects the recognition that rapid diuresis is unnecessary and potentially hazardous due to the limited rate at which fluid can be reabsorbed from the peritoneal cavity. Furthermore, in circumstances where fluid must be removed rapidly, large volume paracentesis has been reported to be more effective and have fewer complications than diuretic therapy [13]. Thus this latter technique has been used instead of diuretics when vigorous fluid and sodium removal is required. Other hypoproteinemic diuretic resistant conditions do not occur with sufficient frequency to determine whether diuretics combined with albumin are beneficial.

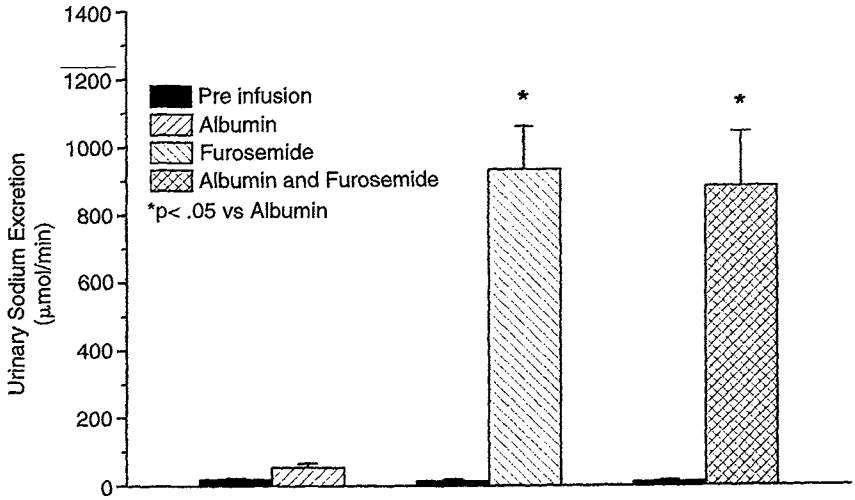

FIGURE 2. Effect of furosemide and albumin alone and in combination on urinary sodium excretion rate in 12 patients with nephrotic syndrome. The addition of albumin to furosemide had no additional effect on sodium excretion compared to that seen with furosemide alone. Adapted from Akcicek (1995, p 162) with permission.

COMPLICATIONS OF ALBUMIN AND DIURETIC COMBINATIONS

Administration of albumin with diuretics may be associated with a number of complications. The most frequently reported problem is hypertension. The acute onset of hypertension of sufficient severity to require treatment is reported in between 10 and 46% of treatment courses with albumin and loop diuretics in some series [6, 14]. Additionally, over one-third of already hypertensive individuals will require upward adjustment of their medications to maintain blood pressure control during treatment with albumin and diuretics. Electrolyte abnormalities are also a commonly observed problem during administration of albumin and loop diuretics [4]. Hypokalemia develops in up to 40% of treatment courses while hypernatremia and metabolic alkalosis have been reported in 17 and 11% of treatment courses, respectively. The high sodium concentration of hyperoncotic albumin (130–160 mEq/liter) undoubtedly contributes to the hypernatremia. Acute respiratory distress and congestive heart failure also occur but are fortunately infrequent. Some investigators have noted an increase in serum creatinine concentration during treatment with albumin and diuretics [14]. This does not appear to correlate with the

magnitude of the diuretic response nor the level of baseline renal function. Although serum creatinine concentrations fell from their peak value following discontinuation of albumin and diuretic therapy, serum creatinine concentrations did not return completely to baseline despite a follow-up of up to 7 weeks in some cases. Whether the increase in serum creatinine reflects a reduction in renal function or change in creatinine production is unclear. The underlying disease in the majority of patients who manifested this change was focal glomerulosclerosis. Finally metal contamination of albumin can occur during processing of albumin from plasma and there have been reports of accumulation of these metals, especially aluminum in patients during albumin replacement. Patients with impaired renal function are more susceptible to this problem. Data on complications of albumin and diuretic therapy in other hypoproteinemic conditions have not been specifically reported.

SUMMARY

Whether combining albumin with diuretics is an effective strategy for sodium removal in edematous conditions associated with hypoproteinemia is unclear. In nephrotics with serum albumin concentrations of less than 2 g/dl, a trial of albumin and diuretic therapy seems reasonable in circumstances where other attempts to induce natriuresis have been unsuccessful. In cirrhotics large volume paracentesis may be a more efficacious strategy than albumin and diuretics for managing a diuretic resistant patient when rapid removal of ascites is necessary. It should be recognized that unless the conditions inducing sodium retention are rectified, the effects of albumin and diuretic therapy will be very transient unless coupled with a significant restriction in sodium intake. Additionally, cost and frequent complications remain a problem.

ACKNOWLEDGMENTS

I thank Mrs. Ruthie Lofton and Mrs. Phyllis Vick for their excellent secretarial assistance. This work has supported in part by research funds from the Mississippi Affiliate of the American Heart Association, Grants HL 51971-02 and HL 38499 from the NIH, and from the Department of Veterans Affairs.

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CHAPTER IVC1

Intensive Diuretic Therapy: High Doses, Combinations, and Constant Infusions

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An edematous patient may be deemed resistant to diuretic drugs when moderate doses of a loop diuretic do not achieve the desired extracellular fluid (ECF) volume reduction. As shown in Fig. 1, the natriuretic dose–response curve for loop diuretics is sigmoidal; the natriuretic portion of the normal diuretic response curve is quite steep. Edematous disorders tend to shift the diuretic dose–response curve rightward. Thus, a diuretic dose that was effective initially ("B" on Fig. 1) may become ineffective ("C" on Fig. 1). In this case, increasing (often doubling) the loop diuretic dose to achieve a higher urinary diuretic excretion rate may return the patient to diuretic sensitivity ("D" on Fig. 1). Such an approach may be continued until the maximal safe or recommended dose of loop diuretic is achieved (Table 1 lists maximal effective doses for loop diuretics). Clearly, adding a second daily dose of a diuretic in the ineffective dose range ("C" on Fig. 1) would be of little or no benefit in increasing urinary NaCl excretion. Because loop diuretics are absorbed and act relatively rapidly, many outpatients will note a distinct diuresis within 4 hr of an effective diuretic dose. If such a response is not observed, increasing each dose is usually appropriate.

Before considering intensive diuretic therapy or combination therapy, it is necessary to exclude reversible causes of diuretic resistance. An inadequate reduction in ECF volume does not necessarily indicate an inadequate *natriuretic* response; as discussed in Chapter IVB1 (see Fig. 1, Chapter on Diuretic Adap-

Diuretic Agents: Clinical Physiology and Pharmacology

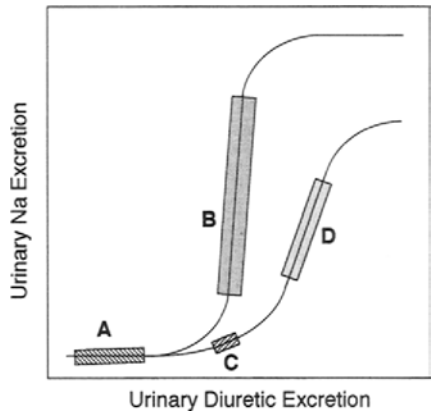

FIGURE 1. Dose–response curve of urinary Na excretion vs urinary diuretic excretion. In a normal individual, or one with mild edema, the dose–response curve is very steep. Whereas a low urinary diuretic concentration is ineffective (box A), a higher concentration leads to significant natriuresis (box B). When more severe sodium retention supervenes (or dietary NaCl intake is reduced), the curve shifts to the right. A previously effective serum concentration is now without effect (box C). At this time, the dose (and urinary excretion rate) of the diuretic must be increased to achieve a natriuresis (box D). Increasing the frequency of diuretic doses has no effect on Na excretion as long as each dose is below the natriuretic threshold (points A and C).

tation), loop diuretics may induce natriuresis without contracting the ECF volume if dietary NaCl intake is excessive. Other potentially treatable causes of diuretic resistance are listed in Table 1, and such causes should be considered before more aggressive diuretic regimens are employed. It should also be emphasized that the "desired" ECF volume may not be associated with an edema-free state and consideration should always be given of the need to reduce ECF volume further. When needed, however, intensive diuretic treatment is usually effective in reducing the ECF volume to acceptable levels; each of the different approaches to intensive therapy is best employed under specific circumstances. Understanding the mechanisms of diuretic action and adaptation, the causes of diuretic resistance, the goals of diuretic treatment, and the mechanisms of intensive diuretic approaches helps one to select an optimal approach to the diuretic resistant patient.

HIGH DOSE DIURETIC THERAPY

High doses of loop diuretics are frequently employed to treat severe volume overload, especially when treatment is urgent. Maximal effective doses of furosemide, bumetanide, and torsemide have been estimated (see Table 2); when

TABLE 1 Causes of Diuretic Resistance

Patient noncompliance
Not taking drug
High NaCl intake
Delayed absorption of poor bioavailability
Congestive heart failure
Idiopathic edema
Use of incompletely absorbed drug
Impaired diuretic secretion by proximal tubule
Renal failure
Old age
Renal transplantation
Congestive heart failure
Drugs
Nonsteroidal anti-inflammatory drugs
Probenecid
Protein binding in tubule lumen
Nephrotic syndrome
Hemodynamic
Hypotension, shock
Hypoxemia
Drugs
Antihypertensive (including ACE inhibitors)
Non steroidal anti-inflammatory drugs
Shift in dose response
Primary
Congestive heart failure
Nephrotic syndrome
Cirrhosis
Secondary to drugs
Nonsteroidal anti-inflammatory drugs
Adaptation to chronic diuretic therapy

given as a bolus, maximal effective doses of furosemide range from 80 mg iv in hepatic cirrhosis to 500 mg iv in severe acute renal failure. Despite these estimates, some investigators have used much higher doses of furosemide and reported therapeutic success [18]. In diuretic sensitive patients, the most common complications of loop diuretics result directly from the diuresis and natriuresis. Hypokalemia, hyponatremia, and hypotension frequently result because of excessive fluid and electrolyte losses. For diuretic *resistant* patients, however, drug toxicity, most commonly ototoxicity, may also occur and is an important consideration during high dose or prolonged therapy. All loop diuretics have been reported to cause ototoxicity in experimental animals [37] and clini-

TABLE 2 Ceiling Doses of Intravenous Loop Diuretics in Clinical Conditions

	Ceiling dose (mg)					
	Furosemide		Bumetanide		Torsemide	
	iv	*po*	*iv*	*po*	*iv*	*po*
Renal insufficiency						
GFR 20–50 ml/min	80	240	2–3	2–3	20–50	20–50
GFR <20 ml/min	200	80–60	8–10	8–10	50–100	50–100
Severe acute renal failure	500	NA	12	NA		
Nephrotic syndrome with normal GFR	120		3		50	50
Cirrhosis with normal GFR	40–80	80–160	1	1–2	10–20	10–20
Congestive heart failure with normal GFR	40–80	160–240	2–3	2–3	20–50	20–50

cal ototoxicity has been reported following ethacrynic acid, furosemide, and bumetanide administration. Ototoxicity is usually reversible, but has been irreversible occasionally; its incidence may be increased in patients exposed to other ototoxic agents, such as the aminoglycosides [37]. Ototoxicity may be especially common following ethacrynic acid administration and appears to be related to the serum concentration of the drug. Furosemide toxicity has been reported to develop when serum levels exceed 100 μg/ml. It has been suggested, and clinical experience seems to confirm, that ototoxicity of furosemide can be minimized by administering at a rate no greater than 15 mg/min [31] (others have suggested infusion at rates no greater than 4 mg/min [37]). Comparable data are not available for bumetanide and torsemide, but it seems reasonable to recommend avoiding rapid bolus administration of loop diuretics in general. Myalgias appear to be more common following high doses of bumetanide. The avoidance of high peak levels and the concomitant toxicity is one reason that continuous infusion of diuretics (discussed below) has become popular as an alternative approach to treating diuretic resistant patients.

It has long been appreciated that many patients suffering from congestive heart failure experience symptomatic relief from intravenous boluses of loop diuretics before significant volume and NaCl losses have occurred. In one study, patients with extracellular fluid volume expansion following an acute myocardial infarction experienced a decline in left ventricular filling pressure and an improvement in dyspnea within 5–15 min of receiving 0.5 to 1 mg/kg furosemide (see Fig. 2 [9]); the decline in left ventricular filling pressure resulted from an increased venous capacitance, rather than diuresis, at this early time point. To investigate whether renal effects of furosemide mediate systemic vasodilation and the decline in left ventricular filling pressure, furosemide was administered to hypervolemic dogs. The furosemide-induced drop in left ven-

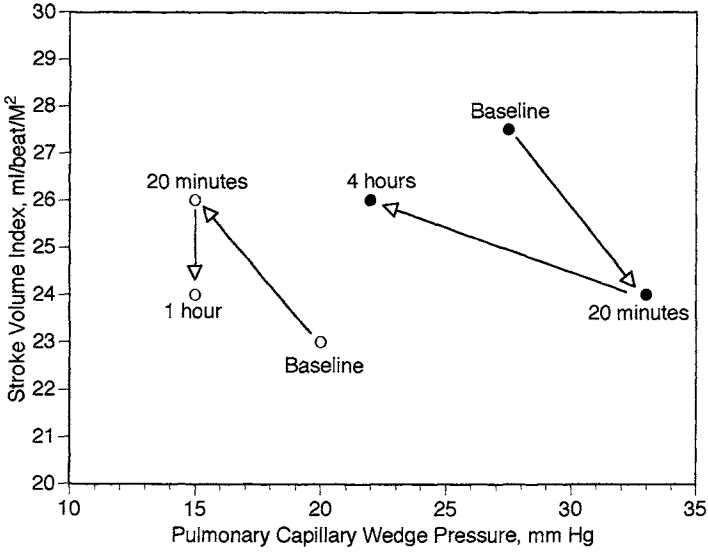

FIGURE 2. Contrasting effects of bolus furosemide administration (0.5–1.0 mg/kg iv) on left-sided filling pressure (pulmonary capillary wedge pressure) and stroke volume index of patients with acute myocardial infarction (open circles [9]) and patients with chronic congestive heart failure (filled circles [15]). In patients with acute myocardial dysfunction (open circles), pulmonary capillary wedge pressure was reduced within minutes of loop diuretic administration, an effect associated with improvement in stroke volume index. In patients with severe chronic congestive heart failure (filled circles), loop diuretics led to a transient increase in pulmonary capillary wedge pressure and deterioration in stroke volume index. By 2–4 hr, however, pulmonary capillary wedge pressure was reduced in both groups. See text for discussion of mechanisms.

tricular filling pressure was not prevented by bilateral ureteral ligation, but was abolished by nephrectomy [3]. These studies suggest that a renal action of the loop diuretic, but independent of diuresis, resulted in the effects on left ventricular filling pressure. Loop diuretics are known to stimulate secretion of vasodilatory prostaglandins. Pretreatment of animals with indomethacin greatly attenuates furosemide-induced venodilation, suggesting that prostaglandin secretion contributes importantly to the effects of loop diuretics on vascular tone. Some investigators have reported that the vascular effects of loop diuretic are maintained even in patients on dialysis [39], whereas others have reported that the early hypotensive effects of these drugs are greatly attenuated in functionally anephric patients [30].

Although venodilation and improvements in cardiac hemodynamics frequently result from intravenous therapy with loop diuretics, more recent reports suggest that the hemodynamic response to intravenous loop diuretics may be more complex. Johnston *et al.* reported that low dose furosemide in-

creased venous capacitance, but found that higher doses did not [21]. It was suggested that furosemide-induced renin secretion led to increases in angiotensin II generation. This vasoconstrictor might overwhelm the prostaglandin-mediated vasodilatory effects in some patients. In two series, 1–1.5 mg/kg furosemide boluses, administered to patients with chronic congestive heart failure, resulted in a transient *deterioration* in hemodynamics (during the first hour), with a decline in stroke volume index, an increase in left ventricular filling pressure [8, 15], and exacerbation of congestive heart failure symptoms (see Fig. 2). These changes were believed to be related to activation of both the sympathetic nervous system and the renin/angiotensin system by the diuretic drug. As discussed elsewhere in this volume, loop diuretics stimulate renin secretion directly at the macula densa, independent of their effects on ECF volume. This potent renin-stimulatory effect may contribute importantly to several counterregulatory effects that occur during loop diuretic administration. Evidence for a role of the renin/angiotensin system in the furosemide-induced deterioration in systemic hemodynamics include a temporal association between its activation and hemodynamic deterioration [15] and the ability of angiotensin I converting enzyme (ACE) inhibitors to prevent much of the pressor effect [19]. Many other studies have shown that acute loop diuretic administration frequently produces a transient decline in cardiac output; whether diuretics administration increases or decreases left atrial pressure acutely may depend primarily on the state of underlying sympathetic nervous system and renin/angiotensin axis activation. While these data provide cautionary information concerning the use of loop diuretics in acute cardiogenic pulmonary edema, it should be emphasized that intravenous loop diuretics remain the most important and useful form of therapy for these patients because they usually do improve symptoms before natriuresis, suggesting that most patients experience a decline in left ventricular filling pressure, even when cardiac output falls. Further, they universally contribute to symptomatic improvement once natriuresis begins, an effect that should begin within 15 to 20 min of diuretic administration. In patients already treated with an angiotensin I converting enzyme inhibitor, immediate symptomatic improvement is likely to result from diuretic administration. In patients who are not on ACE inhibitors, however, especially those in whom cardiac output is markedly reduced, transient hemodynamic deterioration may occasionally occur.

Another interesting complication of high dose furosemide treatment may be thiamine deficiency. Studies in experimental animals have shown that chronic furosemide administration can lead to thiamine deficiency. In humans, some, but not all, workers have detected thiamine deficiency in patients treated chronically with furosemide. In one study, patients with congestive heart failure who had received furosemide 80 mg daily for at least 3 months were randomized to receive intravenous thiamine or placebo. Intravenous thiamine led

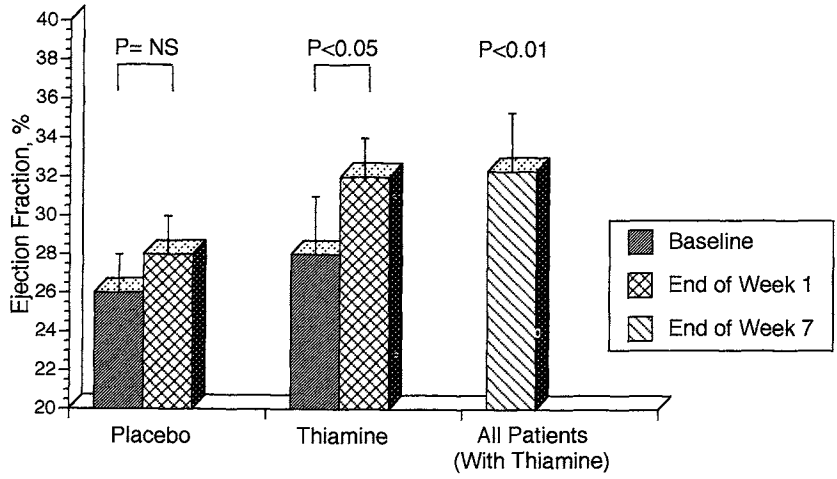

FIGURE 3. Effect of intravenous and oral thiamine administration on ejection fraction in patients with congestive heart failure treated chronically with high doses of furosemide. Patients treated with placebo for 1 week did not experience significant improvement in ejection fraction. Patients treated with 200 mg/day of thiamine had significant improvement in ejection fraction ($P<0.05$). After 1 week, all patients were treated with oral thiamine for 6 weeks. At the 7th week, all patients achieved significant improvement in ejection fraction ($P<0.01$). Data from [40].

to improved hemodynamics and a natriuresis, compared with placebo, and to an improvement in the thiamine-pyrophosphate effect on erythrocyte transketolase activity [40] (see Fig. 3). This work must be confirmed before thiamine can be recommended routinely for patients undergoing high dose loop diuretic treatment, but it raises the possibility that loop diuretics may predispose to nutritional deficiencies.

COMBINATION DIURETIC THERAPY

RATIONALE

A common and useful method for treating the diuretic resistant patient is to administer two classes of diuretic drug simultaneously. Although some authors have advocated alternating two members of the same diuretic class together (for example ethacrynic acid and furosemide), controlled trials suggest little or no benefit from such an approach [6]; our current understanding of molecular mechanisms by which diuretics inhibit renal salt transport provides no obvious rationale for such an approach. In contrast, adding a proximal tubule diuretic or a distal convoluted tubule (DCT) diuretic to a regimen of loop diuretics is

often dramatically effective [13, 33, 35]. DCT diuretics are the class of drugs most commonly added to loop diuretics, and this combination has proven remarkably effective. The combination of loop and DCT diuretics has been shown to be synergistic (the combination is more effective than the sum of the effects of each drug alone) in formal permutation trials (reviewed in [10]).

The addition of DCT diuretics to loop diuretics may enhance NaCl excretion by several mechanisms, none of which is mutually exclusive. DCT diuretics do not appear to potentiate the effect of loop diuretics by altering their pharmacokinetics or bioavailability [26], but DCT diuretics do have longer half-lives than do loop diuretics. The *first* mechanism responsible for the efficacy of combination therapy is that DCT diuretics may prevent or attenuate postdiuretic NaCl retention. As discussed in Chapter IVB1, the natriuretic effects of a single dose of furosemide, bumetanide, and to a lesser extent torsemide generally cease within 6 hr. Before the next dose of diuretic is administered, intense renal NaCl retention frequently occurs (postdiuretic NaCl retention); this NaCl retention can be attenuated by DCT diuretics which will continue to inhibit renal NaCl absorption after the loop diuretic has worn off. A *second* mechanism by which DCT diuretics potentiate the effects of loop diuretics is by inhibiting salt transport along the proximal tubule. When the kidney is strongly stimulated to retain NaCl, proximal NaCl reabsorption is enhanced. Most thiazide diuretics inhibit carbonic anhydrase, thereby reducing Na and fluid reabsorption along the proximal tubule. This leads to increased Na and fluid delivery to the loop of Henle [34], which leads to increases in delivery of Na and Cl into the collecting duct system. Because the loop diuretic drug is inhibiting loop segment solute reabsorption, the delivery of solute to the distal nephron will be greatly magnified (see Fig. 2, Chapter IVB1). The importance of carbonic anhydrase inhibition in diuretic synergism is documented by the efficacy of carbonic anhydrase inhibitors (e.g., acetazolamide) when added to loop diuretics. Although carbonic anhydrase inhibitors are relatively weak diuretics when administered alone (because the loop of Henle and distal convoluted tubule can reabsorb most of the NaCl rejected from the proximal tubule), carbonic anhydrase inhibitors can be very potent when added to a regimen of a loop diuretic [10].

A third mechanism by which DCT diuretics may potentiate the effects of loop diuretics is by inhibiting NaCl transport along the renal distal. When loop diuretics inhibit NaCl transport along the thick ascending limb and thereby increase salt delivery to the distal tubule, Na and Cl uptake into cells along the distal nephron is stimulated (see Fig. 2, Chapter IVB1). When inhibition of loop segment NaCl transport is chronic, such as in a patient treated with high and frequent doses of a loop diuretic for resistant edema, distal nephron cells develop hypertrophy and hyperplasia. The hypertrophic response is associated with an increased density of Na/K ATPase pump sites [38], an increased den-

sity of Na/Cl cotransporters [7, 32], and an increase in the intrinsic capacity of the distal tubule to reabsorb Na and Cl [12]. Thus, when presented with the same NaCl load, distal tubules from animals treated chronically with loop diuretics reabsorb Na and Cl up to 3 times more rapidly than distal tubules of control animals (see Fig. 2, Chapter IVB1 [12]). Because DCT diuretics can inhibit thiazide-sensitive Na/Cl cotransport completely even under these stimulated conditions [11, 12], the effects of the thiazides will be greatly magnified in the patient who has developed distal nephron hypertrophy from high doses of loop diuretics. Most of the studies documenting structural and functional effects of chronic loop diuretic administration have been conducted in experimental animals; evidence of an effect of chronic loop diuretic treatment to enhance distal nephron function in humans was obtained by Wilcox and colleagues (see Fig. 4 [23]). These investigators showed that the effect of chlorothiazide, used to inhibit NaCl transport along the renal distal tubule, on urinary Na excretion was enhanced following 1 month's treatment with furosemide. These data suggest that daily oral furosemide treatment, even in modest doses, may be sufficient to induce adaptive changes along the distal nephron, changes that may be treated with combination drug therapy.

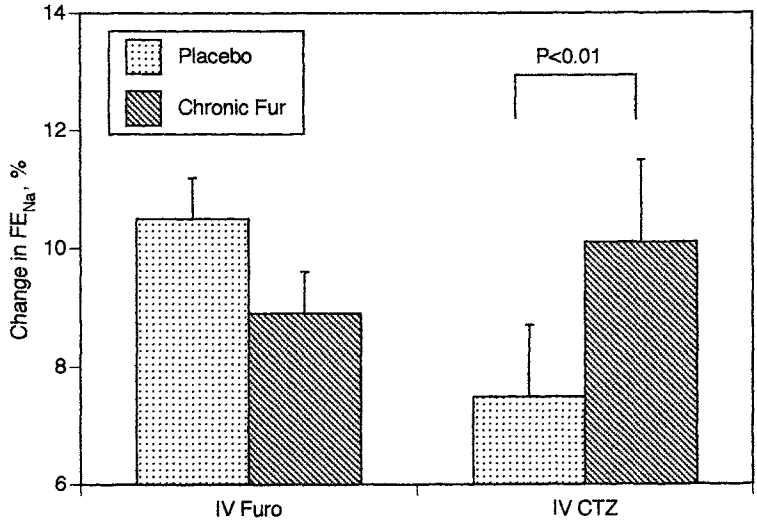

FIGURE 4. Effects of chronic furosemide treatment on the effect of intravenous chlorothiazide (CTZ) and furosemide (FURO). Volunteers received furosemide (40 mg) daily for 1 month or placebo. The responses to intravenous furosemide and chlorothiazide were then compared in the two groups. The effect of iv furosemide was attenuated by chronic furosemide treatment. The effect of iv chlorothiazide was significantly increased after 1 month of furosemide. Data from [24].

Approach

The choice of drugs for combination diuretic therapy has been discussed widely. In most cases, it is appropriate to add a DCT diuretic to a regimen of a loop diuretic. Alternative approaches, however, are appropriate in some circumstances and will be discussed below. In general, when a second class of diuretic is added, the dose of loop diuretic should not be altered. The shape of the steep dose–response curve to loop diuretics (shown in Fig. 1) is not affected by the addition of other diuretics and the loop diuretic must be given in an effective or maximal safe dose. The choice of DCT diuretic to add is arbitrary. Many clinicians choose metolazone because its half-life, in the commonly employed formulation, is longer than that of some other DCT diuretics and because it has been reported to remain effective even when the glomerular filtration rate is low. Yet direct comparisons between metolazone and several traditional thiazides have shown little difference in natriuretic potency when included in a regimen with loop diuretics in patients with nephrotic edema [17], congestive heart failure [5], and azotemia [14].

DCT diuretics may be added in full doses (50–100 mg/day hydrochlorothiazide or 10 mg/day metolazone) when a rapid and robust response is needed, but such an approach is likely to lead to complications if follow-up is not extremely close and may be best reserved for hospitalized patients. Fluid and electrolyte depletion, sometimes massive, occurs commonly during combination diuretic therapy. In a review of combination diuretic therapy, side-effects were noted to have occurred in about ⅔ of papers; most clinicians who have used combination therapy have observed excessive fluid and electrolyte depletion in some patients. One reasonable approach to combination therapy is to achieve control of extracellular fluid volume by adding full doses of DCT on a daily basis initially and then to maintain control by reducing the dose of the DCT diuretic to 3 times weekly. A physiological rationale for such an approach is provided by the observation that chronic treatment with thiazide diuretics causes downregulation of Na/K ATPase activity [16] and transport capacity [29] along the distal convoluted tubule of rat. Thus, it may be speculated that adding a DCT diuretic to a regimen including a loop diuretic may lead to decreases in the structural and functional effects of loop diuretics on the distal tubule.

Another approach is to use combination therapy for only a short fixed course. A recent comparison of different combination diuretic regimens (see Fig. 5) suggested that a limited course of combination therapy may be as effective and perhaps safer than more prolonged courses. Metolazone or bendroflumethiazide was added to furosemide for either a fixed 3-day period or adjusted empirically to achieve volume losses during 5–7 days. Both regimens were effective in reducing extracellular fluid volume and symptoms, but the fixed regimen appeared to be tolerated better; no differences between the effects of me-

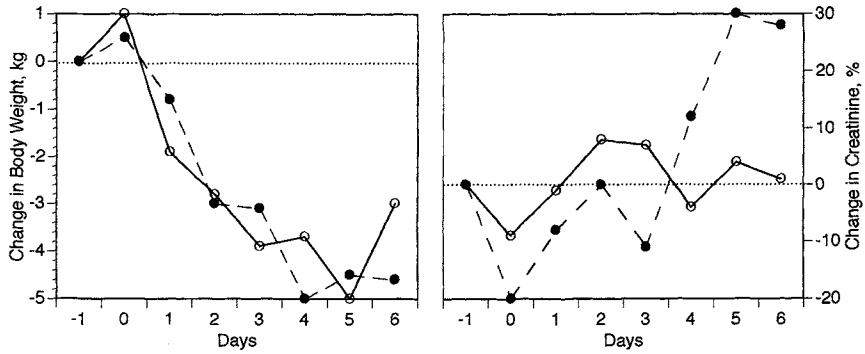

FIGURE 5. Comparison of results of adding a distal convoluted tubule diuretic (metolazone or bendroflumethiazide) to a loop diuretic on either a fixed 3-day regimen (open circles) or a chronic variable regimen (filled circles) adjusted according to changes in body weight and clinical symptoms. Both regimens effected reductions in body weight (left) which continued even after the distal convoluted tubule diuretic was discontinued (open circles). As shown on the right, serum creatinine tended to be higher after 5 days of continuous distal convoluted tubule diuretic therapy. Data from [5].

tolazone and bendroflumethiazide were noted [5]. Thus, for the outpatient, either a small dose of DCT diuretic, such as 2.5 mg/day metolazone, or a limited and fixed course of a higher dose (3 days of 10 mg/day metolazone) may be recommended as effective therapy that is less likely to lead to side-effects. Because DCT diuretics are absorbed more slowly than loop diuretics (peak levels at 1.5–4 hr vs 0.5–2 hr, respectively, Chapter IVA), it may be reasonable to administer the DCT diuretic ½ to 1 hr prior to loop diuretic, although rigorous support for this contention is lacking.

Drugs that act along the collecting duct, such as amiloride and spironolactone, can be added to a regimen of loop diuretic drugs, but their effects are generally less dramatic than those of DCT diuretics, at least acutely. The combination of spironolactone and loop diuretics has not been shown to be synergistic, but these drugs have an important role in preventing hypokalemia while maintaining renal Na excretion. The setting in which collecting duct diuretics are used most commonly is in treating patients with cirrhosis of the liver in whom hypokalemia must be avoided because it can predispose to hepatic encephalopathy. Cortical collecting duct diuretics also reduce magnesium excretion, relative to other diuretics, making hypomagnesemia less likely than when loop diuretics are combined with DCT diuretics. Although the use of angiotensin converting enzyme inhibitors for patients with compromised left ventricular systolic function has improved the prognosis of patients dramatically, there remains a subset of patients in whom symptomatic control is difficult. Recently, a role for spironolactone in treating patients with congestive heart failure has

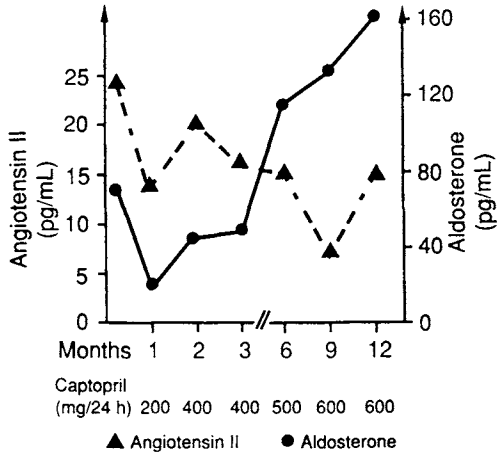

FIGURE 6. Effects of chronic inhibition of angiotensin converting enzyme on angiotensin II and aldosterone levels. Note that angiotensin II levels were suppressed throughout 12 months, whereas aldosterone concentrations rose after 2 months of therapy. From [45] with permission.

been suggested [43]. This suggestion follows from three observations: first, patients with congestive heart failure who are being treated with angiotensin I converting enzyme inhibitors frequently "break through," manifesting elevated levels of aldosterone despite effective doses of ACE inhibitor (see Fig. 6, [44, 45]). Second, mineralocorticoid receptors are located throughout the body, including on cardiac tissue; recent data suggest that hyperaldosteronism may conribute to myocardial dysfunction directly [43]. Third, cardiac arrhythmias, a frequent cause of death in patients with congestive heart failure, may be precipitated or exacerbated by electrolyte disorders such as hypokalemia and hypomagnesemia. Several groups have reported beneficial effects of adding spironolactone to treatment with loop diuretics or DCT diuretics and ACE inhibitors. One common difficulty in treating patients with severe heart failure with ACE inhibitors is the development of hypotension. Because spironolactone is slow acting and modest in effect, hypotension generally does not result from the approach. Barr *et al.* [2] randomized 42 patients with NYHA class II to III congestive heart failure to either 50–100 mg/day spironolactone or placebo (added to a regimen of loop diuretics and ACE inhibitors). Compared with placebo (see Fig. 7), spironolactone increased urinary Na excretion, increased the urinary Na/K ratio, and increased the serum magnesium concentration. Further, spironolactone reduced urinary magnesium excretion and caused a significant reduction in ventricular arrhythmias. Others have reported similar results [42]. An area of concern when adding spironolactone to ACE inhibitor therapy is the potential for hyperkalemia and renal insufficiency. Most studies have excluded patients with preexisting creatinine levels >2.0 mg/dl, the

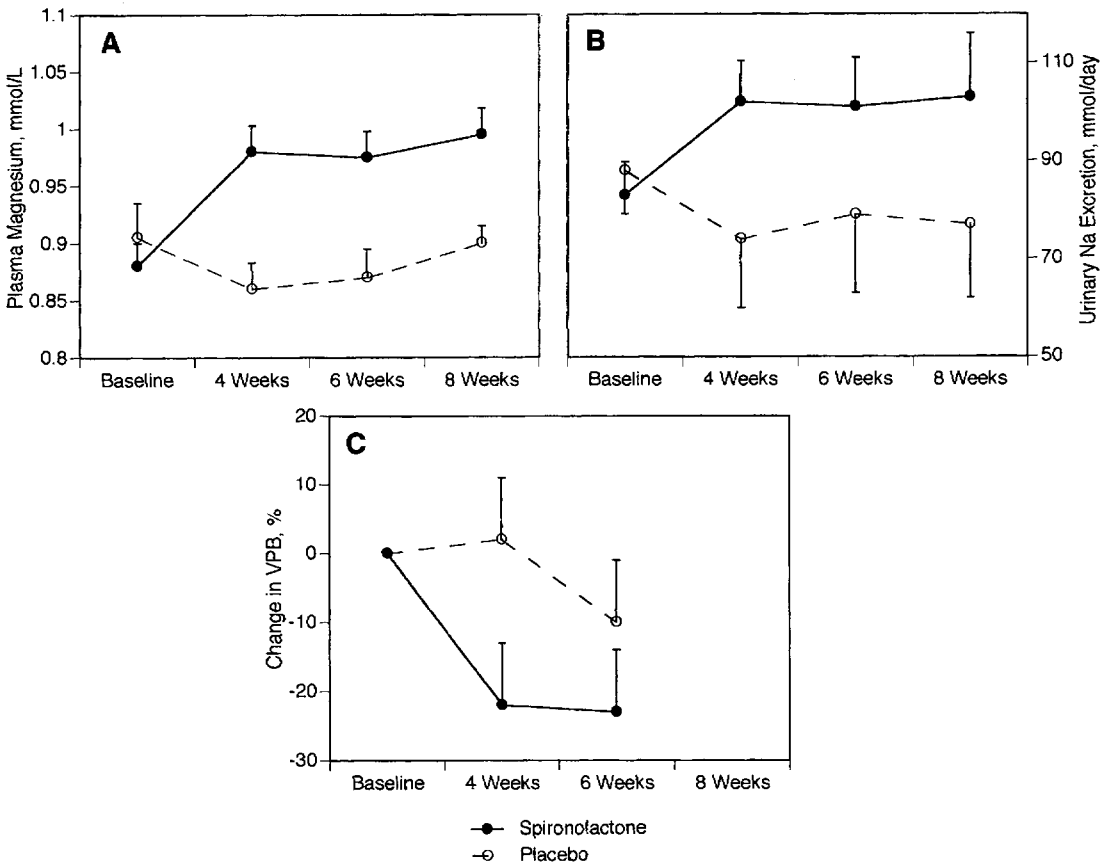

FIGURE 7. Effects of adding 100 mg per day spironolactone or placebo on plasma magnesium concentration, urinary Na excretion, and number of ventricular premature beats (VPB) in patients with chronic congestive heart failure. Data from [2].

group at highest risk for anti-aldosterone therapy. However hyperkalemia has been observed in a significant, albeit limited, fraction of patients treated with the combination of loop and collecting duct diuretics and ACE inhibitors [45]. The precise role of spironolactone in treating congestive heart failure will be clarified by a multicenter cooperative trial that is currently under way.

One situation in which aggressive diuretic therapy is often indicated is for hospitalized patients, especially those in an intensive care unit who need urgent diuresis. While the causes of diuretic resistance delineated above may be present in these patients, many also receive obligate fluid and solute loads, some develop electrolyte complications, and many cannot take medications by mouth. Two intravenous drugs are available to supplement loop diuretics for combination therapy. Chlorothiazide (500–1000 mg once or twice daily) and acetazolamide (250–375 mg up to four times daily) are both available for intravenous administration: chlorothiazide has relatively potent carbonic anhydrase inhibiting capacity in the proximal tubule. It also blocks the "thiazide-sensitive" Na-Cl cotransporter in the distal tubule; and chlorothiazide has a longer half-life than some other thiazides. Both chlorothiazide and acetazolamide have been shown to act syngertistically with loop diuretics when given acutely. Acetazolamide is especially useful when metabolic alkalosis and hypokalemia complicate the treatment of edema. Alkalosis may make it difficult to wean a patient from a ventilator and make it impossible to correct K depletion. The use of acetazolamide can often correct these disorders [28] without the need to administer saline, which would otherwise be used to correct alkalosis in these patients. In other situations, combination diuretic therapy may be targeted at the underlying disease process. Theophylline is a very mild diuretic, but it has been shown to act synergistically with loop diuretics and may be useful when bronchospasm and edema are present together [4]. For patients with left ventricular dysfunction, afterload reduction may enhance diuresis, both acutely and over the longer term, although the effects of ACE inhibitors on diuretic efficacy are complex (see Chapter IVB3). Low doses of dopamine are often employed to potentiate the action diuretics, although the evidence that "renal dose dopamine" is effective is controversial (see Chapter IVB2). Infusions of albumin may potentiate the effects of diuretic drugs when hypoalbuminemia complicates nephrotic syndrome or cirrhosis; mixing albumin and loop diuretics prior to administration has been reported to be more effective than administering each agent along, perhaps by permitting more drug to be delivered to the kidney (see Chapter IVB5 and ref. [20]).

CONTINUOUS DIURETIC INFUSION

For hospitalized patients who are resistant to diuretic therapy, another approach is to infuse diuretics continuously. Continuous diuretic infusions have

several potential advantages over bolus diuretic administration. First, because they avoid troughs of diuretic concentration, they prevent intermittent periods of positive NaCl balance (postdiuretic NaCl retention). When short acting diuretics, such as the loop diuretics, are administered by bolus infusion or by mouth once or twice a day, a period of natriuresis and diuresis lasting about 6 hr ensues. When diuretic serum concentrations decline, urine NaCl concentrations also decline to levels below basal (reviewed in Chapter IVB1 and above). Because 24-nr renal NaCl excretion is the composite of the natriuretic and anti-natriuretic periods, negative salt balance may be limited, especially when dietary salt intake is high. Clearly, a constant infusion that leads to constant serum diuretic concentrations will minimize periods of Na retention and might be expected to be more efficacious. Second, constant infusions appear to be more efficient than bolus therapy. In one study of patients with chronic renal failure a continuous infusion of bumetanide was 32% more efficient than a bolus of the same dose when the amount of NaCl excreted per milligram of administered diuretic was compared [36]. In a crossover study of nine patients with NYHA class III–IV congestive heart failure (see Fig. 8), 60–80 mg/day was more effective when given as a continuous infusion following a loading dose (30–40 mg) than when given as boluses three times daily (30–50 mg/dose). Similar relations probably hold for other loop diuretics, although the efficiency ratios may depend in part in the half-lives of the drugs. Bumetanide has the shortest half-life, torsemide has a longer half-life, and furosemide is in between. It would be reasonable to expect that the ratio of the efficiency of bolus versus continuous infusion would be highest for torsemide and lowest for bumetanide. Thus, bolus torsemide may prove to be an alternative approach to continuous infusion in some patients. Third, some patients who are resistant to large doses of diuretics given by bolus have responded to continuous infusion [18, 41]. Most studies of efficacy in diuretic resistant patients have not compared strictly equivalent doses or administered them in a randomized manner. Yet several studies do provide suggestive evidence that continuous infusion may elicit diuresis in some patients resistant to large boluses. Van Meyel *et al.*, for example, showed satisfactory natriuresis during constant infusion in patients with congestive heart failure who had failed to respond to 250 mg furosemide given as a bolus [41], although the total daily doses of furosemide in that study were quite high. Fractional Na excretion varied in a linear manner with daily furosemide dose between 480 and 3840 mg/day. Fourth, diuretic response can be titrated; in the intensive care unit where obligate solute and fluid administration must be balanced by solute and fluid excretion, control of NaCl and water excretion can be obtained by tritration of diuretic dose. While this is important in every postoperative patient, it is especially important in patients who are hemodynamically compromised. Magovern and Magovern reported successful diuresis of hemodynamically compromised patients after cardiac surgery by continuous furosemide infusion [25]. Because continuous in-

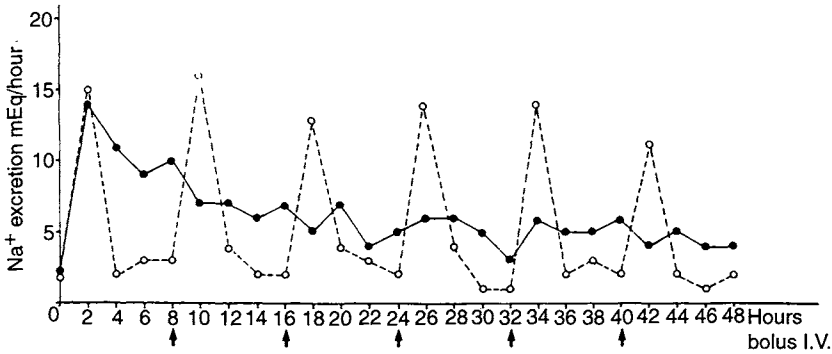

FIGURE 8. Comparison of continuous infusion vs bolus furosemide treatment of patients with chronic congestive heart failure. The filled circles indicate Na excretion during infusion of 2.5–3.3 mg/hr following a loading dose of 30–40 mg furosemide. The open circles depict urinary Na excretion following 30–40 mg furosemide every 8 hr. Total urine output was 18.5% higher during continuous infusion than bolus administration. From [22].

fusion of loop diuretics may reduce the sympathetic discharge, activation of the renin/angiotensin system, and sudden massive solute and fluid losses that may occur following a large intravenous bolus (discussed above), continuous infusions may be the preferred mode of therapy for hemodynamically unstable patients in need of diuresis. Finally, drug toxicity from loop diuretics, such as ototoxicity (observed with all loop diuretics) and myopathies (with bumetanide), appear to be less common when the drugs are administered as continuous infusions. In fact, total daily furosemide doses exceeding 2 g have been tolerated well when administered over 24 hr. Dosage regimens for continuous intravenous diuretic administration are shown in Table 3. Of note, although natri-

TABLE 3 Continuous Infusion of Loop Diuretics

	Bolus (mg)	Infusion rate (mg/hr)[a]
Furosemide	20–80	2–80
Bumetanide	1	0.2
Torsemide	25	1–50

[a] In general, the lowest dose range for continuous infusion will be effective in patients with well preserved renal function and who have not previously been treated with loop diuretics. The highest doses should be reserved for patients with severe renal insufficiency and profound diuretic resistance. At high continuous doses, toxicity may develop, especially during furosemide infusion in patients with impaired renal function. Doses derived from [27].

uretic efficacy may vary linearly with loop diuretic dose, high infusion rates (2 g per day of furosemide, for example) might lead to toxic serum concentrations if continued for prolonged periods. This is especially true in patients with renal failure, in whom larger doses are often required to initiate diuresis. Special care should be taken when administering large daily doses of loop diuretics over prolonged periods; in patients with renal failure, a drug such as torsemide that is cleared, in part, by hepatic metabolism, may be preferred when high or prolonged therapy is attempted.

Most patients who were thought to be resistant to diuretics respond to one of these approaches. Side-effects of diuretic therapy such as prerenal azotemia and metabolic alkalosis, rather than resistance to diuretic therapy, usually limit the ability to reduce extracellular fluid volume further. Controlling extracellular fluid volume without provoking complications requires a thorough understanding of diuretic physiology and a commitment to using diuretics rationally and carefully. When medical diuresis fails despite addressing considerations discussed above, plasma ultrafiltration may be considered. Ultrafiltration, with or without accompanying hemodialysis, effectively removes extracellular fluid and many clinicians have observed surprisingly beneficial effects of ultrafiltration in diuretic resistant patients. Recent data suggest a possible rationale for the use of ultrafiltration in some diuretic resistant patients. Agostoni *et al.* [1] randomized patients with congestive heart failure to volume removal by ultrafiltration or furosemide. Regimens were devised to remove equal amounts of fluid. Whereas both approaches achieved the same volume depletion acutely, volume contraction was maintained significantly better following ultrafiltration than following medical diuresis (see Fig. 9). The secondary deterioration in extracellular fluid volume following furosemide treatment was associated with a brisk rise in renin and angiotensin II secretion. It may be speculated that

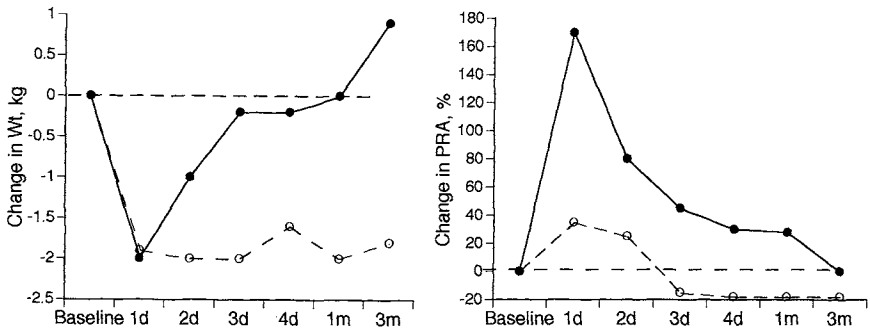

FIGURE 9. Effects in patients with congestive heart failure of bolus furosemide (filled circles) vs plasma ultrafiltration (open circles) on body weight and plasma renin activity (PRA). The *n* in each group was 8. The differences were statistically significant. Data from [1].

volume removal with loop diuretics, which stimulate renin secretion directly via their effects at the macula densa, leads to a more robust counterregulatory hormonal response that produces more rapid fluid reaccumulation. These interesting results highlight the important role that counterregulatory hormones play in attenuating the effectiveness of diuretics and suggest that ultrafiltration may have a role in the rare patient with extracellular fluid volume overload who cannot be controlled using one of the approaches described above.

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CHAPTER IVC2

Circulatory Support, Dopamine, and Dopamine Agonists as Adjuncts to Diuretic Therapy

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INTRODUCTION

Renal NaCl excretion varies directly with renal perfusion pressure (defining the phenomenon of pressure natriuresis; see Fig. 1), renal blood flow, and extracellular fluid (ECF) volume. Thus, it is not surprising that alterations in mean arterial pressure and systemic hemodynamics affect the response to diuretic drugs. Many vasoactive drugs have pronounced effects on renal function and renal Na excretion, both because they affect systemic hemodynamics and because they have direct effects on renal Na and Cl handling along the nephron. In this chapter, the actions of a unique endogenous catecholamine, dopamine, on renal function will be summarized (see also Chapter IIIB), the effects of systemic hemodynamics on renal function will be reviewed, and the use of dopamine and dobutamine to improve systemic hemodynamics in patients with severe congestive heart failure will be discussed. Dopamine in low doses is frequently employed to "protect" the kidney from hemodynamic insults and to improve renal function in acute renal failure. The use of "renal dose" dopamine in these settings will be discussed in the third section of this chapter. Finally, oral drugs that activate dopamine receptors have been developed during the past several years for use in hypertension and in treating chronic congestive heart failure. Some of these drugs are currently available outside the United States. These drugs will be discussed in the last section of this chapter.

Diuretic Agents: Clinical Physiology and Pharmacology

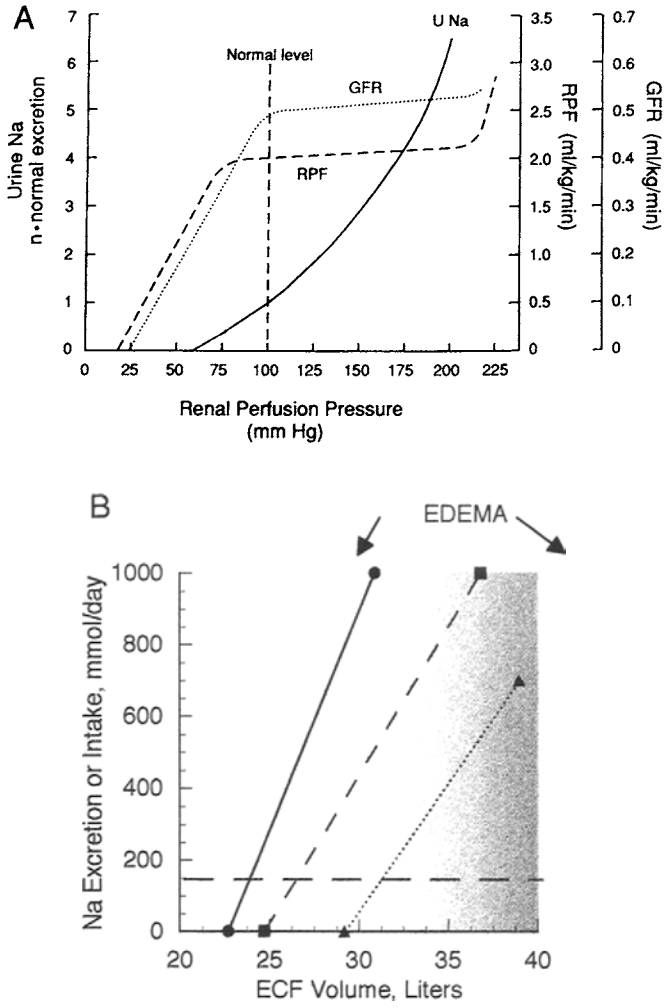


FIGURE 1. (A) Effects of renal perfusion pressure on urinary Na excretion, renal plasma flow (RPF) and glomerular filtration rate (GFR). From Guyton A. C. Science 252; 1813–1816, 1991, with permission. (B) Effects of dietary NaCl intake on extracellular fluid volume at steady state in normal (filled circles and solid line), mildly (squares and dashed line), and severely (triangles and dotted line) edematous individuals. At steady state, dietary intake will equal urinary excretion. A typical Western salt intake is given by the dashed line. From Ellison, D. H. Am. J. Kidney Dis. 23: 623–624, 1994, with permission.

DOPAMINE AND RENAL FUNCTION

Based on the intimate relation between systemic hemodynamics and renal function, it is not surprising that vasoactive drugs affect renal function. Many vasoactive agents have both direct effects on glomerular filtration and salt reabsorption and indirect effects on renal function mediated by changes in systemic hemodynamics. Renin, angiotensin, aldosterone, atrial natriuretic peptide, prostaglandins, adenosine, and other hormones and paracrine factors alter both renal blood flow and ion transport. The effects of these vasoactive substances are reviewed elsewhere in this volume. Catecholamines also affect renal blood flow and ion transport, both directly and indirectly, by interacting with α and β adrenergic receptors. Dopamine (3,4-dihydroxyphenylethylamine) is a unique catecholamine that interacts with α and β adrenergic receptors as well as with specific dopaminergic receptors. Dopamine is produced by the kidney and by dopaminergic neurons by the actions of tyrosine hydroxylase and aromatic L-amino-acid decarboxylase (see Fig. 4, Chapter IIIB). Dopaminergic neurons lack dopamine β-hydroxylase or phenylethanolamine *N*-methyltransferase; therefore catecholamine synthesis halts at dopamine and does not proceed to norepinephrine or epinephrine [25]. In the renal cortex, dopamine is produced primarily from circulating L-dopa, by cells of the proximal convoluted tubule.

Renal dopamine receptors have been classified physiologically as DA_1 and DA_2 (see Fig. 2 [23]). DA_1 receptors, defined functionally, include D_{1A} and D_{1B} receptors. DA_2 receptors include D_2, D_3, and D_4 receptors. DA_1 receptors are expressed by renal arteries, mesenteric, coronary, and cerebral arteries, by proximal convoluted and straight tubules (at both the apical and the basolateral

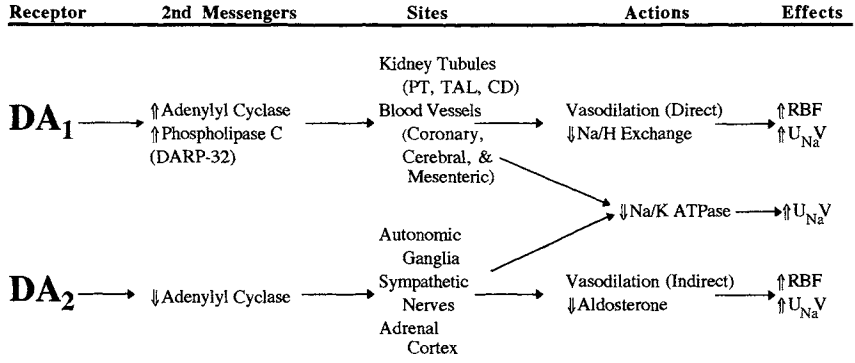


FIGURE 2. Functional classification of dopamine receptors, predominant second messengers, sites of action, and renal effects. Some data suggest that activation of both DA_1 and DA_2 receptors is needed to fully inhibit Na/K ATPase.

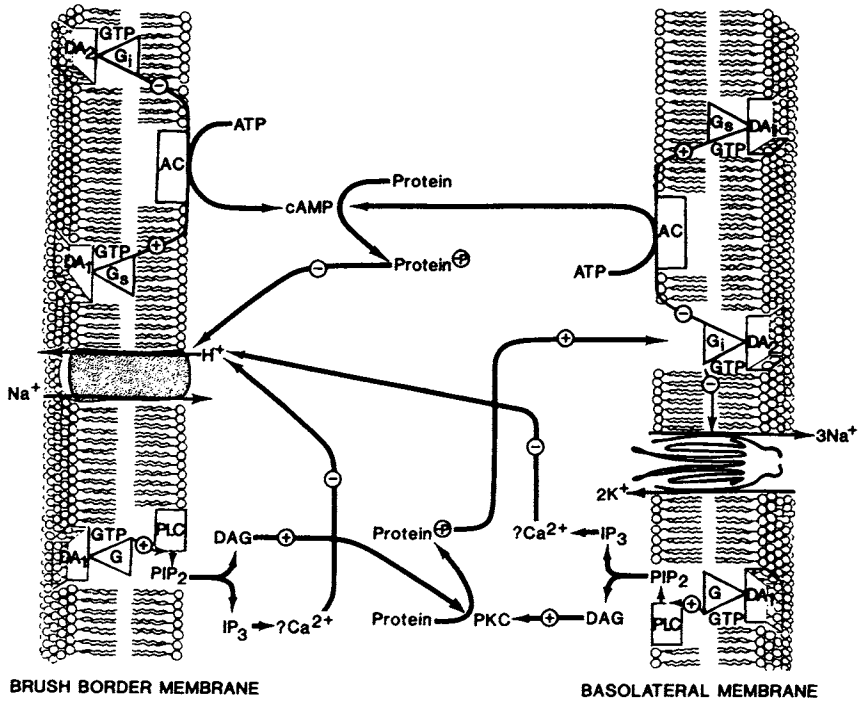


FIGURE 3. Mechanisms of dopamine actions on Na transport pathways of the proximal tubule. AT brush border membrane, stimulatory effect of dopamine on adenylyl cyclase activity predominates, resulting in an inhibition of Na/H antiport activity. At basolateral membrane stimulatory effect of dopamine on phospholipase C predominates, resulting in activation of protein kinase C and inhibition of Na/K ATPase activity. Calcium may also influence transport activities. AC, adenylyl cyclase; PIP_2, phophatidyl inositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; ATP, adenosine trisphosphate. From Felder et al. Am. J. Physiol. 257; F315–F327, 1989, with permission.

cell membranes (see Fig. 3)), by thick ascending limb cells, and along the cortical collecting duct. They do not appear to be expressed by glomeruli. DA_2 receptors are expressed in the adventitia and intima of renal blood vessels and the glomerulus, as well as in renal cortical and medullary tissue. Molecular cloning has identified several classes of dopamine receptors. Dopamine receptors that correspond to DA_2 receptors have been shown to be expressed by glomeruli and proximal tubules [12]. Data for expression of DA_2 receptors along tubules has been contradictory.

Infusions of dopamine into normal animals or humans lead to dose-dependent increases in renal blood flow, glomerular filtration rate, natriuresis, and diuresis. Both the renal vasodilatory effects of dopamine and the direct

effects on tubule epithelial cells appear to be mediated predominantly by DA_1 receptors (see Fig. 3), which stimulate adenylyl cyclase. These receptors appear to be associated with a 32-kDa protein (dopamine-regulated phosphorprotein, DARP-32) that has been postulated to act as a third messenger for dopamine actions in kidney and brain. DA_2 receptors appear to inhibit the activity of adenylyl cyclase and inhibit angiotensin-induced aldosterone secretion from the adrenal gland [25]. Recent data suggest that DA_2 receptors of that D_4 subclass inhibit Na transport and water permeability in rat cortical collecting tubule [43]. Dopamine increases urinary Na excretion both because it increases renal blood flow and, less predictably, glomerular filtration rate, and because it inhibits renal Na/K ATPase, proximal Na/H exchange, and adrenal aldosterone secretion. At low dopamine infusion rates (threshold=0.5 μg/kg/min, maximum=3 μg/kg/min) dopamine activates only the specific dopamine receptors (both DA_1 and DA_2). As doses are increased, β adrenergic receptors (threshold=5 μg/kg/min, maximum=10μg/kg/min) and then α adrenergic receptors (threshold=5μg/kg/min, maximum=20 μg/kg/min) are stimulated. Although dopamine infusion rates <3 μg/kg/min are frequently referred to as "renal dose" it has been noted that these doses can have significant systemic effects as well [45].

Endogenous dopamine is released in response to increases in dietary or exogenous NaCl load and in response to increases in dietary protein intake. Dopamine may play a physiological role in controlling the natriuretic responses to these maneuvers (see Fig. 3). Blocking dopamine synthesis, either systemically or via intrarenal infusion of a DA_2 receptor antagonist, reduces salt excretion in response to dietary salt loading. Intravenous furosemide stimulates urinary dopamine production [24], but evidence for a contributory role of dopamine in the natriuretic response to loop diuretics has been controversial. In isolated perfused rat kidneys and in anesthesized rats, blockade of dopamine synthesis or DA_1 receptors attenuates the natriuretic response to furosemide [36]. In contrast, Jeffrey *et al.* [22] found that complete inhibition of dopamine synthesis did not affect the furosemide response in normal humans.

SYSTEMIC HEMODYNAMICS AND RENAL FUNCTION

In normal individuals, renal blood flow and glomerular filtration rate remain relatively constant until the mean arterial pressure declines to below 80 mm Hg. This is the phenomenon of renal autoregulation. Renal Na excretion, however, is directly related to extracellular fluid volume, in a linear manner across the entire range of dietary NaCl intake and ECF volume (see Fig. 4 [47]). Hypotension may result from hypovolemia, vasodilation, impaired cardiac func-

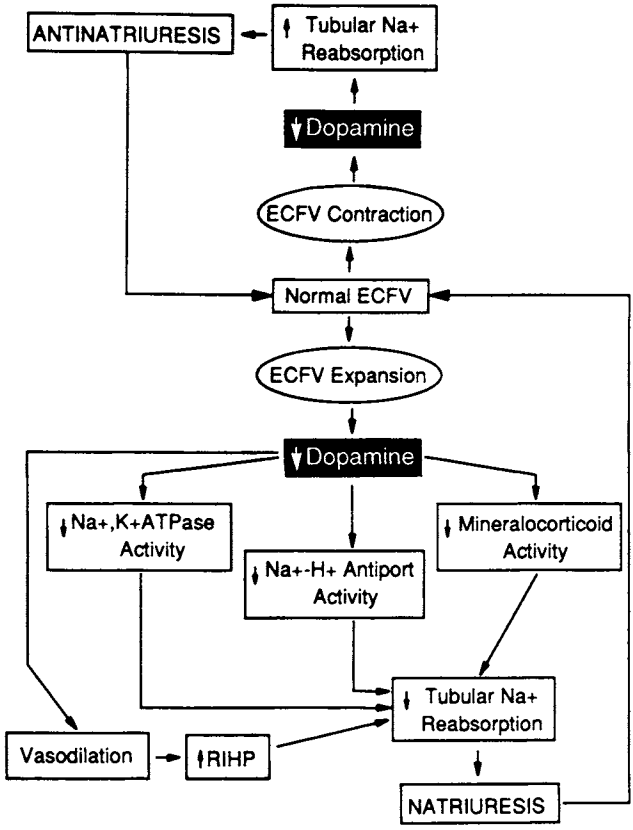


FIGURE 4. Effects of dopamine on extracellular fluid volume homeostasis. RIHP, renal interstitial hydrostatic pressure; ECFV, extracellular fluid volume. From Gonzalez-Compoy, J. M. & Knox, F. G. Chapter 56 in The Kidney: Physiology and Pathophysiology, Eds. Seldin & Giebisch, with permission.

tion, neuropathy, or drugs and may impair diuresis and natriuresis. In the acute setting, hypotensive shock impairs renal function and urinary Na and Cl excretion. The best method of increasing urinary volume and solute excretion in this setting is to improve the systemic hemodynamics; volume losses are replaced, impaired cardiac function is corrected, sepsis is treated. In some patients, however, while attempts to achieve definitive control of the underlying disorder are ongoing, pressor support must be employed to prevent serious organ compromise. The appropriate use of pressor support in these situations is beyond the scope of this chapter, but the importance of maintaining renal perfusion pressure should be emphasized; in general, a systolic pressure of 90 mm Hg (or a

mean arterial pressure of 65 mm Hg) should be targets in the initial treatment of shock. Fluid is usually administered as the primary mode of resuscitation from shock, but in many cases, pressor agents are also employed. It has been suggested that the use of systemic vasoconstrictors in these settings will uniformly compromise renal perfusion, but this view has been challenged recently. In septic shock, in which systemic vasodilation plays a key role, α adrenergic agonists, including norepinephrine and phenylephrine, have been observed to *improve* parameters of renal function, at least in some studies [16]. Some experimental data support adding low dose dopamine in this setting. In a study of dogs, low dose dopamine improved renal blood flow even when added to a high dose of norepinephrine [42].

In the foregoing, the renal perfusion pressure was assumed to be reflected by the mean arterial or systemic pressure. In fact, many patients who receive diuretic drugs are older, have renal arterial atherosclerosis, or take drugs that affect renal perfusion. Renal artery stenosis affects the renal response to diuretics not only by reducing renal perfusion pressure, but also by enhancing the effects of diuretics to activate the renin/angiotensin/aldosterone pathway; diuretic-induced renin/angiotensin system activation predisposes to Na retention and may contribute to sudden ("flash") pulmonary edema, now recognized as a presenting manifestation of renal artery stenosis [6]. Drugs such as agiotensin converting enzyme inhibitors and nonsteroidal anti-inflammatory agents limit the range of blood pressures over which autoregulation of glomerular filtration rate (and renal blood flow) can be maintained. An illustration of the complex interactions between mean arterial pressure, cardiac output, and renal function is the effects of afterload reduction on renal salt excretion in the setting of congestive heart failure. Angiotensin I converting enzyme inhibitors reduce afterload and increase cardiac output in patients with systolic dysfunction. Angiotensin I converting enzyme inhibitors can increase renal Na excretion in these situations by increasing renal perfusion, when combined with a diuretic [8]. On the other hand, excessive doses of angiotensin I converting enzyme inhibitors can be anti-natriuretic. In one study [38], captopril, a short acting angiotensin I converting enzyme inhibitor (50 mg three times daily), and enalapril, a long acting angiotensin I converting enzyme inhibitor (20 mg/day), had similar effects in improving cardiac hemodynamics and symptoms of congestive heart failure. Only treatment with captopril, which led to less sustained reduction in mean arterial pressure, was associated with significant weight loss and natriuresis. Enalapril did not affect either parameter significantly. This difference in renal responses was attributed to the prolonged reductions in mean arterial pressure which tended to counteract the effects of afterload reduction to improve renal NaCl excretion; although both drugs are useful for treating congestive heart failure, this study highlights the central role of renal perfusion pressure in natriuresis and diuresis. It suggests that each patient has an optimal

mean arterial pressure during treatment with afterload reducing agents. Above this pressure, cardiac output is compromised and renal NaCl excretion declines; below this pressure, cardiac output is high, but renal NaCl excretion declines because of inadequate perfusion pressure.

DOPAMINE AND DOBUTAMINE FOR CONGESTIVE HEART FAILURE

Acute dopamine infusion increases renal plasma flow, urinary sodium excretion rate, glomerular filtration rate, and the functional status of patients with moderate to severe congestive heart failure. These effects result from stimulation of dopamine receptors (DA_1 and DA_2) as well as β adrenergic receptors. Beregovich and co-workers [2] studied the dose-related hemodynamic and renal effects of dopamine in patients with classes III and IV congestive heart failure (see Fig. 5). Cardiac output and urinary sodium excretion rates rose progressively as dopamine infusion was increased from 1 to 5 and 10 μg/kg/min. Stroke volume and urinary flow rate, however, tended to plateau above 5 μg/kg/min and several patients developed sinus tachycardia or striking increases in systemic vascular resistance at the highest infused dose. These workers concluded that a dose of 5 μg/kg/min was optimal in terms of overall hemodynamic response in patients with congestive heart failure. While the effects of dopamine infusion on renal sodium excretion and cardiac hemodynamics are often dramatic, the natriuretic effects typically wane after 12–24 hr [3, 31].

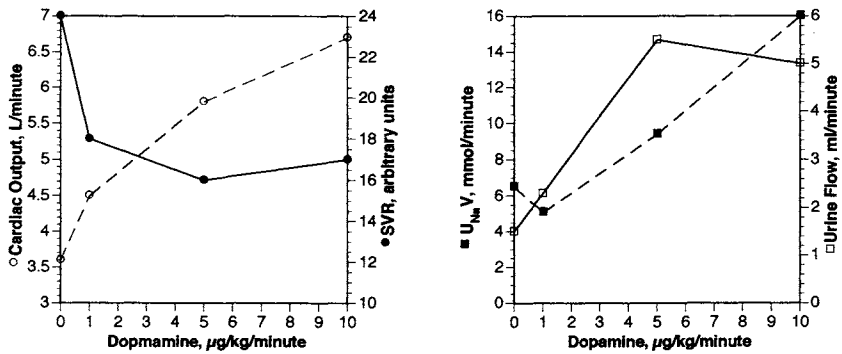


FIGURE 5. Effects of dopamine on cardiac output (○), systemic vascular resistance (SVR, ●), urinary sodium excretion (■), and urine flow rate (□) in patients with congestive heart failure. Data from Beregovich, et al. Am. Heart J. 87:550–557, 1974.

Dobutamine is a dopamine derivative with different hemodynamic effects. Dobutamine is a potent inotrope that does not cause significant mesenteric vasodilation or vasoconstriction even at high doses and has little effect on mean arterial pressure. Because dobutamine does not cause the vasoconstriction that increases cardiac work and limits the maximal dopamine dose in patients with congestive heart failure, it has become the most frequently employed inotrope in such patients. Both dopamine and dobutamine have been reported to improve cardiac output, renal perfusion, and, in some situations, urinary Na excretion. To investigate the role of specific dopamine receptors on the renal responses to dopamine in congestive heart failure, Hilberman *et al.* [20] compared the effects of dopamine and dobutamine in 12 patients who had undergone open heart surgery and developed depressed left ventricular performance postoperatively. The drugs were administered in random order in doses that increased cardiac output equally (dopamine, 5.0 ± 1.8 μg/kg/min; dobutamine, 3.5 ± 1.8 μg/kg/min). At these doses, the drugs had similar effects on renal plasma flow, renal vascular resistance, and glomerular filtration rate but, compared with dobutamine, dopamine increased urinary flow rate by 2.8-fold and Na excretion by 4.6-fold. The differences in renal effects of the drugs could not be attributed to differences in renal blood flow, although changes in intrarenal blood flow distribution could not be excluded. The authors suggested that the greater ability of dopamine to increase renal sodium and water excretion resulted from its actions to inhibit renal NaCl reabsorption at the level of the renal tubule. Other studies showed that dopamine increased urinary Na and water excretion during treatment with dobutamine in patients with congestive heart failure [9] and during treatment with norepinephrine [41] or dobutamine [7], in critically ill hypotensive patients. These studies strongly suggest that dopamine has unique natriuretic properties, even when added to effective doses of inotropes and vasopressors [7], although in a study of 6 patients with chronic stable congestive heart failure, dopamine was not more effective than dobutamine (or placebo) in increasing urine volume [14]. The studies provide a rationale for combining low dose (2–5μg/kg/min) dopamine with dobutamine or vasopressors in critically ill patients.

A recent study provides cautionary data concerning the ability of dopamine to increase urinary Na and water excretion in patients with congestive heart failure. Vargo *et al.* [46] asked whether low dose dopamine would increase Na and water excretion when added to maximally effective doses of a loop diuretic in patients with congestive heart failure. They reasoned that this question was more relevant to the clinical situation in which dopamine is added to a regimen that already includes a diuretic. Most previous studies had examined the use of dopamine in patients who were either off diuretics or were on their typical regimen of oral diuretics. In this randomized cross-over study, dopamine (1 to 3 μg/kg/min) did not increase urinary solute and water excretion when added

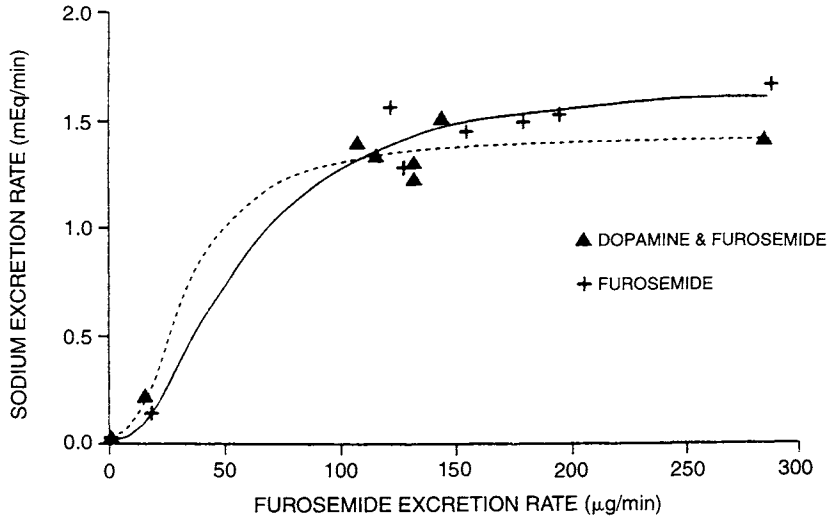


FIGURE 6. Comparison of furosemide excretion rate vs sodium excretion rate with and without low dose dopamine infusion in patients with stable congestive heart failure. Note that the two lines nearly superimpose. With permission from [46].

to a maximally effective dose of furosemide (see Fig. 6). Although this study does not provide evidence supporting the use of low dose dopamine in patients with congestive heart failure, the patients studied were stable patients who *did* respond to furosemide alone. Whether dopamine might elicit diuresis in patients who become refractory to furosemide alone was not addressed.

DOPAMINE FOR PREVENTION AND TREATMENT OF ACUTE RENAL FAILURE

Dopamine augments renal blood flow in normal individuals. This observation suggests that dopamine might be useful for preventing or treating acute renal failure. The results of trials to investigate the role of dopamine in preventing and treating acute renal failure have been reviewed recently. In general, trials of dopamine to prevent or treat acute renal failure have utilized low or "renal" doses of dopamine, doses below the inotropic range. Denton *et al.* [5] reviewed 10 clinical trials of dopamine to prevent the development of acute renal failure in high risk patients. Four studies found no effect of dopamine in preventing acute tubular necrosis following renal transplantation, and three studies found no effect of dopamine in preventing acute renal failure following cardiac or abdominal surgery. One retrospective study of patients undergoing liver trans-

plantation found evidence that dopamine reduced their incidence of acute renal failure [40], whereas a larger prospective study did not [44]. Two small studies have reported that prophylactic dopamine infusion reduces the incidence of acute renal failure following intravenous radiocontrast agents [17, 18], whereas another found no effect [48]. Taken together, these results do not provide strong support for the use of dopamine to prevent acute renal failure in high risk patients, although a small effect would be difficult to exclude because the incidence of acute renal failure in these studies has generally been low [5].

Dopamine has also been recommended to enhance renal perfusion, increase urinary NaCl excretion, and enhance recovery from established acute renal failure. In 1970, Talley *et al.* reported that dopamine (4 μg/kg/min) improved urine output in a small group of patients with postoperative acute renal failure. In subsequent reports [15, 28] dopamine was reported to cause diuresis and natriuresis, and in some cases an improvement in glomerular filtration rate, when administered to patients with acute renal failure undergoing treatment with loop diuretics. These reports, however, involved small numbers of patients and did not include a control group, making interpretation difficult. In one prospective controlled trial of dopamine plus furosemide in malaria induced acute renal failure [29], the combination was more effective than furosemide alone in reversing acute renal failure when started relatively early in the course, but the number of patients in this study was also small, weakening the conclusions. Other convincing studies supporting a role for dopamine in enhancing recovery from acute tubular necrosis in humans are still lacking.

Some additional data support a possible effect of low doses of dopamine in increasing urinary solute and water output in critically ill patients with mild to moderate renal dysfunction. In two uncontrolled studies of critically ill patients, dopamine (1.5–2.5 μg/kg/min) increased urine output by 42–50% in patients with baseline urinary outputs $<$0.5–1 ml/kg/hr [10, 39]. In a controlled cross-over study of critically ill patients comparing dopamine (200 μg/min) vs dobutamine (175 μg/min) vs placebo, dopamine increased urine output significantly without affecting creatinine clearance, whereas dobutamine increased creatinine clearance significantly without affecting urine output [7]. Taken together, these data suggest that dopamine may increase urinary Na and water excretion in some patients with mild to moderate renal dysfunction.

ORAL DOPAMINE AGONISTS

Dopamine has striking effects on cardiac and renal function in patients with congestive heart failure as outlined above. Additionally, alterations of endogenous dopamine production or metabolism may participate in the pathogenesis of hypertension. The fact that dopamine infusion leads to vasodilation and *na-*

TABLE 1 Dopamine Agonists, Antagonists, and Prodrugs

	DA_1	DA_2	Nonselective
Agonists	Fenoldopam (SKF 82526)	Quinpirole (LY 171555)	Gludopa (γ-L-glutamyl-L-dopa)
	SKF 87516	Bromocriptine	
	FPL 63012AR	Dihydroergotoxine	Docarpamine (TA 870)
			Epinine
			Ibopamine
			SIM 2055
			Dopexamine
Antagonists	SCH 23390	Domperidone	Metoclopramide
		(-)-Sulpride	Sulpride (racemic)
		YM 09151	Haloperiedol
			Cis-thiothixene
			Trifluoperazine

triuresis, in contrast to many other vasodilators that are anti-natriuretic, makes oral dopamine agonists potentially attractive as therapeutic agents. Table 1 and Figs. 7 and 8 show dopamine agonists, antagonists, and prodrugs. Some of these agents are currently employed clinically in Europe and elsewhere to treat congestive heart failure, whereas others remain investigational or have generated side-effects that limit their clinical utility. Even those drugs that have not proven clinically useful have helped to define the physiological roles of dopamine receptor subtypes in natriuresis, vasodilation, and neurohumoral regulation.

Dopamine Prodrugs

Ibopamine and SIM 2055

Ibopamine is the di-isobutyryl ester of *N*-methyl-dopamine (or epinine, see Fig. 7). The drug is deesterified in the gut to yield epinine. Like dopamine, epinine stimulates DA_1, DA_2, and α and β adrenergic receptors. In healthy volunteers, ibopamine has been shown to increase renal plasma flow, GFR, and urinary sodium excretion in most studies. In patients with mild to moderate congestive heart failure (New York Heart Association (NYHA) classes II–III), 100 mg ibopamine given orally increased renal plasma flow, glomerular filtration rate, and urinary volume, but it did not affect urinary NaCl excretion or filtration fraction [27]. In patients with more severe heart failure (NYHA class IV), the same group found no effect of 100 mg ibopamine on urinary sodium excretion and fractional sodium excretion, although ibopamine did

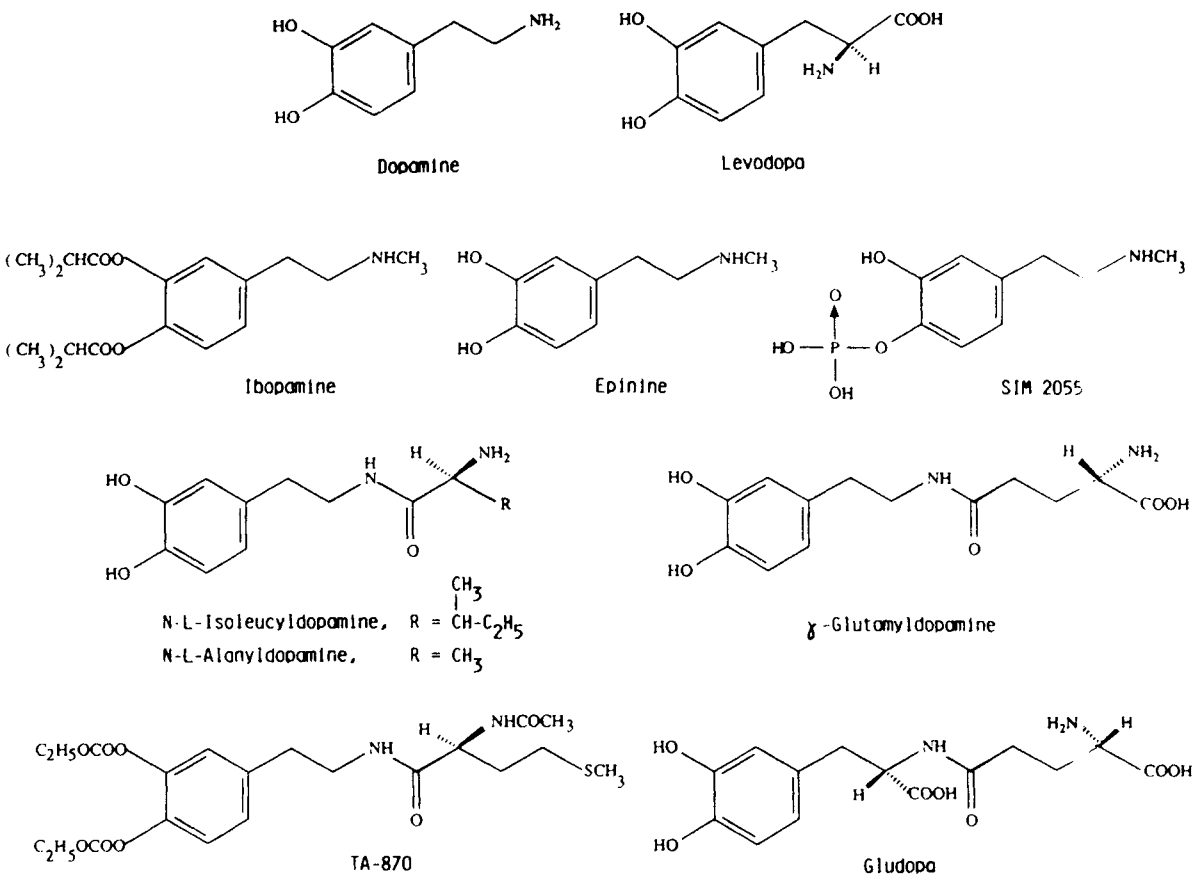
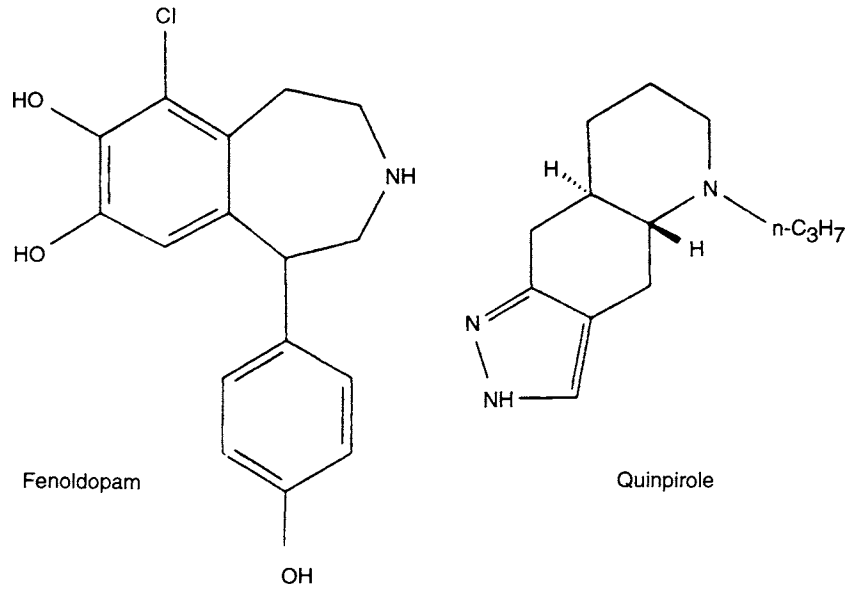


FIGURE 7. Structures of dopamine and dopaminergic prodrugs. From Casagrande, et al. J. Cardiovasc. Pharm. 14 (Supp 8): S40–S59, 1989, with permission.



Selective DA_1- and DA_2-receptor agonists

FIGURE 8. Structures of selective dopaminergic agonists. From Casagrande, et al. J. Cardiovasc. Pharm. 14 (Supp 8): S40–S59, 1989, with permission.

increase glomerular filtration rate and renal plasma flow modestly (15 and 11%, respectively) [13]. Numerous studies have indicated that ibopamine increases cardiac index and reduces systemic vascular resistance when administered to patients with moderate to severe congestive heart failure (reviewed in [32]). The peak hemodynamic changes generally occur about 1–2 hr after an oral dose and persist up to 6 hr. Hemodynamic changes induced by 100 to 200 mg ibopamine orally are generally similar to those that occur during infusion of dopamine at 2–4 μg/kg/min. In several but not all studies, these changes in hemodynamics have been maintained during chronic therapy for several weeks, although doses greater than or equal to 200 mg may be associated with more significant tachyphylaxis [32]. The effects of improving cardiac output reflect primarily peripheral vasodilation rather than positive inotropy, at least at the doses employed clinically. As occurs during therapy with intravenous dopamine or dobutamine, pulmonary and right sided filling pressures frequently do not decline during treatment with ibopamine [32]. In fact, some patients develop a transient rise in pulmonary wedge pressure 15–30 min after a dose of ibopamine. Ibopamine administration also affects circulating levels of neurohormones (see Fig. 9 [33, 34]). Ibopamine inhibits angiotensin II stimulated

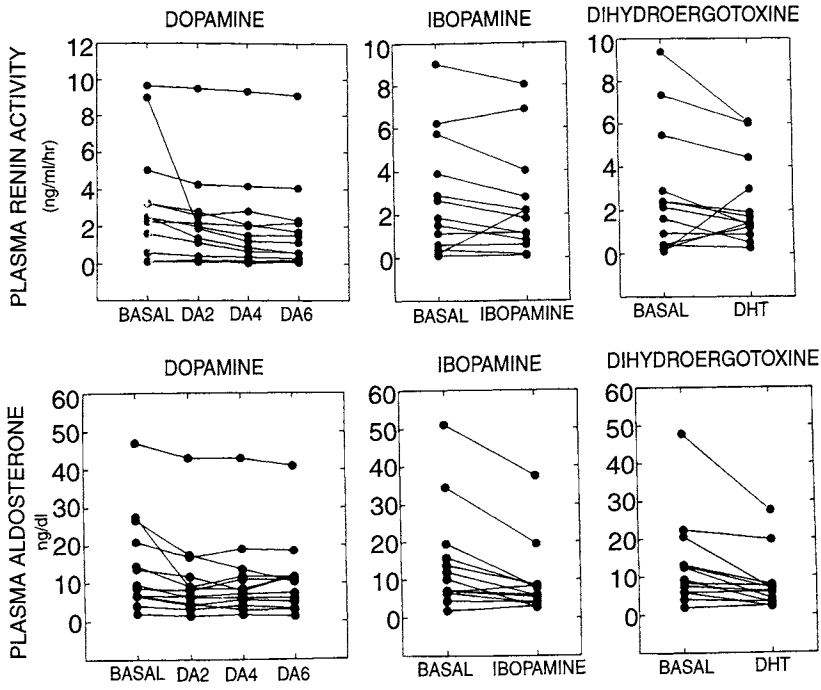


FIGURE 9. Effects of dopamine, ibopamine, and dihydroergotoxine on plasma renin activity and plasma aldosterone. Dopamine was administered at 2–6 μg/kg/min (DA2–DA6). From Metra, et al. J. Cardiovasc. Pharm. 25:732–740, 1995, with permission.

aldosterone secretion, owing at least in part to interaction with DA_2 receptors on the adrenal gland. Ibopamine has also been reported to reduce circulating norepinephrine, perhaps by action on presynaptic DA_2 receptors in the adrenergic nervous system. In contrast, dopamine itself usually increases norepinephrine section.

SIM 2055 (epinine 4-*ortho*-phosphate) is also a prodrug for epinine (see Fig. 7). SIMM 2055 is activated by phosphatases and phosphodiesterases in the gut, liver, and kidney. SIMM 2055 induces hemodynamic and renal effects similar to those of ibopamine.

Gludopa (γ-L-Glutamyl-L-dopa)

Gludopa (Fig. 7) was first investigated as a potential anti-Parkinsonian drug, but it was soon found to have few central nervous system effects. It has been shown to be converted to dopamine in the kidney by the sequential actions of γ-glutamyltransferase and aromatic-L-amino-acid decarboxylaes. Gludopa

is poorly absorbed through the gut, so that it is not useful clinically. However, gludopa has been shown to be natriuretic and hypotensive in humans and to reduce plasma renin activity. These observations have suggested that *intrarenally* produced dopamine may *inhibit* renin secretion by juxtaglomerular cells. The fact that gludopa appears to be activated specifically in the kidney also led to the development of other drugs (see below) that are activated by γ-glutamyltransferase and therefore act primarily in renal tissue.

Docarpamine (TA 870)

Docarpamine is another prodrug for epinine (see Fig. 6). Docarpamine is protected by esterification of the hydroxyl groups at ring positions 3 and 4 and by acylation of the amino group on the side chain. The hydroxyl groups are freed by esterases in the gut (the same process that activates ibopamine) and the amino group is freed by γ-glutamyltransferase in the kidney, rendering this product relatively renal selective. In anesthesized dogs docarpamine increased renal blood flow, glomerular filtration rate, urinary Na excretion and cardiac output [4]. In normal volunteers, docarpamine increased renal plasma flow, urinary Na excretion, and glomerular filtration rate [4]. In 10 patients with NYHA classes III–IV congestive heart failure, docarpamine reduced the left ventricular end-systolic volume [4]. In patients with chronic renal failure, 600 mg of docarpamine increased renal plasma flow and urinary Na excretion [37]. Thus, oral docarpamine has effects that are similar to those of intravenous dopamine.

Direct Agonists

Dopexamine

Dopexamine is a relatively newer agent that combines the ability to stimulate cardiac and systemic β adrenergic receptors with the ability to stimulate DA_1 dopamine receptors. In hypertensive patients [30], dopexamine increased renal blood flow and decreased renal vascular resistance, at a dose that did not lead to systemic vasodilation. In 12 patients [26], dopexamine also increased renal blood flow as well as urine volume and sodium excretion when administered in doses between 0.25 and 1 μg/kg/min. Baumann [1] compared the effects of dopexamine with dobutamine in patients with NYHA classes III–IV congestive heart failure. When administered in doses that increased cardiac output similarly, dopexamine increased urine volume and sodium concentration significantly more than dobutamine, effects that were maintained during 48 hr of infusion. Beta adrenergic receptors downregulate during chronic stimulation, and it was speculated that the better maintenance of dopexamine efficacy reflected stimulation of dopaminergic receptors.

Fenoldopam and FPL 63012AR

Fenoldopam stimulates DA_1 receptors directly and also may inhibit α adrenergic activity. Fenoldopam reduces blood pressure and leads to systemic and renal vasodilation, along with natriuresis and diuresis. In normal volunteers, intravenous fenoldopam increased renal plasma flow (by 40%) and fractional (by 69%) and absolute (by 52%) sodium excretion [21]. In another study of normal volunteers, oral fenoldopam (100 mg) decreased diastolic blood pressure by 10 mm Hg, increased renal plasma flow (by 58%), and increased plasma renin activity [19]. In patients with essential hypertension, intravenous fenoldopam reduced blood pressure and increased sodium excretion with or without prior water loading [35]. In patients with NYHA classes II–IV congestive heart failure, oral fenoldopam (100 mg) acutely increased stroke volume index and decreased systemic vascular resistance, without effects on plasma norepinephrine, plasma renin activity, or plasma aldosterone. When therapy was continued for 3 days, however, renal blood flow declined and urinary Na excretion did not change significantly [11]. The reasons for the disappointing results in congestive heart failure in this study were not clear.

ORAL DOPAMINE AGONISTS: ROLE IN TREATING CONGESTIVE HEART FAILURE

Despite more than 10 years of experience with oral dopamine agonists, their role in the treatment of congestive heart failure remains unclear. They appear to produce short-term benefit in hemodynamics and, in most but not all studies, may improve the hemodynamic profile over the longer term and may increase renal blood flow and urinary NaCl excretion. Yet mortality has not been shown to improve during therapy with the agents, and an inability to document significant functional improvement in some studies has limited enthusiasm for their use. Further studies will be necessary to define their place in the treatment of chronic congestive heart failure.

SUMMARY

Adequate renal perfusion pressure is essential to achieve diuretic-induced natriuresis. Hypotension and shock limit renal perfusion, but in many critically ill patients, renal perfusion pressure may not be reflected by the mean arterial pressure, owing to renal artery stenosis or vasoactive drug use. Adrenergic agonists, especially dopamine, have proven useful in increasing urinary salt and water excretion. In some situations, dopamine appears to have unique effects on the kidney. In patients with congestive heart failure, dopamine is clearly

effective as a natriuretic and diuretic. Dopamine may also increase urine output in patients with acute renal function, but dopamine does not appear to accelerate recovery or to be useful prophylactically. Several specific orally active dopamine receptor agonists and dopamine prodrugs have been developed and tested. Those that activate DA_1 receptors generally cause systemic and renal vasodilation, when given acutely, leading to increases in cardiac output in normal individuals and in patients with congestive heart failure. The chronic administration of oral dopamine agonists, especially ibopamine, to patients with impaired systolic function may improve cardiac hemodynamics and exercise tolerance, although not all results agree. Yet it does not appear that these drugs are especially potent as natriuretic and diuretic agents, on a chronic basis, as they appear to have little effect on cardiac preload. Effects of these drugs on mortality in this population have not been established, but they do not appear to cause the excess mortality that has been reported during administration of several oral inotropic agents. The role of these drugs in treating patients with congestive heart failure or hypertension remains to be established, but the development of oral dopamine agonists has helped to define the role of endogenous dopamine in cardiorenal function under normal and pathological conditions.

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CHAPTER IVC3

Interactions between ACE Inhibitors and Diuretics

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INTRODUCTION

Diuretics and angiotensin-converting enzyme (ACE) inhibitors are commonly used in combination both for patients with heart failure and for those with hypertension. Diuretics activate the renin–angiotensin–aldosterone system (RAAS) which may limit the effects of diuretics on vascular tone and sodium excretion which, in turn, may limit their efficacy in reducing arterial pressure or in improving the symptoms of heart failure. ACE inhibitors can reduce plasma concentrations of angiotensin II and aldosterone, providing a theoretical rationale for use in combination with a diuretic. However, theoretical assumptions should always be tested. Clinical experiments in this field frequently have been unable to uphold theory, have sometimes contradicted it, and have occasionally revealed evidence for a more exciting interaction than predicted.

POINTS OF INTERACTION BETWEEN ACE INHIBITORS AND DIURETICS

ARTERIAL PRESSURE

Both thiazide and loop diuretics reduce arterial pressure in hypertension. Although neither group of agents is noted for its ability to reduce arterial blood pressure in heart failure they almost certainly contribute to the low arterial pressure commonly seen in this condition. Diuretics reduce arterial pressure

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despite activation of neuroendocrine vasoconstrictor systems (*vide infra*). ACE inhibitors should exaggerate the effects of diuretics on blood pressure by blocking such vasoconstriction.

Studies of hypertension confirm that ACE inhibitors enhance the antihypertensive effects of diuretics, though the interaction has appeared more additive than synergistic [41, 49]. Combining diuretics with ACE inhibitors has appeared no more effective than combining them with beta-blockers. However, as diuretics may activate the sympathetic nervous system as well as the RAAS, this cannot be taken as evidence that a neuroendocrine substrate for an ACE inhibitor/diuretic interaction does not exist.

In patients with heart failure those on greater doses of diuretics have a greater initial fall in arterial pressure [22] after the first dose of an ACE inhibitor. The relationship between the magnitude of the initial fall in arterial pressure in patients with heart failure and the occurrence of hypotensive symptoms appears complex. Although patients with more advanced heart failure in the SOLVD study had a significantly smaller fall in arterial pressure after enalapric they were 2–3 times more likely to experience symptomatic hypotension [28]. This may reflect the fact that patients with more severe heart failure have a lower initial blood pressure. Among patients developing a low arterial pressure during maintenance therapy with an ACE inhibitors, renal dysfunction is common; both may resolve when the dose of diuretic is reduced [37].

Renal perfusion pressure is one of the determinants of sodium excretion [35]. Reduction in renal perfusion may reduce the natriuretic response to diuretics and exaggerate the rebound in renal sodium retention in the postdiuretic period. This will be discussed further below.

Plasma Volume

In patients with hypertension addition of an ACE inhibitor to patients receiving chronic diuretic therapy does not appear to alter plasma volume [48].

In patients with untreated heart failure plasma and extracellular fluid volume are expanded [1]. However, in patients treated optimally with diuretics plasma volume may be normal or reduced and extracellular fluid volume normal or only slightly increased [3, 14]. Addition of an ACE inhibitor causes an acute fall in hematocrit, indicating acute plasma volume expansion [15]. In the longer term hematocrit tends to return toward baseline [12, 13], although it may not be completely restored [27]. It is not clear if this reflects changes in plasma volume or a change in red cell mass [27].

SYSTEMIC HEMODYNAMIC EFFECTS

Resolution of massive peripheral edema following diuretic use is associated with a reduction in ventricular filling pressures and systemic vascular resis-

tance and an increase in cardiac output [9]. In the absence of marked peripheral edema there may be more marked activation of the RAAS and, although filling pressures still fall, diuretics may induce a rise in vascular resistance and a fall in cardiac output fall [9].

In patients with ventricular dysfunction ACE inhibitors also reduce filling pressures and vascular resistance and this is associated with a modest increase in cardiac output in the absence of a diuretic [62]. These effects are all exaggerated in the presence of a diuretic presumably reflecting neuroendocrine activation in these patients [23]. Patients on higher doses of diuretics have greater neuroendocrine activation and, in most studies, a greater initial hemodynamic response to ACE inhibition [9, 22, 39]. The relationship between neuroendocrine activation and long-term hemodynamic effects of ACE inhibitors is much more complex, as would be expected [9, 39].

RENAL HEMODYNAMIC EFFECTS

Diuretics tend to increase renal blood flow acutely in normal subjects and patients with hypertension, probably through prostaglandin mediated pathways [15, 29]. Renal vascular resistance must fall substantially as renal perfusion pressure will fall due to the diuretic. Frusemide may also redistribute blood flow toward the renal cortex [15]. During longer term therapy RAAS activation, resulting in a preferential increase in efferent arteriolar tone, may reverse the direct pharmacological effect of the diuretics. Chronic diuretic administration and RAAS activation is probably mainly responsible for the reduction in renal blood flow characteristic of chronic heart failure [15]. In patients with heart failure, in the absence of an ACE inhibitor, acute administration of a diuretic has little overall effect on renal blood flow [15]. This probably reflects the overriding effect of concomitant RAAS activation.

ACE inhibitors increase renal blood flow in left ventricular dysfunction, even in the absence of a diuretic [16]. In patients with heart failure treated with diuretics ACE inhibitors appear to increase renal blood flow even more markedly, reflecting release from the more marked RAAS mediated renal vasoconstriction [15]. ACE inhibitors also enhance furosemide induced renal vasodilation [15].

Filtration fraction, the ratio of glomerular filtration rate to effective renal plasma flow, is increased in patients with heart failure. Filtration fraction is largely determined by the ratio of efferent to afferent arteriolar tone, the former being more sensitive to angiotensin II. In the face of a decline in cardiac output and renal blood flow, efferent arteriolar constriction preserves glomerular filtration at the cost of a further reduction in renal blood flow. Diuretics may increase filtration fraction by their direct vasodilator effects on the afferent arteriole and by increasing angiotensin II-mediated efferent arteriolar tone. Treatment with an ACE inhibitor reverses the preferential efferent arteriolar constriction char-

acteristic of heart failure and reduces filtration fraction. This effect will be exaggerated in the presence of a diuretic [15, 26].

GLOMERULAR FILTRATION

Diuretics have little acute effect on glomerular filtration rate (GFR), any tendency to fall due to the reduction in renal perfusion pressure being balanced by efferent arteriolar constriction. ACE inhibitors reduce both renal perfusion pressure and efferent arteriolar tone and as predicted glomerular filtration rate falls acutely [15, 32]. In the long term, reductions in glomerular filtration rate are modest and serum creatinine rises by only 10–15% [12]. Some radioisotopic studies have shown much greater long-term falls in GFR than the rise in serum creatinine would suggest [12]. These studies have generally been conducted during combined administration of furosemide and ACE inhibitor. It is possible that the diuretic causes direct renal efferent arteriolar dilation that can no longer be countered by an increase in angiotensin II, leading to an exaggerated fall in GFR when the diuretic and ACE inhibitor are acting on the kidney simultaneously. When plasma concentrations of furosemide fall, efferent arteriolar tone and GFR may rise [26].

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM AND EFFECTS ON ELECTROLYTES

Diuretic therapy is one of the principle causes of RAAS activation in heart failure and essential hypertension [23]. Renin release reflects not only volume depletion, but also sympathetic nervous system activation and direct, prostaglandin-mediated, renal renin release. Increases in aldosterone, predominantly under the control of angiotensin II in these settings, may attenuate the natriuretic effect of diuretics and is the principal cause of hypokalemia in heart failure. RAAS activation also contributes to vasoconstriction and structural remodeling of the heart and vasculature in heart failure and, probably, hypertension. Neuroendocrine activation may contribute importantly to the morbidity and mortality associated with these conditions [11].

ACE inhibition reverses or attenuates all of the above effects. With long-term treatment ACE inhibitors correct hypokalemia, plasma potassium increasing by 0.2–0.6 mmol/liter depending on the pretreatment potassium concentration [12]. As plasma potassium rises this becomes an important stimulus to aldosterone secretion and this feedback checks excessive increases in potassium [10–13]. Plasma magnesium also increases [12].

SYMPATHETIC NERVOUS SYSTEM

Diuretics increase plasma noradrenaline in patients with hypertension, probably a baroreflex response to a tendency for plasma volume to fall acutely. In patients with untreated heart failure diuretics may reduce plasma noradrenaline though this has not been subject to controlled studies [6]. In patients treated with diuretics chronically sympathetic activity is generally increased and plasma noradrenaline rises further on administration of a diuretic [15]. ACE inhibitors can reduce basal sympathetic activity in heart failure and attenuate the acute increase in plasma noradrenaline observed after diuresis [15].

RENAL BRADYKININ/PROSTAGLANDIN PATHWAYS

Diuretics exert vasodilator effects through activation of bradykinin/prostaglandin pathways [15, 17, 29]. ACE inhibitors inhibit the degradation of bradykinin and may enhance such responses.

RENAL SODIUM AND WATER HANDLING

There are multiple possible sites of interaction of ACE inhibitors and diuretics on salt and water excretion. Both agents have effects on arterial (renal perfusion) pressure, an important determinant of salt and water excretion, and on renal hemodynamics. Diuretics increase angiotensin II and sympathetic activity, which may enhance proximal tubular sodium retention, and aldosterone, which enhances distal tubular sodium/potassium exchange.

In normal subjects there is some evidence that ACE inhibitors enhance renal salt and water excretion and they may also enhance the effects of furosemide [34]. This may not be true of all diuretic agents. Enalapril has been reported to blunt the natriuretic effect of candoxatrilat, a neutral endopeptidase inhibitor, in healthy volunteers [33].

In patients with hypertension some studies have suggested that ACE inhibitors increase sodium excretion (net cumulative increased excretion of about 100 mmol over the first week [36]. This appears to be independent of sodium intake and renin activation. However, other studies have not observed a natriuretic effect [47].

In untreated patients with heart failure ACE inhibitors have little effect on salt or water excretion [16, 43]. ACE inhibitors are unable to prevent reaccumulation of salt and water in patients previously treated with diuretics and are not effective monotherapy for patients with obvious fluid retention [2, 44].

TABLE 1 Studies of the Effects of Single-Dose or Short-Term ACE Inhibition on the Response to Furosemide in Patients on Chronic Diuretic Therapy for Heart Failure

Study	n=	Agents	Effect of ACE inhibitor on furosemide response
Reed [43]	8. X-over	Captopril Control	Captopril increased GFR but not renal blood flow. No effect on sodium output.
McLay [30]	25. Parallel Design Study	Captopril vs Placebo	Urine volume reduced to 43% of control ($P<0.02$). Natriuresis is reduced to 38% of control ($P<0.001$). Rise in GFR after furosemide inhibited.
Motwani [31]	10. X-over	Captopril 25 mg Captopril 1 mg Placebo	Captopril 1 mg enhanced natriuresis ($P<0.05$). Captopril 25 mg reduced natriuresis and GFR.
Flapan [19]	12. X-over	Captopril Control	Captopril reduced urine volume over 4 hr to 59% of control and natriuresis to 57% of control (both $P<0.05$). GFR fell to 53% of control.
Flapan [20]	12. X-over	Captopril Control	As above. Effects reported to be more evident in the erect than the supine position.
Cleland [15]	12. Sequential	Enalapril 10 mg Control	Treatment for 5 days. Weight gain. Urine volumes reduced

The balance of evidence suggests that ACE inhibitors actually promote salt and water retention and a rise in body weight in the first few days after their initiation in patients with heart failure treated chronically with diuretics [15, 18, 30, 19] (Tables 1 and 2; Figs. 1–5). This may reflect a fall in the filtered load of sodium and increased proximal tubular sodium absorption [8]. Water retention is usually in excess of sodium retention resulting, generally, in a small fall in serum sodium in the first few days of treatment [8, 18, 15]. Thereafter

TABLE 2 Studies Investigating the Interaction of Chronic ACE Inhibitor and Diuretic Therapy in Patients with Heart Failure

Study	n=	Agents	Effect of ACE inhibitor on furosemide response
Flapan [21]	20. Parallel Design Study	Enalapril 10 mg bd Control	Urine volumes and natriuresis greater in control group in the supine position. Trend in the opposite direction in the erect position
Good [26]	8. X-over	Background ACEi: Captopril 12.5 mg Placebo	Captopril enhanced urine volumes and natriuresis by 20–30%. GFR reduced.

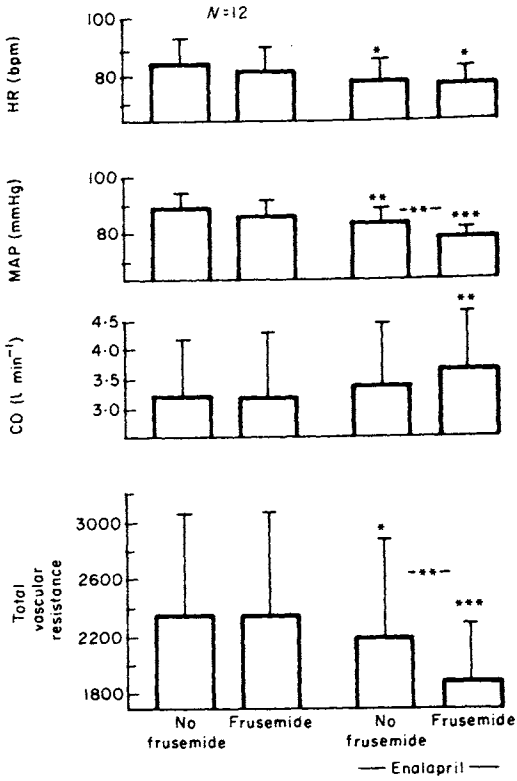

FIGURE 1 Comparison of the effects of frusemide, enalapril, and their combination on heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), and total vascular resistance. Figures are mean ±SD. An asterisk over the error bar indicates an effect of enalapril, but between error bars signifies an effect of frusemide (*$P<0.05$; **$P<0.02$; ***$P<0.001$).

serum sodium concentrations tend to rise though responses may vary [38]. Patients with marked falls in blood pressure increase their plasma concentration of anti-diuretic hormone, presumably an effect designed to support the arterial pressure, resulting in a fall in serum sodium concentration. In other patients, inhibition of angiotensin II production appears to correct hyponatremia.

The initial salt and water retention with ACE inhibitors may be a generic response to arteriolar vasodilation in heart failure. Minoxidil, prazosin, nifedipine, and hydralazine have all been shown to promote fluid retention [9]. In the case of minoxidil and prazosin this may be marked and progressive [5, 24]. The difference with ACE inhibitors is that fluid retention may be limited or indeed reversed with long-term treatment. The overriding reason for fluid re-

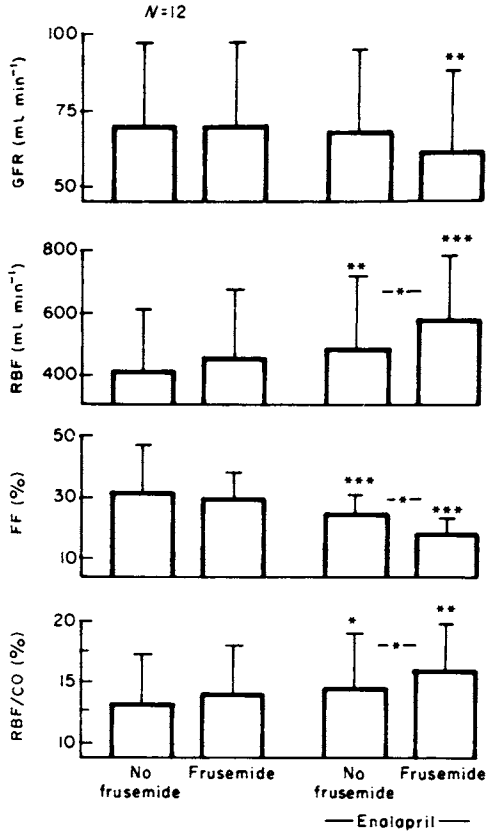

FIGURE 2 Comparison of the effects of frusemide, enalapril, and their combination on glomcrular filtration rate (GFR), renal blood flow (RBF), filtration fraction (FF), and the percentage of the cardiac output delivered to the kidneys (RBF/CO). Figures are mean ±SD. An asterisk over the error bar indicates an effect of enalapril, but between error bars signifies an effect of frusemide (*$P<0.05$; **$P<0.01$; ***$P<0.001$).

tention with arteriolar vasodilators may be complex and dependent on the peripheral as well as renal microcirculation but the fall in renal perfusion pressure could be a central factor. The autonomic effects of ACE inhibitors, in contrast to conventional vasodilators, may alter the "set-point" for salt and water retention, allowing increased excretion at a lower renal perfusion pressure.

Over 30 medium- to long-term double-blind studies of heart failure have been conducted. Only one has documented a significant fall in weight [7]. All others that have reported weight indicate no change and there has not generally even been a trend for weight to fall. This suggests that ACE inhibitors do not enhance salt and water retention in diuretic-treated heart failure, although it must be pointed out that ACE inhibitors could increase muscle mass, a re-

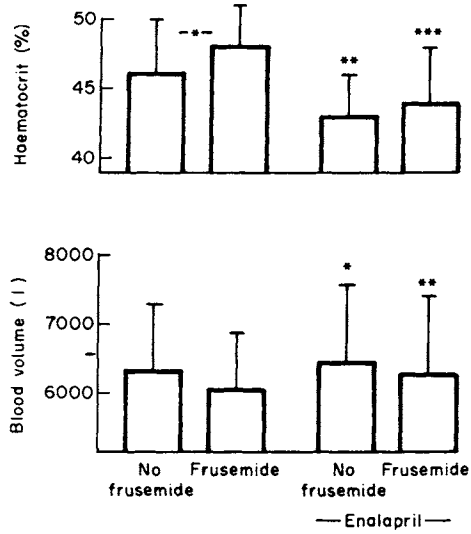

FIGURE 3 Comparison of the effects of frusemide, enalapril, and their combination on haematocrit and blood volume. Figures are mean ±SD. An asterisk over the error bar indicates and effect of enalapril, but between error bars signifies an effect of frusemide (*$P<0.05$; **$P<0.02$; ***$P<0.001$).

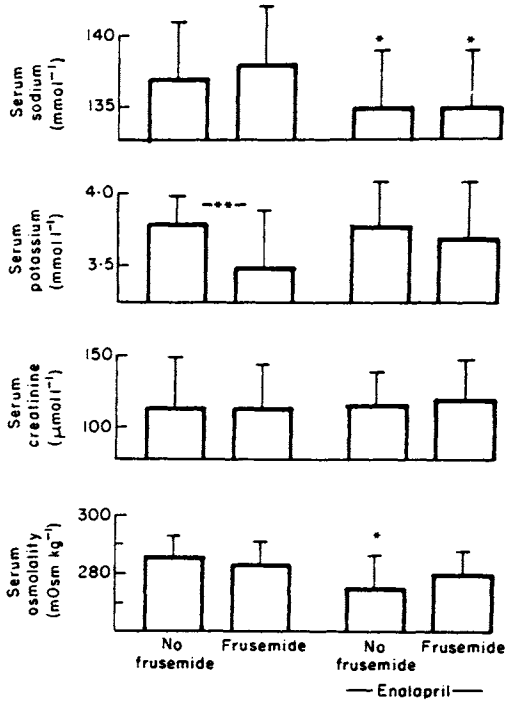

FIGURE 4 Comparison of the effects of frusemide, enalapril, and their combination on serum biochemistry. Figures are mean ±SD. An asterisk over the error bar indicates and effect of enalapril, but between error bars signifies an effect of frusemide (*$P<0.05$; **$P<0.01$).

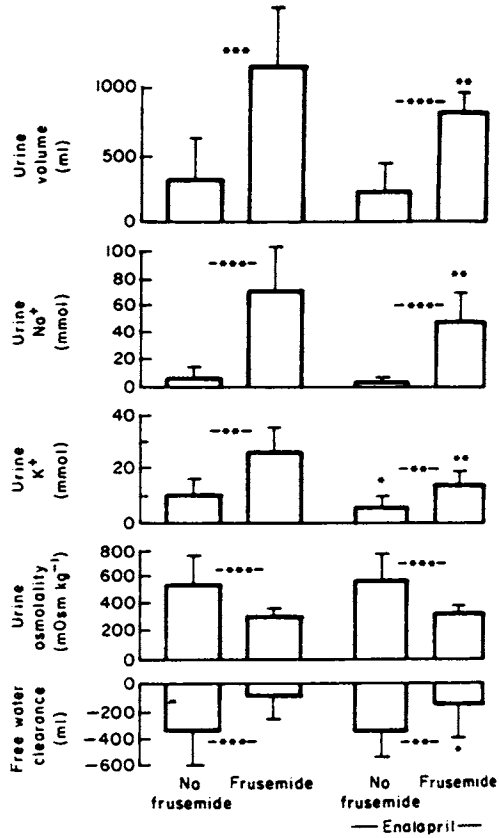

FIGURE 5 Comparison of the effects of frusemide, enalapril, and their combination on urine volume and biochemistry (Na, sodium; K, potassium). Figures are mean ±SD. An asterisk over the error bar indicates and effect of enalapril, but between error bars signifies an effect of frusemide (*$P<0.05$; **$P<0.01$; ***$P<0.001$).

sponse to an improvement in heart failure that may mask any reduction in extracellular fluid volume.

DO ACE INHIBITORS ALTER RENAL EXCRETION OF DIURETICS?

Studies in hypertension [25] and heart failure [26] indicate that urinary excretion of furosemide is not affected by captopril.

INTERACTION WITH SPIRONOLACTONE

Although plasma aldosterone is initially reduced by ACE inhibitors, during long-term therapy plasma aldosterone rises again. The rise in aldosterone can be suppressed, to a large extent by increasing the dose of ACE inhibitor [10], or the effects of aldosterone can be blocked by an antagonist. The rise in potassium during ACE inhibition is one potential mechanism for the secondary rise in aldosterone. Alternatively, breakthrough of ACE inhibition may lead to a resumption of angiotensin II formation. Both are probably responsible in part. The increase in aldosterone prevents the more frequent occurrence of ACE inhibitor induced hyperkalaemia.

Addition of spironolactone (50–100 mg/day) to patients with heart failure already receiving a loop diuretic and an ACE inhibitor increases plasma potassium and magnesium and enhances natriuresis [4]. The addition of spironolactone has also been reported to improve symptoms and reduce ventricular arrhythmias and increase cardiac norepinephrine uptake as assessed by an MIBG scan [4]. Other studies have suggested that the risks of hyperkalaemia are unacceptably high with the use of conventional doses of spironolactone and that doses of 12.5–25 mg/day may be sufficient [40]. A study investigating the effects of spironolactone on mortality/morbidity on top of conventional diuretics and ACE inhibitors in heart failure is underway.

MORBIDITY AND MORTALITY

Diuretics reduced the risk of stroke and the magnitude of benefit is close to what is predicted by the fall in blood pressure. In contrast the reduction in coronary events and overall mortality is less than expected. This could reflect the benefits of blood pressure reduction being balanced by adverse metabolic effects including, possibly, neuroendocrine activation.

Patients with left ventricular dysfunction requiring treatment with a diuretic have a worse prognosis than those that do not [45]. It is not clear whether this reflects the more advanced stage of the heart failure or neuroendocrine activation. Neuroendocrine activation may be largely responsible for adverse ventricular remodeling, myocardial fibrosis, and arrhythmias in heart failure. Patients with heart failure and marked neuroendocrine activation have a worse prognosis and derive greater mortality benefits from treatment with an ACE inhibitor [46].

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CHAPTER IVC4

Atrial Natriuretic Peptide

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INTRODUCTION

The natriuretic peptide system consists of three peptides with similar structures. These peptides cause a wide range of actions in the kidney, the vasculature, the heart, and the central nervous system. Atrial natriuretic peptide (ANP) was first sequenced in 1984 [1] and has subsequently been the subject of extensive investigation. This peptide is secreted from the cardiac atria and has profound natriuretic and diuretic properties, as well as vasodilatory effects [2]. Brain natriuretic peptide (BNP) was subsequently discovered in porcine brain [3]—hence its name—but in humans this peptide is secreted extensively from the heart, predominantly from the ventricles [4]. It has actions similar to those of ANP and has more recently been called B-type natriuretic peptide. The third member of the group, C-type natriuretic peptide (CNP), is present mainly in the central nervous system and the vascular endothelium, and it appears to have very limited natriuretic properties [5].

The structures of the natriuretic peptides are shown in Fig. 1. They share a common central ring structure with variable carboxy (C-) and amino (N-) terminal tails [6, 7]. Each peptide also exists as a relatively high-molecular-weight storage form; this is cleaved prior to release into the circulation and these larger peptides are detectable in the peripheral blood, although their

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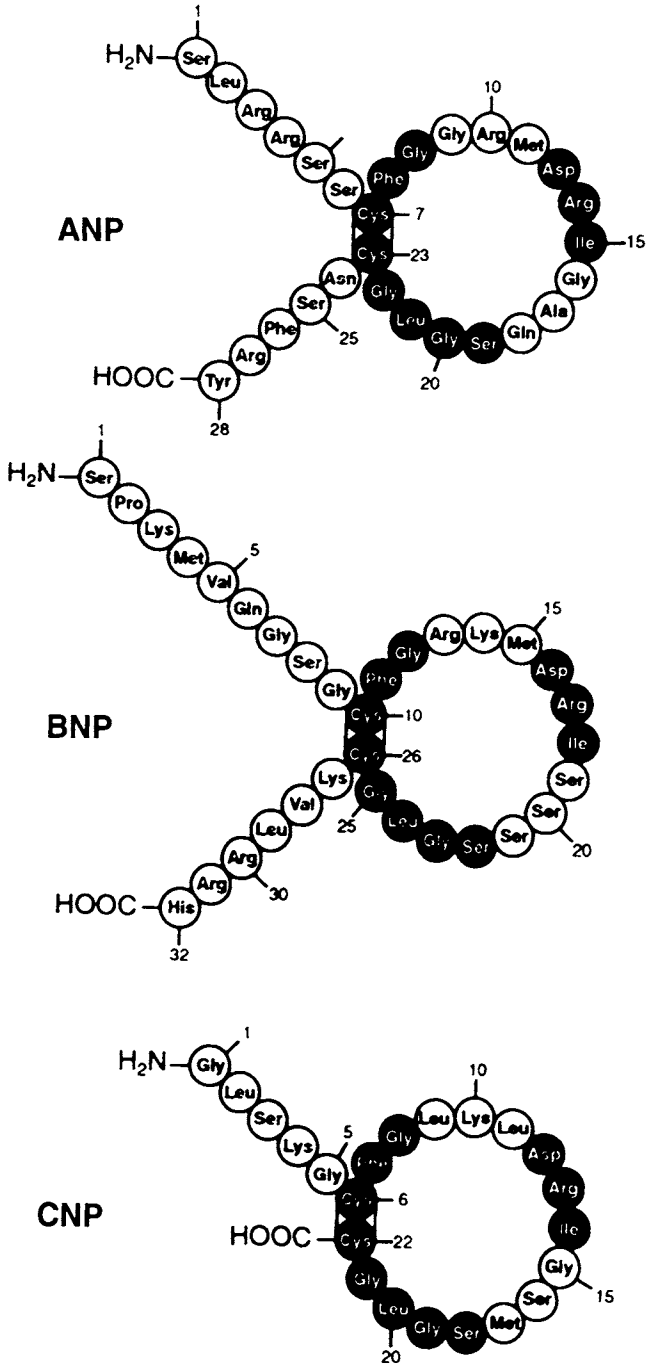

FIGURE 1. Structure of predominant circulating forms of human atrial and natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).

biological significance is uncertain. ANP and BNP are released from storage granules in the myocardium; animal studies have suggested that the main trigger for their secretion is stretching of the atrial and ventricular walls, respectively. In patients with heart failure a recent study has demonstrated that the release of both ANP and BNP is regulated by the tension of the wall of the left ventricle [8]. The physiological factors that control the release of CNP have not been defined. In patients with heart failure, the plasma levels of ANP and BNP—but not CNP—are markedly elevated [9].

Three different natriuretic peptide receptors have been identified and unfortunately, although these have been named A, B, and C, the designations do not correspond to their relative affinities for ANP, BNP, and CNP [6, 7]. The A and B receptors are linked to guanylate cyclase and cause increased production of cyclic guanosine monophosphate (cGMP), which acts as a second messenger for most of the known biological effects of natriuretic peptides. The C receptor was originally described as a clearance receptor with no function other than the removal of natriuretic peptides from the circulation, but it is now recognized that the receptor may be linked with biological actions that are mediated by a reduction in cAMP [10].

Clearance of natriuretic peptides from the circulation occurs via two mechanisms: first, via receptor-mediated endocytosis, and second, via degradation by a zinc-containing enzyme, neutral endopeptidase 24.11 (NEP) [11]. This is a nonspecific enzyme that is present in the kidney and in vascular beds and that catalyses the degradation of many endogenous peptides including substance P and angiotensin II. The approximate plasma half-lives of natriuretic peptides in humans are as follows: ANP, 3 min [12]; BNP, 22 min [13]; and CNP, 2.6 min [5].

THERAPEUTIC USES

The recognized natriuretic, diuretic, and vasodilatory properties of natriuretic peptides make them very attractive as therapeutic agents for both hypertension and heart failure. In contrast with loop diuretics and many vasodilators, natriuretic peptides have the advantage of causing inhibition rather than stimulation of the renin–angiotensin–aldosterone system.

RENAL EFFECTS

ANP appears to induce natriuresis and diuresis without significantly increasing potassium excretion. Most studies show that ANP increases both the filtration fraction and the fractional sodium excretion. The glomerular filtration rate

(GFR) is increased sometimes but only by large doses of ANP, while natriuresis normally occurs after ANP without any changes in GFR. The main intrarenal effect of ANP is to inhibit sodium transport in the inner medullary collecting duct, some of which is due to ANP lying in the tubular lumen and some to blood borne ANP. Other sites of action include an inhibitory effect of ANP on angiotensin II-induced antinatriuresis at the level of the proximal tubule and inhibition of the tubular actions of arginine vasopressin (AVP) and aldosterone. It is probable that loss of medullary solute gradient ("renal medullary washout") also contributes to natriuresis, possibly because ANP increases medullary blood flow.

Many studies in normal man have shown that ANP infusions cause an increase in urinary sodium and cyclic GMP and that this occurs with infusions which raise plasma ANP levels within the normal physiological range. In hypertensive subjects, prolonged (5 day) infusions of high doses of ANP cause a fall in BP and induce a negative cumulative sodium balance (approximating 80 mmol) [14]. This negative sodium balance is not progressive but plateaus as systolic arterial pressure falls. Prolonged low dose ANP infusion also often causes a waning of the natriuresis as systolic blood pressure falls. This is thought to be because ANP-induced natriuresis is dependent on renal perfusion pressure. By contrast, increases in renal perfusion pressure, as may occur in plasma volume expanded states, augment the natriuretic effect of ANP and could explain in part the renal "escape" from persisting sodium retention which occurs in primary hyperaldosteronism. Clearly changes in renal perfusion pressure are not the only possible explanation for why total body sodium is able to regulate the magnitude of ANP induced natriuresis. Changes in ANP receptor sensitivity or in coincidental antinatriuretic hormones are also possible contributory mechanisms.

In contrast to healthy volunteers and essential hypertensives, patients with heart failure, especially of severe degree, exhibit a blunted diuresis and natriuresis with high-dose ANP infusion. The same has been demonstrated in a variety of animal models of heart failure. This renal hyporesponsiveness to ANP in heart failure has been attributed to various mechanisms such as a low renal artery perfusion pressure, receptor downregulation, or the opposing antinatriuretic/antidiuretic action of angiotensin II, the renal sympathetic system, and vasopressin, all of which are stimulated in severe grades of cardiac failure. However, it should be stated that this renal hyporesponsiveness to infused exogenous ANP does not necessarily mean that the high endogenous ANP levels found in patients with heart failure are not contributing to natriuresis. Indeed studies with inhibitors of ANP show that blocking the effect of endogenous ANP does cause sodium retention in animal models of heart failure [15]. More selective inhibitors of ANP are required to further define the pathophysiological role of ANP in cardiac failure. Interestingly, Yoshimura *et al.* [16] found that,

in stark contrast to ANP, BNP caused a greater rather than a diminished natriuresis in human heart failure as compared to normal man. In as yet unpublished work, we have confirmed this. This is intriguing since most of the proposed mechanisms for renal hyporesponsiveness to ANP in heart failure would also apply to BNP.

THERAPEUTIC POTENTIAL OF ANP

Since ANP and BNP can be given only intravenously their therapeutic potential has had to be explored by alternative means. The most promising strategy is to use oral inhibitors of the enzyme neutral endopeptidase, which normally metabolises ANP and BNP. NEP inhibitors do indeed produce natriuresis and diuresis although curiously with only a small or no rise in plasma ANP levels [17]. However, an elevation in urinary cGMP excretion is seen after a NEP inhibitor, which suggests that they do indeed act by increasing the biological activity of ANP, even although plasma ANP levels change little. The natriuretic response to NEP inhibition is markedly potentiated in situations of elevated plasma ANP levels. Physiological maneuvers including acute volume expansion or partial nephrectomy increase endogenous ANP and clearly augment the renal response to NEP inhibitors.

Interestingly, however, not all data support the expected idea that NEP inhibitors induce natriuresis by way of potentiating ANP. The observations which support this idea are as follows. First, as mentioned above, most studies which measured plasma ANP levels found small but significant increases in plasma ANP after NEP inhibition, particularly when pretreatment ANP levels are already elevated [17]. Second, several studies have shown that the natriuretic effects of NEP inhibitors are accompanied by increases in urinary *ir*-ANP [17, 18]. Third, the natriuretic effects of NEP inhibitors are accompanied and paralleled by increases in urinary cGMP, a marker of ANP activity [17, 10]. Fourth, the effects of NEP inhibitors are blocked or significantly attenuated by antibodies raised against ANP [19].

However, a crucial disparity is that the natriuretic response to NEP inhibitors is more pronounced than the natriuretic response to ANP infusion alone. This is especially true in heart failure. Indeed the magnitude of the NEP inhibitor induced natriuresis is too great to be explained by the rise in plasma ANP levels alone [19]. Several possibilities may explain this disparity.

NEP inhibitors break down a wide range of peptides as well as ANP and it could be that NEP inhibitors affect sodium excretion by modulating the activity of more than just ANP or even BNP. Other peptides, such as kinins, may contribute to the natriuretic response to NEP inhibition. Another possibility is that the disproportionate natriuretic response to NEP inhibition is due to enhanced

local action of ANP. NEP inhibitors may well modify the intrarenal action of ANP (and other members of the natriuretic peptide family) rather than simply increasing circulating levels. NEP is abundant in the proximal tubule and normally metabolizes filtered ANP (and BNP) before it reaches the papilla. NEP inhibition may allow filtered ANP/BNP access to distal nephron receptors from which it is normally shielded. This idea is supported by the presence of increased amounts of *ir*-ANP in the urine during E-24.11 inhibition [17–19].

If NEP inhibitors are to ever become a therapeutic option in heart failure, then it is likely that they will be combined with angiotensin-converting enzyme (ACE) inhibitors, since the latter are an integral part of the treatment of heart failure. In animal models of heart failure, NEP inhibitor induced natriuresis appears to be potentiated by ACE inhibitors [17], whereas the opposite appears to be true in man. In normal man, a single dose of enalapril blunts the natriuresis due to NEP inhibition [20], and in as yet unpublished work, we found the same thing in patients with heart failure. Having said that, NEP inhibition does still produce a natriuresis in the presence of an ACE inhibitor and therefore the magnitude of the natriuresis produced is unlikely to be crucial in deciding whether the combination of NEP and ACE inhibition has a therapeutic future. More likely is whether NEP/ACE inhibition improves symptoms and survival in heart failure and whether NEP/ACE inhibition has any antiatherosclerotic activity.

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PART V

Indications

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CHAPTER VA1

The Pathophysiology of Edema Formation: General Concepts

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INTRODUCTION

Edema is the clinical manifestation of an accumulation of fluid within the interstitial spaces of the body. It develops when the normal balance between the flow of fluid out of capillaries and the return of fluid to the vascular space via capillary reabsorption and lymphatic flow is disrupted. Edema may be generalized, localized to a portion of the body (i.e., dependent edema), or confined to a single limb or organ (cerebral edema, pulmonary edema, etc.). Edema which accumulates in the subcutaneous space is most readily detected by patients and clinicians.

Generalized edema is almost always associated with a significant increase in body weight which is due to the retention of dietary salt and water by the kidneys. Usually, generalized edema does not become clinically detectable until body weight increases by at least 10%. Renal salt and water retention must accompany the development of generalized edema or cardiovascular collapse would occur. The acute capillary leak syndromes are examples of large translocations of fluid from the vascular into the interstitial space which occur so rapidly that renal salt retention cannot compensate. Therefore hypotension and shock are common with these disorders.

In some disorders the renal retention of salt and water is the primary process

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which drives the development of edema (i.e., overflow edema). This occurs when renal function is markedly impaired or in patients with acute glomerulonephritis. Some forms of edema associated with cirrhosis and nephrotic syndrome may also be triggered by primary renal salt and water retention. These issues are discussed in Chapters VA3 and VA4. Localized edema in one extremity or organ may develop with minimal renal salt retention due to the much smaller volume of fluid which moves from the vascular compartment.

In this chapter, we review the physical forces which govern fluid movement across capillaries, the role of lymphatic drainage in the return of interstitial fluids to the vascular compartment, the various derangements which can result in the formation of edema. Subsequent chapters focus on the major disorders which produce generalized edema: congestive heart failure, cirrhosis, and the nephrotic syndrome. They will emphasize those aspects of pathophysiology and therapy which are unique to each of these clinical disorders.

THE MICROCIRCULATION–NORMAL FLUID EXCHANGE [2, 4, 6, 10]

The total *potential* capillary surface area which could be available for fluid exchange is enormous at over 1000 m^2. However, under basal resting conditions constriction of precapillary sphincters restricts the flow of blood to only about 25–30% of the total capillary bed. The vast majority of fluid, gas, and solute which crosses the epithelium of perfused capillaries does so via diffusive mechanisms. Over 60 liters of fluid and dissolved solute normally diffuses across the adult capillary epithelia each minute. Diffusion of fluid and electrolytes across capillaries is equal in each direction so that minimal net transport of water and most solutes occurs via this mechanism. However, diffusion is the major mechanism responsible for net gas (O_2 and CO_2) transport across systemic and pulmonary capillaries.

The second major mechanism for water and solute transport across capillary membranes is convection. Such movement is also called bulk, or hydrodynamic, water and solute flow. This represents the movement of fluid and solute through epithelial pores under the influence of hydrostatic and osmotic forces. These forces cause fluid and solutes to move out of the arterial end of perfused capillaries into the interstitium and then return from the interstitium into the distal capillary domains. Some capillaries have relatively higher hydrostatic pressures and may filter fluid throughout their length. Other low hydrostatic pressure capillaries may primarily reabsorb fluid.

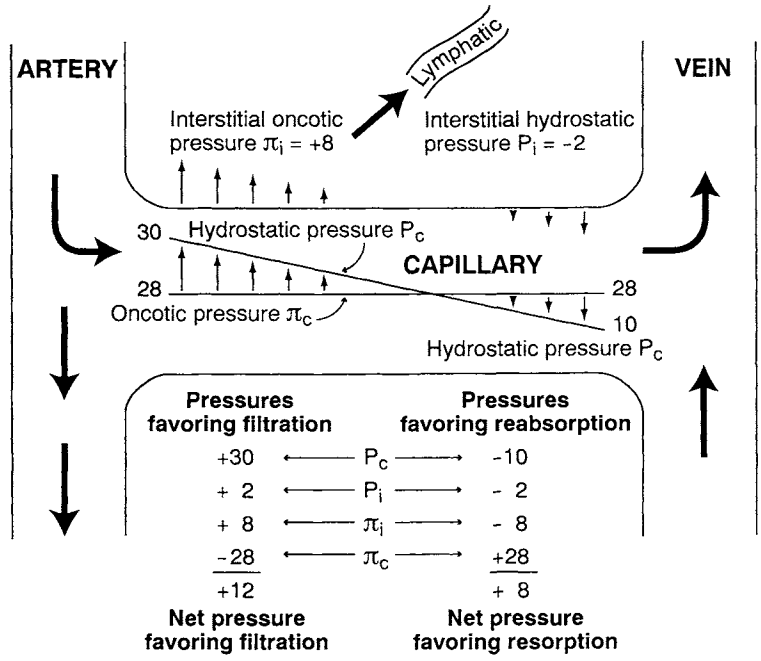
In most capillary beds, outward convective movement slightly exceeds inward movement and this difference in bulk fluid flow is normally returned to the vascular compartment by lymphatic drainage. Finally, a very small fraction

of fluid, solute, and particulate material pass through capillary endothelial cells by the process of pinocytosis.

Physical Forces Affecting Fluid and Solute Transport

Starling Forces [2,3]

The physical forces controlling the bulk movement or convection of fluid and dissolved solute across capillary epithelia were first clearly described over 100 years ago by Dr. E. H. Starling [9]. Figure 1 shows how these forces pro-



$$Jv = K\,[(P_c - P_i) - \alpha\,(\pi_c - \pi_i)]$$

FIGURE 1. A schematic diagram of an idealized systemic (subcutaneous) capillary. The pressure profile along the length of the capillary and in the subcutaneous interstitial space are shown. Capillary hydrostatic pressures fall progressively from 30 to 10 mm Hg. The oncotic pressure of about 28 mm Hg increases trivially along the length of the capillary because the fraction of fluid which is filtered is very small (less than 1%). In the arterial portion of the capillary the pressure gradients favor filtration (+12 mm Hg), while pressure gradient in the venous end of the capillary favors fluid reabsorption (+8 mm Hg).

duce fluid filtration and reabsorption in an idealized systemic (i.e., subcutaneous) capillary. Hydrostatic intracapillary pressure favors outward movement of fluid and solute, while interstitial hydrostatic pressure opposes this flow. Thus, net hydrostatic pressure ΔP represents the difference between intracapillary hydrostatic pressure and interstitial hydrostatic pressure ($P_c - P_i$) and causes filtration of fluid out of the capillaries. This outward movement of fluid is opposed by plasma colloid osmotic or oncotic pressure (π_c). The interstitial colloid osmotic pressure (π_i) favors flow of fluid out of capillaries into the interstitium. The net colloid osmotic pressure $\Delta\pi$ is the plasma colloid osmotic pressure minus the interstitial colloid osmotic pressure ($\pi_c - \pi_i$). $\Delta\pi$ favors reabsorption of fluid into capillaries. At any point along the length of a capillary the physical forces determining net fluid movement are described by the Starling equation:

$$J_v = K(\Delta P - \Delta\pi), \qquad [1]$$

where

J_v = net water flux
K = constant
ΔP = hydrostatic pressure gradient ($P_c - P_i$)
$\Delta\pi$ = colloid osmotic pressure gradient ($\pi_c - \pi_i$).

Along the length of a perfused capillary, hydrostatic pressure falls progressively as the result of resistance to flow and the outward movement of fluid. Most systemic capillary epithelial membranes are relatively impermeable to plasma proteins. Consequently, as filtration reduces the volume of fluid within the capillary lumen, the concentration of proteins, and the oncotic pressures they exert, increase. The magnitude of this increase is proportional to the quantity of fluid which leaves the capillary.

In the arterial end of most capillaries (and the entire length of certain high pressure capillaries) net hydrostatic pressure exceeds net oncotic pressure so that an ultrafiltrate of plasma enters the interstitial space. As blood flows along the length of the capillary, net hydrostatic pressure falls and net oncotic pressure increases. Filtration stops at the point at which hydrostatic pressure falls to equal oncotic pressure. Continued downstream flow of blood further reduces the hydrostatic pressure so the gradient favors fluid reabsorption from the interstitial space back into the capillary. (Certain low pressure capillaries may absorb fluid throughout their length.) The magnitude of fluid movement generated by these gradients is dependent on several physical characteristics of the capillary epithelial membrane.

Reflection Coefficient

The hydraulic effect of a colloid osmotic pressure gradient across a semipermeable epithelium varies with the permeability of that epithelium for the col-

loid (i.e., plasma proteins). The epithelial reflection coefficient is a measure of the membrane's protein permeability. A protein reflection coefficient of 1.0 indicates that the protein cannot cross the epithelium and therefore exerts a maximal osmotic effect. Conversely, a reflection coefficient of zero indicates that the protein can freely penetrate the membrane and thus exerts no osmotic or hydraulic effect.

Reflection coefficients of capillary beds range from near one (glomerular capillaries) to near zero (hepatic sinusoids). The protein permeability of a capillary may change along the length of that capillary so that oncotic pressure exerts a greater effect in the venous end of the vessel. Capillary permeability may also change in response to changes in serum protein concentration. For example, patients with congenital hypoalbuminemia may develop a higher reflection capillary coefficient for albumin and thereby increase the oncotic efficiency of serum proteins.

Hydraulic Permeability or Conductivity

This is a measure of the quantity of water which will flow across a given membrane surface area per unit time in response to a given net hydraulic pressure gradient across that membrane.

Surface Area

The quantity of fluid which crosses an epithelial membrane per unit time varies with the membrane's surface area. The surface area of a vascular bed is proportional to the number of perfused capillaries which can be rapidly modulated by constriction or dilation of arterioles and precapillary sphincters.

These variables can be mathematically incorporated into the basic Starling equation (Eq. [1]) to yield the Starling–Steverman equation,

$$J_v = K_f[P_c - P_i) - \alpha(\pi_c - \pi_i)], \qquad [2]$$

where

J_v = net water flux,
K_f = filtration coefficient,
$K_f = L_p \cdot S$,
L_p = specific hydraulic conductivity,
S = surface area,
α = reflection coefficient.

Although the hydrostatic and colloid osmotic pressures which exist in the interstitial spaces are difficult to define precisely, several indirect methods of measurement are available. These measurements indicate that the interstitial hydrostatic and oncotic pressures vary widely in different body compartments and

organs. The protein concentration of subcutaneous interstitial fluid is about 25% of the plasma level, yielding an interstitial oncotic pressure of about 7 mm Hg. The subcutaneous interstitial space hydrostatic pressure is slightly negative (i.e., lower than atmospheric). The negative hydrostatic pressure in this compartment is partially due to the pumping action of lymphatic vessels. The interstitial hydrostatic pressure in many solid organs is greater than atmospheric levels.

Donnan Effects [3]

The osmotic pressure generated by proteins increases substantially if the proteins carry a net electric charge at physiologic pH. This effect is due to the asymmetric electrolyte distribution created by the presence of charged proteins. This phenomenon, called the Donnan effect, is illustrated in Fig. 2.

Assume that saline solution with an initial NaCl concentration of 130 mEq/liter is separated into two 1-liter compartments by a semipermeable membrane. Then the sodium salt of a negatively charged impermeant protein (NaPr) is added to compartment A. In the example, 1 mmol or 69 g of albumin salt (MW = 69,000 mg/mmol) is added to compartment A. In solution at pH = 7.4 this protein carries a net charge of about −18 so that 18 mEq of sodium ions are released into compartment A. Water and electrolytes in the two compartments will then distribute across the semipermeable membrane to minimize the osmotic, chemical, and electrical gradients. Na moves down its concentration gradient from compartment A (148 mEq/liter) to compartment B (130 mEq/liter), but to maintain electroneutrality Cl must accompany the Na because the membrane is impermeable to the only other anion, albumin. However, this movement of Cl generates a concentration gradient because the Cl concentration increases in compartment B and decreases in compartment A. Donnan demonstrated that such a system reaches equilibrium when the product of the Na and Cl concentrations within each of the two compartments are equal. Therefore at equilibrium,

$$[Na_A][Cl_A] = [Na_B][Cl_B].$$

The final Na concentration in compartment A (the side containing the charged protein) will be higher and the final Cl concentration lower than their respective concentrations in compartment B. Water also moves from compartment B to compartment A. Donnan also showed that the Na + Cl concentrations in compartment A (the compartment containing the protein) will always exceed the Na + Cl concentrations in compartment B:

$$[Na_A + Cl_A] > [Na_B + Cl_B]$$

Therefore, the asymmetric electrolyte concentrations which occur in response to the presence of an electrically charged impermeable protein generates

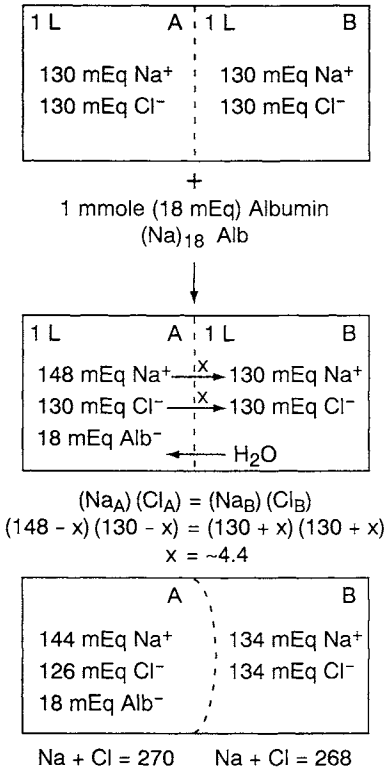


FIGURE 2. Schematic demonstration of the Donnan disequilibrium effect. Sodium chloride solutions with identical concentrations of 130 mEq/liter are separated by a semipermeable membrane. Each compartment contains 1 liter of solution. One millimole of a sodium albumin salt which contains 18 mEq of sodium is added to compartment A. In this example 18 mEq of sodium dissociates, increasing the sodium concentration in compartment A transiently to 148 mEq/liter. Sodium moves down its concentration gradient into compartment B accompanied by chloride. Water moves from compartment B into compartment A. At final equilibration the thermodynamic state of the entire system will be minimized. The Donnan calculations indicate the final NaCl concentration in compartment B will equal about 134 mEq/liter. The concentration of the sodium and chloride in compartment A are about 144 and 126 mEq/liter, respectively. The calculations also show that the final sodium plus chloride concentrations in compartment A will slightly exceed those in compartment B, producing an osmotic pressure gradient which also favors the movement of water from compartment B into compartment A. The final differences in osmotic pressure match the energy generated by the tendencies of sodium and chloride to move down their respective and opposite electrochemical gradients.

a concentration gradient for the permeable electrolytes across the membrane. This produces a higher total permeable electrolyte concentration (Na + Cl) in the compartment containing the protein and this contributes to the osmotic pressure in this compartment. Consequently, the osmotic pressure in compart-

ment A is due to both the albumin and the asymmetrical electrolyte concentration. Finally, the side of the membrane facing compartment A (the side containing the protein) develops a negative electric charge.

The total osmotic pressure generated by a normal concentration of plasma proteins is about 28 mm Hg. Of this, about two-thirds, or 19 mm Hg, is due to the colligative properties of the protein itself, while the asymmetric Donnan electrolyte distribution accounts for about one-third of the total osmotic pressure, or about 9 mm Hg.

Filtration in Systemic Capillaries and Lymphatic Drainage [6, 10]

The total body capillary filtration rate (not including the glomerular filtration rate (GFR)) is about 10–15 ml/min, or 15–20 liters/day. About 90% of this filtered fluid is reabsorbed in more distal portions of the capillaries or by other low pressure capillaries. The remaining 10% of filtered fluid, about 2 liters/day, returns from the interstitial space to the vascular compartment via lymphatic drainage. Systemic capillary filtration of 15–20 liters/day represents less than 0.5% of total blood volume which flows through the capillaries, i.e., the systemic capillary filtration fraction is extremely low. This produces a very small rise in plasma oncotic pressure along the length of the capillary. Consequently, the fall in net filtration pressures along the length of most systemic capillaries is primarily due to a decrease in hydrostatic pressure rather than an increase in oncotic pressure (see Fig. 1). However, certain specialized capillary beds with much higher filtration rates generate very different hydrostatic and oncotic pressure profiles. For example, the glomerular capillary bed has an extremely high hydraulic permeability resulting in a filtration rate of 140–190 liters/day. This represents a filtration fraction of about 20% of the blood flowing through these capillaries. (The capillaries of stimulated salivary glands also filter up to 20% of the plasma which flow through these vessels.) The effect on Starling forces produced by these variations in hydraulic permeabilities and filtration fractions are discussed below.

Filtration in Glomerular Capillaries [5]

The hydrostatic and osmotic pressure gradients which develop in the glomerular capillaries are very different from those in systemic capillaries. An idealized glomerular capillary pressure profile is shown in Fig. 3. Contrast the hydrostatic and oncotic pressures along the length of this capillary with those in a systemic capillary (Fig. 1). These differences result from several characteristics

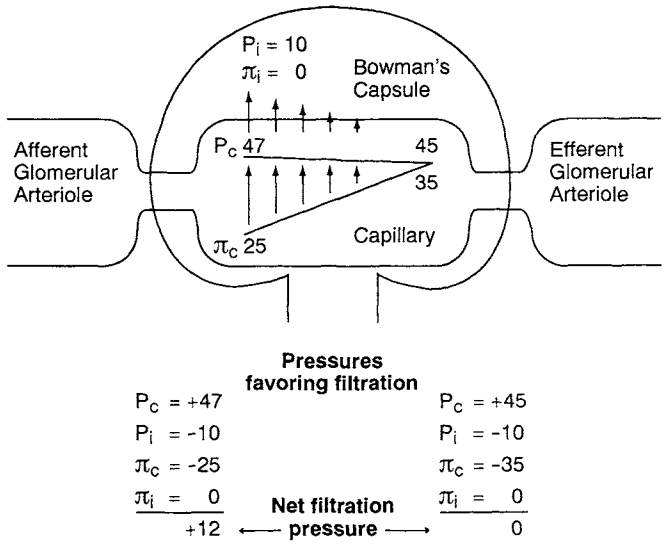


FIGURE 3. An idealized glomerular capillary hemodynamic profile. The hydrostatic pressure falls slightly along the length of glomerular capillaries as a result of efferent arteriolar constriction. The extremely high hydraulic permeability of the glomerular capillaries results in a very high filtration fraction (normally about 20%). Consequently a large increase in oncotic pressure develops along the length of the capillary. In this example, filtration equilibrium is reached because the oncotic pressure increases to equal the net capillary hydrostatic pressure (45 − 10 = 35).

unique to glomerular capillaries. (i) Most capillary beds are positioned between an arteriole and a venule. The glomerular capillary bed is instead positioned between two arterioles. This permits independent modulation of the afferent and efferent arteriolar resistances and creates a mechanism which permits fine control of hydrostatic pressures within the glomerular capillary bed. (ii) The blood flow rate through the glomerular capillary bed is very high and the hydrostatic pressure drop is relatively small in comparison with systemic capillaries. Efferent arteriole constriction maintains glomerular capillary hydrostatic pressure. (iii) The protein reflection coefficient of the glomerular epithelium for plasma proteins approaches 1 so that the ultrafiltrate passing into Bowman's capsule is normally protein free. (iv) The hydraulic permeability of glomerular capillaries is extraordinarily high, resulting in a normal glomerular ultrafiltration rate of 120–140 ml/min in adults. (v) The filtration fraction of blood plasma perfusing the glomeruli is very high (about 20%) as opposed to about 0.5% in systemic capillaries. The very high filtration rate and high reflection coefficient of glomerular capillaries combine to markedly increase plasma protein concentration and oncotic pressure as blood perfuses these vessels.

The transition from fluid filtration to fluid reabsorption in systemic capillar-

ies occurs primarily because hydrostatic pressures fall. The oncotic pressure profile along the length of systemic capillaries increases minimally (Fig. 1). In contrast, in the glomerular capillaries filtration falls primarily because plasma oncotic pressure increases, while hydrostatic pressure falls only slightly. The hydrostatic and oncotic pressure gradients and the filtration fraction of glomerular capillaries also have major downstream effects on fluid and solute reabsorption by the proximal peritubular capillaries. These interrelationships are described in Chapter VA2.

EDEMA FORMATION [1, 4]

STARLING FORCE DERANGEMENTS\ ANTI-EDEMA FORCES

As discussed above, about 15–20 liters/day of plasma water filters across the systemic capillaries into the interstitial space via filtration and an equal volume is returned to the vascular compartment. About 90% of the filtered fluid is reabsorbed by the downstream capillaries and 10% returns via lymphatic drainage of the interstitial space. Edema develops when an imbalance which favors filtration over reabsorption develops or lymphatic return is impaired. Increased capillary hydrostatic pressures, reduced plasma oncotic pressures, increases in capillary permeability, or some combination of all these alterations may be responsible.

A number of mechanisms exist to oppose edema accumulation and they must be overcome before edema accumulates. The interstitial space is not an open fluid-containing compartment but has a structure composed of collagen, elastin, and large quantities of glycosaminoglycans. Fluid which enters the interstitium moves relatively slowly through this space and the compartment has a low compliance. The initial accumulation of fluid within the interstitial space produces a sharp increase in hydrostatic pressure which opposes continued edema formation. However, as the interstitial space gradually expands, its compliance also increases. Therefore, once the initial high resistance is overcome, additional fluid can more easily accumulate. (This phenomenon is somewhat analogous to blowing up a balloon. Greater pressures are required at very low volumes and then less pressure becomes necessary at higher volumes.) Increased interstitial hydrostatic pressures also cause a marked increase in lymph flow. Lymphatic drainage may increase 100-fold in patients with edema-forming conditions. Increased lymphatic flow returns interstitial fluid to the vascular compartment and opposes edema formation. Expansion of the interstitial space also reduces the interstitial protein concentration via two mechanisms. (i) The interstitial proteins are diluted by the accumulation of protein-

TABLE 1 Causes of Edema

I. Increased capillary pressure
  A. Vascular and ECF expansion produced by primary renal salt and water retention
  B. Increased venous capillary pressures
    1. Congestive heart failure
    2. Venous blockage
    3. Ineffective venous pumping action
      a. Paralysis
      b. Immobilization
      c. Venous valve failure
  C. Reduced arteriolar resistance
    1. High temperature
    2. Adrenergic sympathetic nervous system dysfunction
    3. Arteriolar Vasodilators (especially calcium channel blockers)

II. Decreased plasma protein concentration
  A. Nephrotic syndrome
  B. Burns and large wounds
  C. Severe liver disease
  D. Severe malnutrition

III. Increased capillary permeability
  A. Immune reactions—anaphylaxis, angioedema, etc.
  B. Toxins
  C. Bacterial infections
  D. Vitamin deficiencies
  E. Ischemia
  F. Burns

IV. Lymphatic blockage
  A. Carcinomatosis
  B. Infections such as filariasis
  C. Congenital abnormalities

poor edema fluid. (ii) The high rate of lymphatic flow transports proteins from the interstitial to the vascular compartment. Lower interstitial protein concentration and oncotic pressure favors capillary reabsorption of edema fluid.

The edema forming conditions can be classified as shown in Table 1. Increased capillary hydrostatic pressure, decreased plasma oncotic pressure, increased capillary permeability, and reduced lymphatic drainage are the major causes of systemic edema.

Renal Salt and Water Retention [7, 8]

The presence of clinically apparent generalized edema represents the translocation of a large volume of fluid from the vascular to the interstitial space. If

this occurs acutely, circulatory shock may result. This can occur when an acute increase in capillary permeability is produced by an allergic reaction or extensive burn. More commonly, edema develops relatively gradually and intravascular volume is maintained by avid renal salt and water retention. Consequently, in addition to the local hemodynamic derangements which produce peripheral edema, renal salt and water retention also contributes importantly to most states of generalized edema formation.

Renal retention of salt and water in the edema forming conditions is usually triggered by one of two general mechanisms: (i) secondary renal salt and water retention which produces underfill edema, (ii) primary renal salt and water retention which produces overflow edema.

Secondary Renal Salt and Water Retention—Underfill Edema

The stimulus for this form of renal salt and water retention is a reduced effective arterial blood volume (EABV). EABV does not describe any specific measurable anatomic space. The EABV concept, first proposed by Dr. John Peters, describes the fullness of the arterial circulation and/or adequacy of blood flow within the arteries. This fullness or adequacy is determined by the integrative effects of two forces. The first is the filling of the arterial vessels which is a function of venous return to the heart and left ventricular performance. The second is the magnitude of arterial runoff which relates to the size and compliance of the arterial resistance vessels.

Reduced EABV may result from an absolute decrease in total arterial volume (as with acute left ventricular heart failure or hypovolemic shock) or excessive peripheral arterial runoff which reduces EABV despite an expanded absolute arterial volume (as occurs with a large A–V shunt or generalized arteriolar vasodilation). Reduced EABV also occurs when the compliance of the arterial vasculature increases disproportionately to the volume of blood in this compartment, as occurs in deconditioned individuals or in pregnant women as a result of their slack circulation.

The major baroreceptor sensors which monitor the EABV status are located in the carotid sinuses, aorta, kidneys, and cardiac ventricles. Detection of a low EABV by these sensors triggers a neurohormonal response which causes systemic vasoconstriction and avid renal salt and water retention. Renin, angiotensin, aldosterone, antidiuretic hormone, catecholamines, and sympathetic activity all increase. Local vascular mediators such as endothelin also participate in this response.

The ECF includes the vascular and interstitial spaces. In normal individuals these compartments and the EABV increase, or decrease, symmetrically. Salt restriction, or the loss of sodium-rich fluid, contracts each of these compartments and volumes. Conversely, they all normally expand in response to a high

salt diet or saline loads. However, many edema forming conditions can dissociate the EABV from the ECF compartments. For example, heart failure often reduces EABV despite massive expansion of the vascular and interstitial spaces. Hepatic cirrhosis also often dissociates the EABV from the ECF compartments through different mechanisms. Under such circumstances, renal salt and water retention may develop in response to the low EABV despite increased total blood volume and an expanded ECF. The retained fluid further expands the ECF but may not be able to correct the EABV deficit. Relentless salt and fluid retention can therefore produce massive edema and ascites, yet the persistently low EABV signals the kidneys to continue retention of salt and water. Some patients with the nephrotic syndrome also retain salt and fluid on the basis of an underfilled EABV. However, the EABV seems to be normal or expanded in many others with the nephrotic syndrome. These individuals have primary renal salt retention, or overflow edema physiology (see Chapter VA3). Overflow physiology also exists in patients with glomerulonephritis or renal insufficiency.

Primary Renal Salt and Water Retention—Overflow Edema

Patients with acute or chronic renal failure or glomerulonephritis retain salt and water as a result of a primary renal salt excretory defect. The salt retention expands the ECF volume and also the EABV. Many patients with overflow physiology manifest symmetrical ECF expansion. Their major ECF subcompartments, the vascular and interstitial spaces, as well as the EABV enlarge together. Cardiac output, blood pressure, and heart size increase, and edema develops. Expansion of the EABV reduces levels of renin, angiotensin, aldosterone, ADH, catecholamines, and sympathetic nervous activity. Local vascular mediators such as vasodilatory prostaglandins and nitric oxide are stimulated. Atrial dilation will cause release of atrial natriuretic factors. These neurohormonal responses should signal the kidney to excrete salt and water. However, the renal pathology which has initiated the overflow process prevents or blunts a natriuretic and diuretic response.

Some patients with nephrotic syndrome also have many features consistent with overflow pathophysiology (see Chapter VA3). However the pattern of distribution of the retained salt and water in these patients is different from that which develops in patients with acute glomerulonephritis or renal failure. Patients with nephrotic syndrome preferentially accumulate the retained fluid in their interstitial spaces. They rarely develop cardiomegaly, pulmonary congestion, or hypertension (unless their GFR is also reduced by the pathologic process). Yet, their neurohormone profile may suggest EABV expansion rather than contraction. The differences in the relative magnitude of expansion of the spaces and the pattern of distribution of retained fluid may, in part, be the result

of severe hypoalbuminemia and possibly increased systemic capillary permeability which may exist in patients with the nephrotic syndrome. These issues are more fully discussed in Chapter VA3. A subset of patients with hepatic cirrhosis also seems to have overflow physiology. The specific pathophysiology responsible for salt and water retention and the development of edema and ascites in patients with congestive heart failure, cirrhosis, and nephrotic syndrome are discussed in Chapters VA2, VA3, and VA4, as are the specifics of diuretic therapy for these disorders.

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CHAPTER VA2

Use of Diuretics for the Treatment of Heart Failure

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INTRODUCTION

The congestive states are those disorders which create steady-state expansion of blood and extracellular fluid volume. They include congestive heart failure due to primary and secondary cardiac disorders of multiple etiologies. Heart failure may be defined as an inability of the heart, at normal filling pressures, to pump the quantity of blood necessary to meet the body's metabolic demands. This definition encompasses various forms of myocardial dysfunction, mechanical abnormalities which restrict the flow of blood into or out of the heart, cardiac arrhythmias, and mechanical or metabolic abnormalities which increase cardiac demands. Congestion and cardiac failure can be due to noncardiac disorders such as severe anemia, thyrotoxicosis, primary salt overload, and beriberi which expand plasma volume and increase cardiac demands beyond the normal heart's capacity to respond. Salt overload secondary to acute or chronic renal disease can also produce congestion. Table 1 lists the major causes of the congestive states.

When left ventricular cardiac performance deteriorates markedly, a systemic congestive state characterized by peripheral and pulmonary edema often results. This chapter will focus principally on forms of congestive heart failure which result from either primary or secondary left ventricular myocardial

Diuretic Agents: Clinical Physiology and Pharmacology

TABLE 1 Causes of Congestive States

I. Low cardiac output congestive states
  A. Myocardial fiber dysfunction
    1. Cardiomyopathy
      a. Idiopathic
      b. Infiltrative (e.g., amyloid, sarcoid, etc.)
      c. Connective tissue diseases
      d. Toxic/metabolic (e.g., diabetes mellitus, hemochromatosis, myxedema, ETOH, cobalt)
      e. Drugs (e.g., adriamycin)
      f. Hereditary muscle disease (e.g., congenital, muscular dystrophies, and ataxias)
      g. Hereditary metabolic disease (glycogen storage, Fabry's)
      h. Ischemia
      i. Peripartum
      j. Pressure overload
        1. Left-sided (hypertension, aortic valve stenosis, coarctation of aorta)
        2. Right-sided (pulmonary hypertension, pulmonary valve stenosis)
      k. Volume overload
        1. Aortic regurgitation
        2. Mitral regurgitation
        3. Tricuspid regurgitation
    2. Myocarditis
  B. Inflow obstruction
    1. Bilateral
      a. Myocardial restriction
      b. Endocardial restriction
      c. Pericardial restriction
    2. Into the left ventricle (right-sided overload)
      a. Mitral stenosis and tumors (pulmonary congestion)
      b. Pulmonary hypertension (peripheral venous congestion)
    3. Into the right ventricle (peripheral venous congestion)
      a. Tricuspid stenosis and tumors
      b. Vena cava obstruction
  C. Arrhythmias

II. High cardiac output congestive states
  A. Peripheral structural A-V shunts
  B. Cardiac and/or central shunts (e.g., ASD, PDA)
  C. Severe anemia
  D. Thyrotoxicosis
  E. Beriberi
  F. Paget's disease

III. Salt overload congestive states
  A. Excessive salt loads
  B. Acute and chronic renal failure

dysfunction. However, the concepts and principles also apply to other forms of congestion.

Heart failure, regardless of etiology, reduces the effective arterial blood volume (EABV) and causes the arterial circulation to become "underfilled" (see Chapter VA1). The EABV describes the fullness of the arterial circulation and/or adequacy of blood flow within the arterial circuit. This fullness or adequacy is determined by the integrative effects of two forces. The first is the filling of the arterial tree which is a function of venous return to the heart and left ventricular performance. The second is the magnitude of arterial runoff which relates to the size and compliance of the arterial resistance vessels. The reduction in EABV is detected by volume, pressure, and flow sensors located in the systemic and pulmonary circulation and within the heart. They trigger a neurohormonal response which serves to correct the sensed volume deficit by means of generalized vasoconstriction and increased renal salt and water retention. The mediators responsible for the response include the adrenergic nervous system, circulating catecholamines, antidiuretic hormone (ADH), renin, angiotensin, aldosterone, endothelin, thromboxane and undoubtedly other hormonal, paracrine and autocrine factors yet to be elucidated. Simultaneously, a series of counterregulatory neural, hormonal, and autocrine mediators which oppose vasoconstriction and renal salt retention are activated. These counterregulatory mediators include natriuretic peptides, vasodilatory prostanoids, dopamine, nitric oxide, and bradykinin. These mediators block the release and/or action of the aforementioned vasoconstricting and salt-retaining factors. Some may also cause direct vasodilation and inhibition of renal sodium reabsorption. The vasoconstricting and salt-retaining neurohormonal response usually dominates the clinical picture in patients with overt heart failure.

NEUROHORMONAL COMPENSATORY RESPONSES TO HEART FAILURE

MEDIATORS WHICH STIMULATE RENAL SALT AND WATER RETENTION AND CONSTRICT BLOOD VESSELS

The major neurohormonal responses which increase renal salt and water retention and cause vasoconstriction are portrayed in Fig. 1.

Adrenergic Activation

The low EABV associated with heart failure activates sympathetic adrenergic nerves and elevates systemic catecholamine levels which produce both systemic and cardiac effects. Systemic arteriolar constriction mitigates the fall in

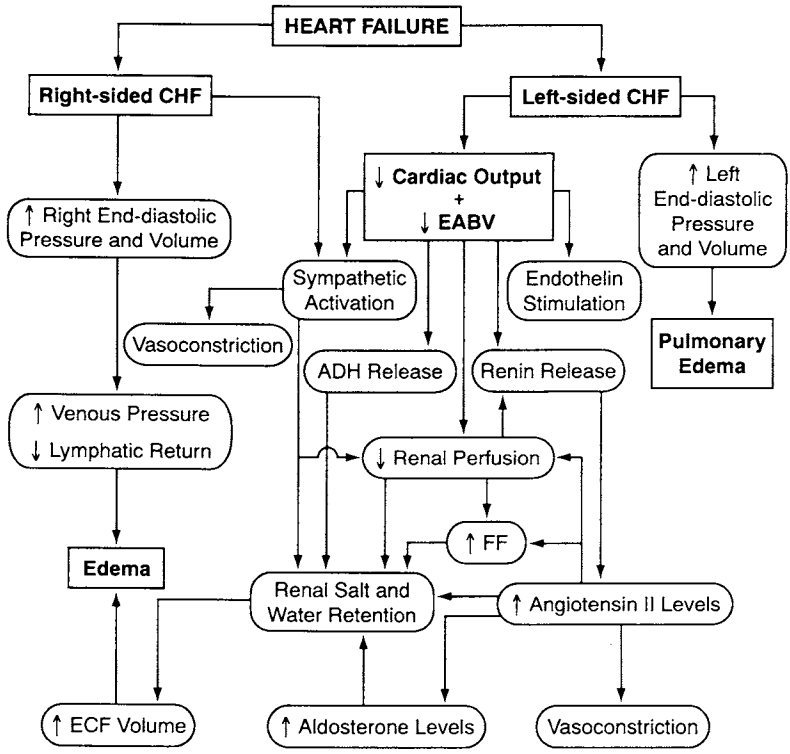

FIGURE 1. The pathophysiology of salt and water retention and edema formation in patients with heart failure. Only the vasoconstricting and salt retaining mediators are shown. ADH, antidiuretic hormone; FF, filtration fraction; ECF, extracellular fluid; EABV, effective arterial blood volume.

blood pressure owing to a low cardiac output. However, the intensity of vasoconstriction is not identical in all arterioles or organs. Selectivity between organs and within organs characterizes the vascular response (Fig. 2). Vessels supplying organs and tissues which are relatively tolerant of ischemia, such as skeletal muscles, abdominal viscera, and the skin, constrict markedly. In contrast, the arterioles of the brain and heart do not constrict, and indeed may dilate despite a high level of systemic vasoconstricting forces. Selective vasoconstriction causes a greater fraction of the reduced cardiac output to be delivered to certain vital organs [29]. Consequently, cerebral and cardiac blood flow remain relatively protected despite the systemic vasoconstriction characteristic of heart failure [29]. The organ-specific vascular response is due to the differences in densities and subtypes of both adrenergic nerves and neuroreceptors which exist in various vascular beds, as well as differences in local generation and response to O_2, CO_2, lactate, and vasoactive molecules including nitric oxide, prostaglandins, C-natruretic peptides, etc.

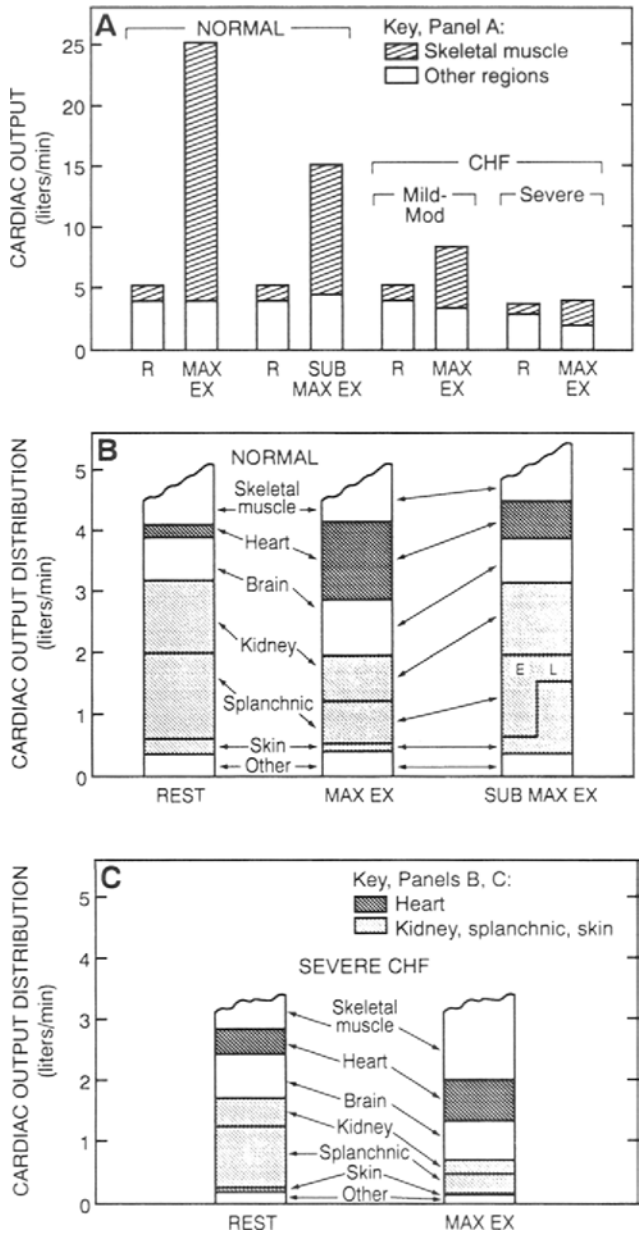

FIGURE 2. (A) The regional distribution of cardiac output at rest (R) and during submaximal (submax) and maximal (max) exercise (EX) in normal subjects and patients with congestive heart failure. (B) Distribution of blood flow to vascular beds other than skeletal muscle in normal subjects during rest and exercise. E, early; L, late. (C) Distribution of blood flow to vascular beds other than skeletal muscle in patients with severe CHF during rest and exercise. (Adapted from Zelis, R., and Flaim, S. F. (1982). "Alterations in vasomotor tone in congestive heart failure." Prog Cardiovasc Dis. 24, p. 440.

Heart failure decreases total renal blood flow, but selective intrarenal vasoconstriction develops and stabilizes the glomerular filtration rate (GFR). Postglomerular efferent arterioles constrict more vigorously than the preglomerular afferent arterioles. This pattern of constriction will maintain or increase hydrostatic pressure within the glomerular capillaries despite the fall in EABV. The renal hemodynamic response to congestive heart failure (CHF) is more fully described under Renal Function in Heart Failure, below.

The catecholamines released from sympathetic nerves impinging on the heart combine with those present in blood plasma to activate cardiac adrenergic receptors. Both cardiac contractility and heart rate increase. However, the response of the failing heart to these sympathetic stimuli is blunted as a result of reduced cardiac β-adrenergic receptor density (especially the β_2 receptors), partial uncoupling of these receptors from cyclic AMP generation, and reduced intracardiac norepinephrine synthesis [11]. Therefore, although sympathetic cardiac stimulation improves the failing heart's performance, contractility does not increase to the extent that it would in a normal subject's heart.

In general, adrenergic activation is beneficial for most patients with heart failure. The increment in cardiac output and contractility, higher peripheral vascular resistance, and the selective vascular response stabilize blood pressure and divert a greater fraction of the cardiac output to critical vital organs. However, excessive adrenergic stimulation may become maladaptive and produce adverse effects. For example: (i) Intense constriction of skeletal muscle arterioles prevents the usual dilation response to exercise. This contributes to the profound fatigue experienced by these patients and partially accounts for their susceptibility to exertion-induced lactic acidosis. (ii) The failing heart is very sensitive to increased levels of afterload which reduces cardiac output sharply (see Factors Which Increase Cardiac Contractility and Output, below, and Fig. 3). (iii) Increasing afterload raises cardiac oxygen requirements. (iv) High catecholamine levels can produce direct cardiotoxicity.

Consequently, although seemingly counterintuitive, β blockers have recently been effectively utilized to reduce the morbidity and mortality of certain subsets of patients with heart failure [21]. Arterial vasodilators, such as hydralazine, and drugs which reduce angiotensin II induced vasoconstriction, such as angiotensin-converting enzyme inhibitors, or angiotensin II receptor (AT1) blockers also reduce afterload and may improve cardiac output, ameliorate symptoms, and prolong the life of patients with congestive heart failure.

Renin–Angiotensin Activation

Normal Physiology

The renin–angiotensin systems (RAS) exist in both systemic and local hormone/autocrine/paracrine forms. The systemic RAS was described first. Its

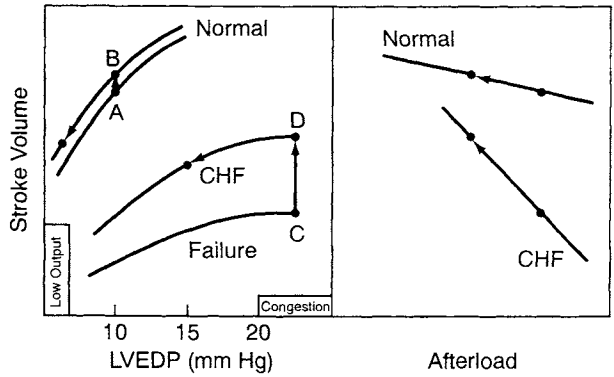

FIGURE 3. Frank–Starling relationships between stroke volume and left ventricular end-diastolic pressure (LVEDP) and between stroke volume and afterload in normal and failing hearts. The normal heart functions on the sharply rising portion of the Frank–Starling curve where small changes in filling pressure produce large changes in stroke volume. Note that large changes in afterload have only minor stroke volume effects in the normal heart. The Frank–Starling curve of the failing heart is shifted to the right and downward. Higher LVEDP is required to produce acceptable, though still reduced, stroke volume. When the LVEDP exceeds 20 mm Hg pulmonary congestion becomes likely. Cardiac performance may move from curve C to curve D if cardiac contractility increases due to catecholamines or the administration of an inotropic agent. Note, the stroke volume of the failing heart is markedly affected by the level of afterload. (Adapted from Sonnenblick, E. H. (1994). Pathophysiology of heart failure. *In* "The Heart: Arteries and Veins" (J. W. Hurst, R. C. Schlant, et al., eds.) p. 398, McGraw Hill, New York.

components include renin released from the kidneys, angiotensinogen released from the liver, angiotensin-converting enzyme present in vascular tissue (especially in the lungs), and angiotensin II receptors in vessels, the adrenal gland, kidneys, brain, heart, and many other organs. The juxtaglomerular apparatus (JGA), located between the afferent renal arteriole and the distal tubule, is the principal renal site of renin synthesis and storage. Renin released by the juxtaglomerular apparatus is delivered to the systemic circulation via the renal veins (and also acts locally within the kidney—see below). The major activating stimulus for the systemic RAS is a reduction in systemic blood pressure and/or a low EABV. This reduces renal arteriole perfusion pressures and activates renal baroreceptors, thereby triggering the release of renin. Sympathetic adrenergic nervous activation also causes renal renin release and participates in the response to hypotension. Prostaglandins are also involved in the renal renin response mechanism and drugs which inhibit prostaglandins may reduce systemic renin levels.

Renin is a proteolytic enzyme which catalyzes the cleavage of the decapeptide angiotensin I from its protein substrate angiotensinogen. The angiotensin I is then converted to the potent vasoactive octapeptide, angiotensin II, by angiotensin-converting enzyme (ACE). ACE exists in high concentration in the

endothelium of pulmonary vessels and is also present at lower concentrations in vessels and tissues throughout the body. Systemic effects of angiotensin II include arteriolar vasoconstriction, stimulation of adrenal aldosterone synthesis and release, increased thirst, and others. Angiotensin II also increases renal salt reabsorption through several mechanisms: (i) direct stimulation of renal epithelial sodium transport, (ii) renal hemodynamic effects which enhance renal tubule salt reabsorption, (iii) stimulation of adrenal aldosterone synthesis and release which increases distal tubule sodium reabsorption. These multiple effects of high angiotensin II levels oppose the fall in blood pressure and/or EABV which is the physiologic trigger for the cascade. If the blood pressure improves and/or EABV normalizes, then renin levels decrease. This defines a classic closed loop endocrine system.

The RAS also has major paracrine effects in the kidney, heart, blood vessels, and probably many other organs and tissues. The entire array of enzymes and substrates required to generate and respond to angiotensin II exists as a self-contained system within many tissues including the kidney. The local RAS in the kidney regulates the distribution of intrarenal blood flow and the rate of glomerular filtration. Renal underperfusion increases local renin and angiotensin II generation which causes more intense constriction of postglomerular efferent arterioles than the afferent arterioles. This pattern of selective vasoconstriction mitigates the reduction in glomerular hydrostatic pressure associated with underperfusion and thereby stabilizes the GFR (see Renal Function in Heart Failure, below).

The intrarenal RAS also participates in tubuloglomerular feedback control mechanisms. Changes in distal tubule delivery rates are detected by the macula densa, which monitors alterations in chemical composition produced by variations in tubule flow. Signals from the macular densa regulate renin releases from the JGA. This feedback system increases the GFR when distal delivery of filtrate falls and reduces the GFR when distal sodium chloride and volume delivery increase. The macula densa–JGA interaction thus synchronizes the glomerular filtration and the tubule solute and fluid reabsorption rates. The precise role of the renal and systemic RAS in this feedback loop continues to be elucidated [4].

Heart Failure

Heart failure generally reduces the EABV and severe left ventricular dysfunction produces overt hypotension. As a result, the systemic RAS and the local renin–angiotensin systems in the kidney, heart, and blood vessels are activated. Systemic RAS activation causes generalized vasoconstriction, which mitigates the fall in blood pressure and stimulates the adrenal gland to synthesize and release aldosterone. Intrarenal RAS activation mitigates the fall in glomerular filtration by causing greater constriction of efferent arterioles than afferent ar-

terioles. High angiotensin II levels directly increase salt reabsorption by the proximal renal tubules. The renal hemodynamic effects of angiotensin II on proximal tubule salt reabsorption are discussed below under Renal Function in Heart Failure. Activation of the cardiac RAS increases myocardial contractility and contributes to hypertrophy and remodeling of the heart [7,14]. The RAS in the walls of arterial vessels also participates in the vascular hypertrophic and remodeling response [7].

Aldosterone

Angiotensin II is the principal regulator of adrenal aldosterone synthesis and release. Therefore, circulating renin (and angiotensin II) and aldosterone levels usually increase or decrease in parallel. However, these hormone levels can be dissociated by certain pathophysiologic conditions. For example, simultaneous high aldosterone and low renin levels suggest autonomous aldosterone secretion, such as primary hyperaldosteronism, while high renin and low aldosterone levels may suggest an adrenal synthetic defect. The potassium concentration can also affect aldosterone levels. Hyperkalemia stimulates aldosterone synthesis and hypokalemia inhibits its synthesis.

Aldosterone, the major endogenous mineralocorticoid, increases distal renal tubule and collecting duct sodium reabsorption and simultaneously increases the secretion of potassium and protons. Aldosterone also increases sodium absorption by the colon and reduces the sodium concentration of saliva and sweat.

Patients with congestive heart failure generally have high renin, angiotensin II, and aldosterone levels as a result of their reduced EABV. These elevated hormone levels increase further when the cardiac status decompensates. The kidneys of these patients will then retain salt and water very avidly.

Antidiuretic Hormone

Antidiuretic hormone (ADH) is normally released in response to increases in plasma tonicity. This hormone increases the hydraulic permeability of the renal distal tubules and the cortical and medullary collecting ducts where urine is concentrated and water conserved. This response serves to correct the state of hypertonicity. ADH is also released nonosmotically in response to hypotension and/or a low EABV. In this loop, the hormone has systemic vasoconstricting effects and hence its other name is vasopressin. The low EABV which exists in heart failure increases ADH levels and this hormone contributes to their state of systemic vasoconstriction. The persistent high ADH levels are a response to the hemodynamic derangements of heart failure and result in renal concentration and water retention irrespective of the patient's plasma tonicity or sodium concentration.

It should be noted that the maximal urine concentration which can be

achieved by patients with heart failure is not as great as that produced by normal subjects given exogenous ADH. Patients with CHF cannot generate normal medullary osmotic gradients. Nonetheless, the urine osmolality of these patients is often inappropriately high for their plasma sodium concentration.

Patients with heart failure typically have a reduced GFR and increased proximal solute reabsorption. This decreases delivery of filtrate to the thick ascending limb of Henle (TALH), thereby reducing the kidney's capacity to generate free water. These abnormalities and the high ADH levels cause frequent development of hyposmolar hyponatremia. When progressive hyponatremia develops in patients with heart failure, their state of cardiac deterioration is usually advanced and the low sodium concentration is indicative of a poor prognosis [17].

Endothelin, Thromboxane, and Other Vasoconstrictors

Endothelin, proconstrictive prostanoids, including thromboxane, and other vasoactive mediators also contribute to the vasoconstricted state of heart failure. However, the precise roles played by of these molecules have not yet been defined.

Mediators Which Oppose Renal Salt Retention and Vasoconstriction

Activation of the above-described vasoconstricting and salt-retaining mechanisms is associated with simultaneous or sequential activation of opposing counterregulatory neurohormonal mediators. They modulate and reduce the intensity of vasoconstriction and renal salt retention. These counterregulatory mediators include atrial natriuretic peptides, vasodilatory prostanoids, dopamine, and nitric oxide.

Natriuretic Peptides [34]

Normal Physiology

Over the past 15 years, a family of natriuretic peptides synthesized primarily by the heart has been identified and characterized. Atrial natriuretic peptide (ANP) was the first to be identified. ANP is synthesized within the atrium and is released in response to atrial stretching. This peptide inhibits the release and activity of multiple vasoconstricting and salt-retaining mediators. For example, ANP reduces release of renin by the kidney, ADH by the pituitary, aldosterone by the adrenal cortex, and catecholamines from sympathetic nerve terminals and the adrenal medulla [5]. It also opposes the action of each of these mediators at their respective targets [5, 28, 34].

In normal subjects, ANP causes renal vasodilation, especially of the afferent glomerular arterioles, and relaxes glomerular mesangial cells. Renal blood flow and glomerular filtration rates increase. ANP also inhibits sodium reabsorption by cortical and medullary collecting tubules. The increased GFR, reduced filtration fraction (see Renal Function in Heart Failure, below), and inhibition of distal tubule sodium reabsorption combine to produce a brisk natriuresis when normal subjects are given an infusion of ANP [5, 34].

Another member of this peptide family is brain natriuretic peptide (BNP), which is not only produced by the brain but also by the myocardium. The physiologic effects of BNP are similar to those produced by ANP. The third peptide in this family is C-natriuretic peptide (CNP), which is synthesized by brain and by vascular endothelial cells. CNP is principally an autocrine and/or paracrine mediator. The very low systemic plasma concentrations of CNP have uncertain clinical significance.

Heart Failure

Atrial dilation develops very early with heart failure and causes prompt release of ANP from atrial cells. Consequently, increased ANP levels are an early and sensitive biochemical marker of heart failure [23]. Chronic heart failure causes ventricular myocardial cells to synthesize and release both ANP and BNP [25]. The extremely high plasma BNP levels which develop in these patients may exceed their ANP levels.

Despite the very high plasma levels of natriuretic peptides which occur in patients with heart failure, their renal and systemic vascular and diuretic effects are markedly blunted. This resistance to endogenous peptides may be due to the potent physical, humoral, and neural vasoconstricting and salt retaining signals. Infusions of exogenous ANP in patients with heart failure also produces a subnormal response. Nonetheless, it is likely that high levels of ANP may be of some benefit to patients with heart failure. Furthermore, compounds which inhibit ANP degradation may improve the status of selected groups of heart failure patients [10].

Vasodilatory Prostanoids

The renal vasoconstrictive response to heart failure is opposed by multiple vasodilatory prostaglandins including prostaglandin E_2, prostaglandin $F_{2\alpha}$, and prostacyclin. These prostanoids are synthesized by renal vascular endothelial, interstitial, and tubule cells. The prostanoids dilate the afferent preglomerular vessels to a greater degree than efferent postglomerular arterioles. This selective vascular response contributes to the development of a high glomerular filtration fraction (see Renal Function in Heart Failure, below).

The prostanoids also have direct tubular epithelial transport effects. They inhibit sodium chloride reabsorption in the TALH and in the collecting ducts

[26] and oppose the hydroosmotic action of ADH in the cortical and medullary collecting ducts. Thus, in the kidney the vasodilatory prostanoids oppose renal vasoconstriction, sodium reabsorption, and water retention.

Vasodilatory prostanoids released from the kidneys also have significant systemic effects which dilate systemic arteries and venous capacitance vessels. These effects are described under Diuretic Therapy of Acute Pulmonary Edema, below.

Dopamine [13]

The two major systemic dopamine receptors are designated the DA_1 and DA_2 receptors. (These receptors are to be distinguished from the better defined CNS dopamine receptors D_1 through D_5.) DA_1 receptors are located in the neuromuscular junctions of blood vessels, in renal tubules, and in sympathetic ganglia. Stimulation of the DA_1 receptors dilates blood vessels, inhibits renal tubule sodium reabsorption, and reduces postganglion sympathetic outflow. The DA_2 receptors are primarily located in postganglionic sympathetic nerve terminals and in the adrenal gland. Activation of the DA_2 receptors inhibits norepinephrine release from nerve endings and aldosterone and epinephrine release from the adrenal gland.

The physiologic vascular effects of dopamine and dopamine agonists produce renal, mesenteric, and coronary arteriolar dilation [13]. In normal subjects, the infusion of dopamine at low concentrations (2–5 μg/kg/min) produces dilation of the above-listed vascular beds, reduces systemic catechol and aldosterone levels and causes a diuresis and natruresis. However, infusion of larger quantities of dopamine stimulates cardiac β adrenergic receptors, which increases heart rate and contractility, and also systemic vascular α receptors which causes generalized vasoconstriction. High dose dopamine infusions will thereby decrease renal perfusion and have an antidiuretic action.

The role of the endogenous dopaminergic system in patients with heart failure remains unclear. While some studies report that CHF increases plasma dopamine levels, other studies indicate that the dopamine levels of these patients are normal or reduced [20]. Some of these conflicting results may reflect systematic technical problems with plasma dopamine assays. It is now clear that a large portion of dopamine in plasma is in a conjugated form which is biologically inactive. The free dopamine in plasma is in equilibrium with this larger inactive conjugated pool. The ratio of free to conjugated dopamine can change rapidly in response to clinical status. These two plasma dopamine pools have not been adequately differentiated in many clinical studies [20].

The effect of dopamine on renal function is further complicated by recent observations which indicate that renal and urine dopamine is largely synthesized within the kidney. L-DOPA, filtered by the glomeruli, is converted by renal

tubule epithelial cells to dopamine [16]. Thus, dopamine in the kidney acts as a neurotransmitter, a hormone and an autocrine/paracrine mediator. In fact, the renal effects of endogenous dopamine may be independent of the dopamine plasma levels.

Patients with severe heart failure retain salt despite very high plasma and urine dopamine levels. This suggests that they may be relatively resistant to the diuretic effects of endogenous dopamine. CHF patients are generally also resistant to the diuretic effects of low dose dopamine infusions [24]. Potent vasoconstricting and salt retaining stimuli may block the dopamine effects.

Nitric Oxide (NO) or Endothelium Relaxation Factor (EDRF) and Other Vasoactive Peptides [18, 22]

Nitric oxide is the principal vasodilating molecule produced by vascular endothelial cells. This compound acts locally, very close to its site of production. NO contributes importantly to the regulation of vascular tone in patients with heart failure. Inhibition of NO synthesis with nitro-L-arginine methylester (L-NAME) in these patients increases their systemic, pulmonary, and renal vascular resistances [22]. Therefore, basal NO synthesis and activity must moderate the degree of vasoconstriction in these patients. However, the vasodilatory response to NO is not normal in patients with heart failure. Infusions of acetyl choline, which generate nitric oxide, or of nitroglycerin, which dilates vessels via the NO receptors, generate subnormal vascular responses in patients with chronic CHF [15,18,22]. It is possible that persistent stimulation of nitric oxide synthesis in these patients depletes essential chemical precursors. It is also likely that endothelin receptors downregulate. Endothelial injury may also compromise nitric oxide synthesis and response.

Bradykinin, kallidin, and neuropeptide Y are other potent vasoactive peptides which undoubtedly participate in the vascular response to heart failure, but their specific contributions in this disorder remain poorly defined.

RENAL FUNCTION IN HEART FAILURE

About 20% of the cardiac output is normally delivered to the kidneys and virtually all of the renal blood flow (>98%) passes first through the glomeruli. Hydrostatic pressures within glomerular capillaries are regulated by constriction, or dilation, of preglomerular afferent arterioles and postglomerular efferent arterioles and by contraction or relaxation of periglomerular capillary mesangial cells. The hydrostatic pressures, surface area, and epithelial hydraulic permeability of glomerular capillaries determine the fraction of blood plasma perfusing the glomeruli which is filtered.

The filtration fraction (FF) represents the ratio of the rates of glomerular filtration (GFR) to renal plasma flow (RPF):

$$FF = GFR/RPF.$$

The magnitude of the FF has a major impact on solute and water reabsorption by the proximal renal tubules. The capillaries which surround the proximal tubules are principally supplied by the postglomerular efferent arterioles (Figs. 4 and 5). Changes in the FF alter the oncotic and hydrostatic pressures in these vessels and these parameters affect renal tubule backleak. Backleak refers to the reverse movement of reabsorbed solute and water across the tubule epithelium to return into the lumen.

Net proximal tubule salt and fluid reabsorption is equal to total reabsorption minus the rate of backleak. Therefore, regulation of backleak magnitude is an important control mechanism. The oncotic and hydrostatic pressures in the peritubule capillaries are major regulators of the backleak rate. A high oncotic pressure and low hydrostatic pressure in these capillaries increases the reabsorption of solute and fluid by reducing backleak. Low oncotic and high hydrostatic pressures have the opposite effect.

The plasma oncotic pressure within the postglomerular arterioles and the peritubular capillaries is a function of the plasma protein concentration and the glomerular filtration fraction. A high FF increases the protein concentration and oncotic pressure in these vessels (Figs. 5 and 6). Usually, a high FF is produced by increased efferent arteriolar resistance which markedly reduces the downstream hydrostatic pressures in the peritubular capillaries.

Cardiac failure due to ventricular dysfunction reduces cardiac output, EABV, and renal perfusion. The low EABV elicits the vasoconstricting neurohormonal cascades described above. They increase afferent and efferent arteriolar resistances and contract glomerular mesangial cells. However, differential sensitivity of the efferent and afferent arterioles to vasoconstricting and vasodilating stimuli causes relatively greater contraction of the efferent vessels. This pattern

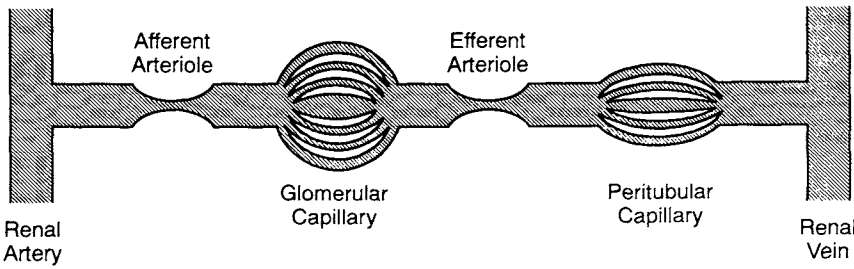

FIGURE 4. The renal microcirculation showing the relationship of the major resistance vessels (the afferent and efferent arterioles) to the glomerular and peritubular capillary beds. (Adapted from Marsh, D. J. (1983). Renal Physiology. Raven Press, New York, p. 62.)

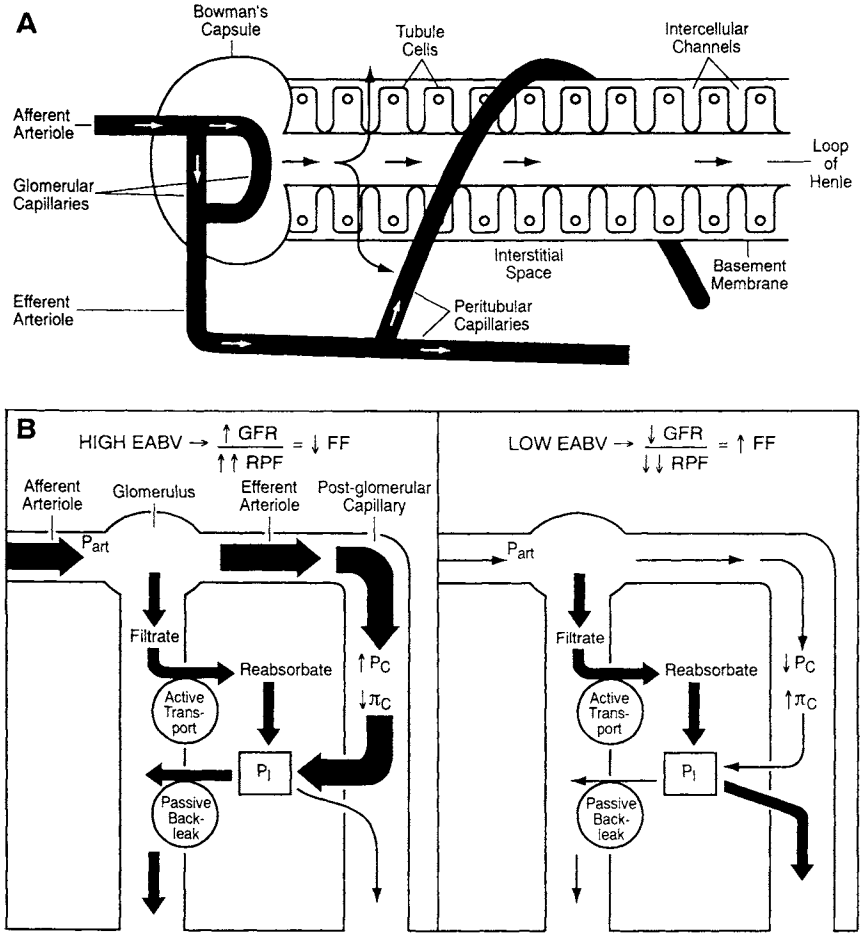

FIGURE 5. (A) The vascular supply of the glomerulus and proximal tubule. (Adapted from Marsh, D. J. (1983). Renal Physiology. Raven Press, New York, p. 74.) (B) The effect of filtration fraction (FF) on peritubular capillary hydrostatic and oncotic pressures. High effective arterial blood volume (EABV) reduces the FF by causing dilation of the efferent arteriole. Backleak increases (reabsorption falls) because high peritubule hydrostatic (P_c) and low oncotic (π_c) pressures develop. A low EABV increases the FF because of relatively greater constriction of the efferent arteriole compared with the afferent arteriole. Backleak decreases (net reabsorption increases) because hydrostatic pressure (P_c) falls and oncotic pressures (π_c) increase in the peritubule capillaries. GFR, glomerular filtration rate; RPF, renal plasma flow; P_i, interstitial hydrostatic pressure. See text for details.

of sequential resistances will increase intraglomerular hydrostatic pressure and thereby partially counteract the fall in glomerular filtration produced by renal underperfusion. Disproportionate efferent arteriolar constriction also elevates

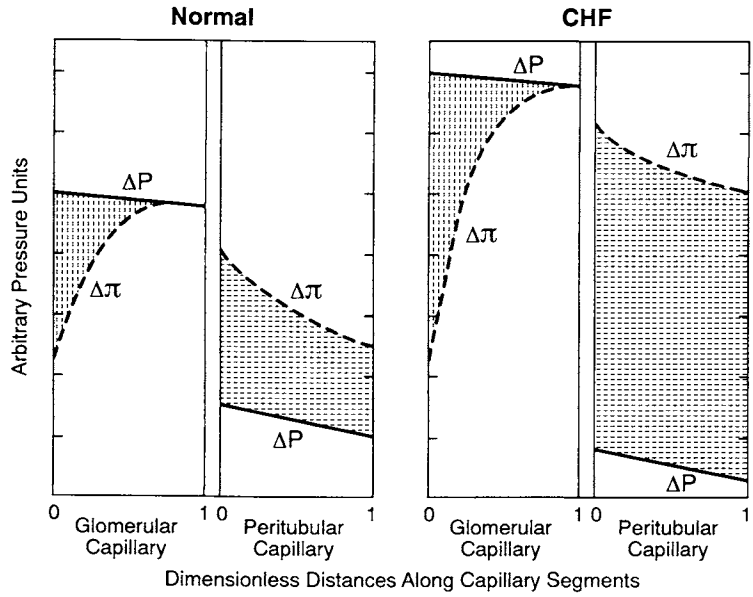

FIGURE 6. Representation of the changes in net hydrostatic pressure (ΔP) and net oncotic pressure ($\Delta\pi$) over the length of an idealized glomerular and idealized peritubular capillary. The pressures expected in normal subjects are shown on the left and in subjects with congestive heart failure on the right. 0 represents the afferent end and 1 the efferent portion of these capillaries. $\Delta\pi$ increases along the length of the glomerular capillary as the result of ultrafiltration of protein-free fluid and ΔP decreases slightly. The net driving force for ultrafiltration, ΔP-$\Delta\pi$, falls mainly because of the increasing $\Delta\pi$. When $\Delta P = \Delta\pi$, the driving force for filtration is zero and filtration ceases. Hydrostatic pressures in the peritubular capillary are much lower as a result of the resistance to flow through the postglomerular arteriole. ΔP is reduced below $\Delta\pi$ so that ΔP-$\Delta\pi$ becomes negative and the gradient will favor solute and fluid reabsorption from the proximal tubule. In this example, the patient with heart failure has much higher glomerular capillary hydrostatic pressures. This results from intense efferent postglomerular arteriolar constriction. Note that the increase in $\Delta\pi$ is much greater than in normals, reflecting the higher filtration fraction characteristic of CHF. Marked efferent arteriolar vasoconstriction also causes a greater reduction in hydrostatic pressures within the peritubular capillaries. The lower hydrostatic and higher oncotic peritubule capillary in patients with heart failure reduces their backleak and increases tubular reabsorption of salt and water. (Adapted from Brenner, B. M. (1978). The kidney in congestive heart failure. *In* "Sodium and Water Homeostasis" (B. M. Brenner and J. H. Stein, eds.) p. 54, Longman, New York.

the FF, which increases efferent arteriolar and peritubular capillary protein concentration and also reduces hydrostatic pressures in the postglomerular arterioles and peritubular capillaries. The net effect of these changes in pressure on proximal tubule transport is less backleak and therefore increased reabsorption of fluid and solute from the proximal tubule.

Proximal tubule reabsorption of sodium salts is also enhanced by high levels of angiotensin II, catecholamines, and sympathetic nerve activity, which de-

velop in response to EABV contraction. These neurohormonal mediators activate Na/H antiporters in the apical membrane of the proximal tubule cells which directly increases $NaHCO_3$ reabsorption and also indirectly increases NaCl reabsorption by raising the chloride concentration in tubule fluid which increases passive outward diffusion of chloride [19, 36].

ADH stimulates sodium reabsorption in the TALH and aldosterone stimulates sodium reabsorption in the distal renal tubules and collecting ducts. Beyond the TALH, ADH also increases water reabsorption. ANP, prostaglandins E_2 and $F_{2\alpha}$, prostacyclin, nitric oxide, bradykinin, and dopamine oppose sodium and water reabsorption, but the net effect of all of these factors favors reabsorption of sodium and water.

FACTORS WHICH INCREASE CARDIAC CONTRACTILITY AND OUTPUT

Myocardial dysfunction reduces the fraction of blood ejected by the ventricles which increases ventricular end-diastolic volumes and pressures. Stretching increases the intrinsic contractility of myocardial fibers, in part, because it sensitizes the myofilaments to the effects of ionized calcium. Thus, a malfunctioning heart may initially maintain adequate cardiac output by virtue of diastolic dilation or stretch. Adrenergic stimulation and angiotensin II generated systemically and within the heart also raise cardiac contractility.

The opposing neurohormonal cascades which are activated by heart failure favor generalized vasoconstriction and renal retention of salt and water. These responses are initially beneficial for most heart failure patients. Right and left ventricular end-diastolic volumes and pressures and central and pulmonary venous pressures all increase. This increases cardiac contractility, stroke volume, and output (Fig. 3). In normal subjects, contractility and stroke volume increase in response to diastolic pressure alteration until pressures of about 12–15 mm Hg are reached. The normal cardiac response curve then becomes flat. However, the failing heart requires a higher end-diastolic pressure to generate maximal contractility and stroke volume. This is due to the decreased ventricular compliance, or increased stiffness, of the failing myocardium. Left ventricular end-diastolic pressures of 18–22 mm Hg may be necessary to achieve optimal contractility in patients with heart failure. However, left ventricular end-diastolic pressures are transmitted to the pulmonary capillaries, where high pressures produce pulmonary edema. Analogously, transmission of high right ventricular end-diastolic pressures into the systemic venous system produces hepatic engorgement, ascites, and peripheral edema. High systemic venous pressures also reduce lymphatic flow into the great veins and this contributes to the development of ascites and edema.

At the opposite extreme, the failing heart may not be able to tolerate end-diastolic pressures below 12–15 mm Hg. Below this range cardiac contractility, stroke volume and output fall rapidly. Thus, the optimal end-diastolic pressure for patients with heart failure are elevated but have a narrow range.

Figure 3 also shows the effect of afterload on stroke volume. Cardiac afterload is related to systemic blood pressure and the arterial impedance to blood flow. (More accurately, afterload is the sum of all forces that the heart must contract against and is also affected by blood viscosity, the mass of blood in the aorta, and end-diastolic pressure.) The systemic vasoconstricting response to heart failure stabilizes blood pressure and may improve perfusion of certain organs (i.e., brain, heart, etc.). However, higher afterload levels will also decrease stroke volume and cardiac output. The failing heart is more sensitive to changes in afterload. Thus, increasing preload and afterload can have both beneficial and detrimental effects in patients with heart failure. The hemodynamic impact of these alterations will depend on their magnitude and the individual patient's myocardial and vascular responsiveness. Hemodynamic parameters must be finely balanced to achieve optimal tissue and organ perfusion.

SALT RESTRICTION AND DIURETIC THERAPY [30–33]

Contraction of extracellular fluid (ECF) and plasma volumes can be achieved with dietary salt restriction and diuretic therapy. This may be of great benefit to patients with chronic or acute congestive heart failure. Volume contraction reduces central and pulmonary venous capillary pressures which reverses pulmonary congestion and edema, as well as peripheral edema, ascites, and hepatic congestion.

ECF and plasma volumes can be manipulated by varying salt intake. When normal individuals switch from a normal salt intake to a low salt diet, urine sodium excretion does not fall immediately to match the lower intake level. Usually, a brief period of negative salt and water balance ensues. During this time, ECF and plasma volumes decrease and this activates vasoconstricting and salt retaining mediators which include renin, angiotensin, aldosterone, catecholamines, sympathetic nerves, etc. Salt excretion gradually decreases and after several days is reduced to levels equal to those ingested. At this point sodium balance is restored. Note that although balance is reestablished, the ECF volume, plasma volume, and weight are lower than they were on a normal salt intake. These parameters will remain "reduced" as long as salt intake remains at the lower level.

An increase in salt intake produces the opposite sequence. Urine salt excre-

tion initially lags behind the higher levels of salt intake. Positive salt balance increases the ECF volume, plasma volume, and weight. Vasoconstricting and salt retaining factors are suppressed while vasodilating and salt excretory factors are activated. Renal salt excretion increases and after several days matches the higher intake level. Balance is thus reestablished at higher ECF and plasma volumes and weight. These parameters all remain greater than baseline as long as the increased level of salt intake continues.

Figure 7 shows the relationship between urinary sodium output (which under balance conditions becomes equivalent to sodium intake) and ECF volume. The slope of the relationship indicates that the change in ECF sodium content is equal to about (1.3) × (change in sodium intake). Thus, if sodium intake increases by 100 mmol/day, the Na^+ content of the ECF will increase by about 130 mmol. This will expand ECF volume by about 900 ml (assuming that the

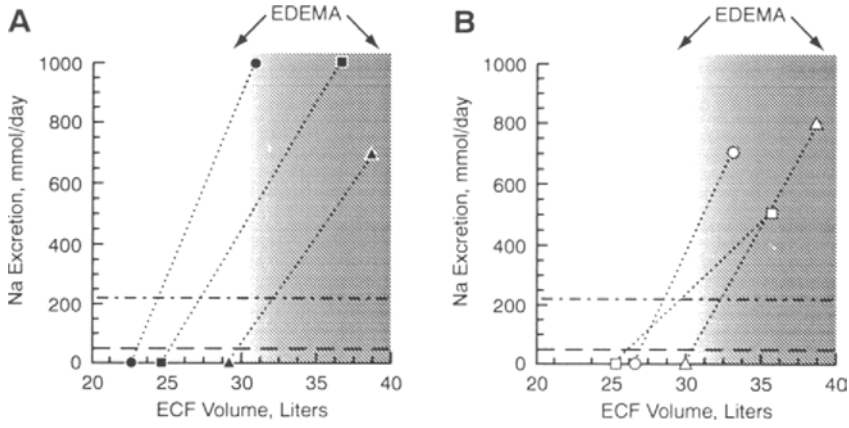

FIGURE 7. (A) The effect of dietary Na excretion (intake) on ECF volume in normal subjects and patients with CHF. Steady-state conditions exist so that Na excretion becomes equivalent to Na ingestion. The dashed lines indicate daily Na intake of about 1 and 5 g, respectively. The ECF volume of normal individuals expands when Na intake increases, but edema will not develop unless Na intake is enormous. The patient with mild congestive heart failure in this example develops edema at an intake of 200–300 mEq (5–8 g) of Na/day. The patient with severe heart failure remains edematous despite severe Na restriction. (B) The effect of diuretics and salt intake in patients with severe congestive heart failure. Diuretics shift the relationship to the left so for any given level of Na excretion (intake) ECF volume is lower. Loop diuretics may also alter the slope of the relationship. The flatter slope indicates that any change in salt intake will cause larger change in ECF volume. Note the important impact of salt intake on ECF volume whether or not diuretics are utilized (see text). ●, Normal subject; ■, patient with mild CHF; ▲, patient with severe CHF; ○, patient with severe CHF treated with a thiazide; △, patient with severe CHF; □, patient with severe CHF treated with a loop diuretic. (Adapted from Ellison, D. H. (1994). "Diuretics drugs in the treatment of edema: From clinic to bench and back again." Am. J. Kidney Dis. 23, 624–625, Figures 1 and 2.)

plasma [Na] = 140 mEq/liter). A 100 mmol/day decrease in dietary Na^+ reduces ECF sodium content and volume by similar amounts [33].

Figure 7 also shows the abnormal relationship which exists between ECF volume and sodium intake in patients with congestive heart failure. The line defining this relationship shifts to the right so that any given level of sodium excretion (i.e., intake) is associated with a larger ECF volume. The slightly flatter slope also indicates that any change in salt intake will generate a greater change in ECF volume. Reducing salt intake will clearly decrease ECF volume. However, in patients with severe CHF even extreme salt restriction may not reduce ECF volume adequately. Relationships similar to those shown in Fig. 7 also exist between salt intake and measurements of plasma volume or body weight.

In a carefully controlled environment, sodium intake can be reduced to about 250 mg (about 10 mEq) per day. However, a more reasonable goal for the outpatient setting is 1000–1500 mg (about 40–65 mEq) of Na^+ per day. Accurate quantitation of dietary salt intake may prove difficult. Under relative steady-state conditions, daily salt intake can be assumed to equal the sodium content of a 24-hr urine collection (as in Fig. 7). However, equivalence between salt intake and renal excretion does not exist during periods of rapid weight gain or loss (i.e., when sodium and fluid balance is positive or negative) or if sodium is lost via nonrenal routes such as diarrhea, vomiting, NG suction, etc.

When dietary salt restriction cannot reduce ECF and plasma volumes to a desired level, then diuretic therapy is indicated. Figure 7 also shows the effect of diuretics on the relationship between sodium excretion (again assume this is equivalent to intake) and ECF volume in patients with heart failure. Chronic diuretic treatment shifts this relationship to the left, so that any given level of sodium intake will result in lower steady state ECF volumes (and plasma volume and weight). When dietary salt intake remains constant, the initiation of a diuretic produces a relatively short-lived period of negative sodium balance. This decreases the patient's weight, reduces ECF and plasma volumes, and activates salt retaining mediators. Sodium balance is then restored at a lower weight and lower ECF and plasma volumes. Chronic diuretic therapy does not produce persistent negative sodium balance, which would, of course, be fatal. Note that dietary sodium continues to have an important impact on the size of the ECF and plasma volumes after initiation of diuretics. The level of salt intake affects the reduction in volume which will be generated by a diuretic. Ditary salt intake also impacts the frequency and severity of diuretic-associated side effects (see Diuretic Complications, below).

Another action of diuresis is a reduction in systemic vascular resistance and cardiac afterload which often improves cardiac output (Fig. 3). However, overdiuresis can reduce arterial blood pressures to levels which compromise organ perfusion so that diuretic therapy must be carefully monitored.

Loop diuretics of the furosemide class also produce acute venodilation by nondiuretic mechanisms. This effect is due to increased in synthesis and release of vasodilatory prostaglandins from the kidney. These acute hemodynamic effects reduce venous return to the heart and thereby decrease central venous and pulmonary capillary pressures [2, 6]. Thus, diuretics may have at least three different beneficial actions in patients with heart failure:

1. Diuresis and natruresis reduce ECF and plasma volumes, reduce cardiac preload, and improve pulmonary and systemic congestive symptoms.
2. Diuretics reduce systemic vascular resistance and cardiac afterload which often increases cardiac output.
3. Furosemide class loop diuretics cause renal release of prostaglandins and prostacyclines which result in systemic venodilation. The fall in preload can rapidly improve congestive symptoms.

Chronic Diuretic Therapy for Heart Failure [30–33]

Patients with mild heart failure generally respond favorably to the initiation of a low salt diet and thiazide diuretics. The relatively long biologic half-life of this class of diuretics can produce an almost continuous diuretic effect which is generally advantageous. Hydrochlorothiazide, at a dose of 25–50 mg/day, or equivalent doses of other thiazides, or thiazide-like diuretics, are reasonable choices. Loop diuretics generate more dramatic diuresis over a shorter period of time. However, when the loop diuretic action wanes, avid renal salt retention develops. Therefore, these drugs produce a brief, intense period of diuresis followed by a period of avid salt retention which can blunt or reverse the benefits produced by the diuretic phase. Indeed, weight, ECF, and plasma volume may not decrease despite seemingly effective (i.e., periods of brisk diuresis) loop diuretic therapy, especially if patients ingest a relatively high salt diet.

Thiazides become less effective when renal function deteriorates and are often ineffective when the GFR falls below 30 ml/min. Thiazides (and loop diuretics) must be secreted by the proximal tubule via the organic acid pathway to gain access to their principle sites of action within the lumen of the early distal tubule (and TALH). Secretion of diuretics by the proximal tubule decreases as the GFR falls in part as a result of competition with other accumulating organic acid anions. To the extent that thiazides are secreted and delivered to their active site, they still inhibit sodium reabsorption. However, the small incremental increase in fractional sodium excretion that thiazides are capable of producing has minimal clinical impact. As the GFR declines, fractional sodium reabsorption decreases proportionately. When the GFR falls by one-half, fractional sodium reabsorption must double to maintain salt balance. Patients

with very low GFRs have fractional excretions of sodium which exceed 10%. The additional 5% increase produced by a thiazide diuretic represents a very modest degree of diuresis. Consequently, thiazides often become inadequate when patients with heart failure develop coexistent renal insufficiency. Under these circumstances loop diuretics and diuretic combinations can be effectively utilized.

The loop diuretics currently available for use in the United States include furosemide, bumetanide, torsemide, and ethacrynic acid. The first three drugs are in the same subclass and have a similar mechanism of action. Similar to the thiazides, they must be secreted by the proximal tubule to reach their active site within the lumen of the TALH where they inhibit the Na/K/2Cl transporters. These three diuretics are available in oral and parenteral formulations; they do have different potencies and very different effective therapeutic ranges. Other significant distinctions include the following: (i) The GI absorption and bioavailability of oral furosemide varies widely between individuals and even within a single individual at different times. Compatible iv/oral furosemide doses range from 10 to 80% with an average of about 50%. Bumetanide and torsemide are much better and more predictably absorbed than furosemide. Their oral bioavailability is 80–90% [3]. Therefore, when oral loop diuretics are used in patients with renal insufficiency, who generally require high peak plasma levels to generate adequate secretion, bumetanide or torsemide may be better choices. (ii) The half-life of torsemide is significantly longer than the other available loop diuretics. Consequently, torsemide produces a more continuous diuretic effect and is less likely to cause rebound salt retention as discussed above.

Bowel wall edema may impair the gastrointestinal absorption of diuretics and some diuretic resistance which occurs in patients with heart failure has been attributed to this mechanism. More recent studies have shown that patients with congestive heart failure and severe peripheral edema who presumably also have GI edema, absorb normal quantities of orally administered loop diuretics. However, the time course of absorption is altered [27]. Heart failure delays and reduces peak blood levels, although the area under the plasma drug concentration vs time curve (representing the total quantity of absorbed diuretic) is not reduced; i.e., the drug is absorbed more slowly. This may affect the efficacy of loop diuretics when they are used to treat patients with advanced renal failure as well as CHF and high peak blood levels are required for adequate secretion.

Several studies have reported the efficacy of continuous intravenous loop diuretic infusions. This method of delivery may be more effective, and possibly safer, than intermittent bolus infusion. The dose ranges utilized are furosemide 20–160 mg/hr and bumetanide 0.5–2 mg/hr [25A].

When patients with heart failure become resistant to high doses of loop di-

uretics, combinations of two or more different classes of diuretics may prove effective. The addition of a thiazide to a loop diuretic is often synergistic [8]. This combination is effective because the two diuretics have different active sites in different nephron segments. The loop diuretics block NaCl reabsorption in the TALH and also increase renal blood flow. The thiazides have a modest proximal tubule carbonic anhydrase inhibiting effect and more potently block NaCl transport in the early distal tubule. Chronic loop diuretic therapy increases the delivery of NaCl from the TALH to the thiazide-sensitive early cortical distal tubule. Chronic increases in salt delivery to these tubule segments produces compensatory physiologic and anatomic hypertrophy which markedly increases NaCl reabsorption [9]. Consequently, subsequent inhibition of NaCl reabsorption at this site with a thiazide produces a potent synergistic effect. Commonly used combinations include metolazone 5–10 mg po (or via nasogastric tube) qd with furosemide 80–160 mg iv q 6–8 hr. Alternatively, intravenous hydrochlorothiazide 500–1000 mg may be administered once or twice daily together with a loop diuretic.

Diuretic Therapy of Acute Pulmonary Edema [6, 30]

Acute pulmonary edema is an obvious clinical indication for aggressive diuretic therapy. Loop diuretics of the furosemide class are particularly useful for the treatment of acute pulmonary edema for two reasons: (i) their acute potent diuretic effect and (ii) their capacity to rapidly produce acute venodilation by a nondiuretic mechanism. Diuresis reduces ECF and plasma volumes, cardiac inflow (preload), and left ventricular end-diastolic pressures. This reduces pulmonary capillary hydrostatic pressures so that interstitial and alveolar pulmonary edema fluid may be reabsorbed.

The loop diuretics generate a diuresis within 5 min of intravenous infusion and the effect peaks within 30 min. If given by mouth, loop diuretics are rapidly absorbed from the GI tract and diuresis begins about 60 min following ingestion (as discussed above, bumetanide and torsemide are more completely and predictably absorbed than furosemide). Loop diuretics have a high natriuretic ceiling and large doses will deliver 20–25% of the filtered sodium load into the urine. Consequently, these drugs can rapidly reduce plasma volume and ventricular end-diastolic pressure.

Within minutes of parenteral infusion, furosemide also produces major dilation of systemic venous capacitance vessels which may expand by more than 50%. This acutely reduces the volume of blood returning to the heart and preload falls. Right and left ventricular filling pressures and pulmonary pressures decrease rapidly. Left ventricular end-diastolic pressures may fall 15–20 mm

Hg within minutes of furosemide infusion. Furosemide-class diuretics have this hemodynamic effect because potent renal vasodilatory prostaglandins are released into the systemic circulation [6]. Although furosemide may also cause local vasodilatory prostaglandins release from the epithelia of systemic vessels, studies indicate that a major venodilation response requires an intact renal circulation [2]. This acute response may be a subclass effect, but has been best documented with furosemide.

Furosemide also causes renal prostaglandin release which results in renal arteriolar vasodilation. The GFR increases, more blood flows to the outer renal cortex, and the glomerular filtration fraction decreases. These hemodynamic actions increase the delivery of sodium to the TALH where its reabsorption is blocked by the loop diuretic. In addition, the prostaglandin E_2, released in response to furosemide, directly inhibits sodium reabsorption by the TALH [26]. These prostaglandin related natruretic effects are additive to the inhibition of epithelial sodium transport produced by the loop diuretics.

The acute systemic vascular and diuretic effects of loop diuretics are of great benefit to most patients with acute pulmonary edema. However, hypotension and hemodynamic collapse may occur in those patients whose cardiac performance places them on the steep ascending portion of the Frank–Starling curve (Fig. 3). These patients may have poorly compliant and stiff ventricles which require high end-diastolic volumes to maintain cardiac output.

Diuretics for Patients with Diastolic Dysfunction [1, 30]

Diastolic dysfunction is a cardiac disorder which reduces or impairs normal ventricular diastolic filling. Although diastolic dysfunction often develops in patients who also have systolic cardiac dysfunction, it may exist as an isolated abnormality. The presence of high diastolic pressures, a normal left ventricular ejection fraction, and normal or decreased ventricular volumes are indicative of isolated or predominant diastolic dysfunction. These ventricles are abnormally stiff and cannot relax appropriately during diastole. Isolated diastolic dysfunction may be due to primary myocardial or infiltrative processes, cardiac ischemia, and/or pericardial disorders.

When diastolic dysfunction causes very high diastolic pressures, patients will develop pulmonary and/or systemic edema and often present with "flash" pulmonary edema. Diuresis may be of great benefit when pulmonary and/or severe peripheral edema exist. However, because the ventricles of patients with diastolic dysfunction are usually very stiff, steep Frank–Starling relationships exist (Fig. 3). Therefore, reducing diastolic pressure can also sharply reduce cardiac output. Consequently, diuresis in patients with diastolic dysfunction is

associated with a high frequency of side-effects and diuretics are not considered first line drugs for these patients. Instead, efforts should be directed at the underlying abnormalities (ischemia, hemochromatosis, amyloidosis, pericardial constriction, etc.). β-Blockers and calcium channel blockers are often useful because these drugs can reduce myocardial stiffness and improve diastolic filling. To the extent that they slow heart rate, these drugs will also increase diastolic filling time. Diuretics are generally reserved for treatment of symptomatic fluid retention which persists after other therapeutic modalities have been deployed.

End Points for Diuresis

Diuresis reduces right and left ventricular diastolic pressures, reverses pulmonary congestion, ameliorates dyspnea and orthopnea, improves exercise tolerance, and controls peripheral edema. Vasodilation, lower blood pressure and afterload reduction can improve cardiac output. However, lower diastolic filling pressures can also decrease cardiac output and excessive diuresis can compromise organ perfusion and cardiac performance. Clearly, patients whose cardiac performance is on the descending limb of the Frank–Starling curve are at greatest risk from diuretic therapy.

The balance between the beneficial and adverse effects of diuresis may be difficult to achieve and maintain. Patients with heart failure who are treated with diuretics must be very carefully monitored. Clinical parameters including supine and upright pulse and blood pressure and serial weights should be monitored regularly. Diuretics should be reduced, or stopped, if progressive reduction in organ perfusion is detected.

Renal perfusion is an excellent marker of the EABV status. The BUN and creatinine concentrations and the BUN/creatinine ratio are easily monitored and very helpful parameters. Urea and creatinine are small compounds which are both freely filtered by glomeruli. However, their proximal tubule transport characteristics are very different. Urea is reabsorbed by the proximal tubules while creatinine is secreted by the proximal tubules. When the kidney is underperfused and proximal fluid and solute reabsorption increases, urea reabsorption also increases. However, creatinine continues to be secreted into the proximal tubule by the organic acid pathway. When the GFR falls as a result of underperfusion, filtration of both urea and creatinine fall to the same extent. Avid proximal tubule reabsorption of filtered urea further reduces its renal clearance, while proximal tubule secretion of creatinine increases the creatinine clearance above the GFR. In consequence, renal underperfusion increases the blood urea nitrogen concentration (BUN) disproportionally compared with the increase in blood creatinine concentration. Other factors which also affect

the BUN and creatinine concentrations can confound the interpretation and must also be considered. For example, large dietary protein loads, blood in and absorbed from the GI tract, parenteral amino acid loads, glucocorticoid therapy, and accelerated rates of catabolism increase urea generation and elevate the BUN. Ingestion of a low protein diet and severe hepatic disease reduce the rate of urea generation and the BUN. The major site of endogenous creatinine generation is skeletal muscle so that the creatinine concentration also varies directly with muscle mass. Small, poorly muscled individuals have lower creatinine concentrations and large muscular men have higher creatinine concentrations. Rhabdomyolysis causes creatinine release from necrotic muscles and acutely increases creatinine concentrations. Consequently, a number of variables other than EABV and renal function may affect the BUN, creatinine, and BUN/creatinine ratio. Nonetheless, after these other factors are considered the BUN, creatinine, and BUN/creatinine ratio remain useful indicators of renal perfusion and help to guide the intensity of diuretic therapy.

Diuretic Complications

Treatment with thiazide and/or loop diuretics can produce multiple electrolyte abnormalities including hyponatremia, hypokalemia, hypomagnesemia, and metabolic alkalosis. Patients with heart failure usually have elevated ADH levels and urine flow through the distal nephron is reduced due to the low GFR and avid proximal tubule reabsorption. These factors combine to cause persistent concentration of the urine. The maximal urine osmolality achieved by these patients is not as high as that generated by normal subjects given ADH. Patients with heart failure have reduced renal medullary osmotic gradients which reduce maximal concentration. Nonetheless, the urine is often inappropriately concentrated (for the sodium prevailing concentration) and water loads cannot be normally excreted. The contracted EABV and high angiotensin II levels also stimulate thirst, which exacerbates the tendency to develop, and severity of, hyponatremia. Hyponatremia and hypotonicity would suppress ADH levels in otherwise normal individuals, but the low EABV in patients with CHF causes unrelenting ADH secretion The existance of hyponatremia in patients with heart failure usually indicates that major counterregulatory responses have been triggered, the state of heart failure is advanced, and the prognosis is ominous [17].

Thiazides will often exacerbate the tendency of these patients to develop hyponatremia. These drugs block NaCl reabsorption in the early distal tubule (diluting segment) but do not affect NaCl reabsorption in the TALH which is critical for generating medullary osmotic gradients. Consequently, when patients are treated with thiazides their concentrating capacity is not further com-

promised but diluting mechanisms are impaired. Thiazide diuresis also stimulates proximal tubule reabsorption which reduces distal delivery of filtrate. This will decrease the quantity of free water which the kidney can generate even in the absence of ADH.

Loop diuretics reduce the kidney's capacity to dilute as well as concentrate the urine. Urine produced by patients receiving loop diuretics tends to become isotonic. Therefore, loop diuretics which reduce both dilution and concentration are less likely to exacerbate hyponatremia than thiazides which do not compromise concentrating capacity. Excessive diuresis with any diuretic will reduce EABV, decrease the GFR, and elevate ADH levels. This will exacerbate the tendency to develop hyponatremia. However, if successful diuresis improves cardiac function, plasma sodium concentrations may return toward normal.

The potassium loss produced by thiazide or loop diuretics results from increased distal tubule delivery of sodium salts and fluid as well as elevated aldosterone levels. High distal tubule flow rates dilutes the intraluminal potassium concentration and thereby improves the gradient for potassium secretion into the tubule. Delivery of large amounts of sodium salts to distal tubules and collecting ducts, which are primed to reabsorb sodium by high aldosterone levels, further accelerates potassium and proton secretion. Elevated ADH levels and metabolic alkalosis also increase distal tubule potassium secretion (see Fig. 8). Hypokalemia is of special concern in patients with heart disease because it increases their risk of severe and life-threatening arrhythmias. This risk is magnified if patients are receiving cardiac glycosides. Hypokalemia will also exacerbate hyponatremia [12]. Therefore, hypokalemia and potassium depletion should be avoided and when it does occur in these patients it must be treated aggressively.

A high salt diet results in the delivery of a large quantity of sodium to distal tubule segments where potassium and protons are secreted. This increases renal potassium loss and the tendency to develop hypokalemia. Moderate salt restriction should be combined with diuretic therapy to reduce the severity of this complication. However, extreme dietary salt restriction can also exacerbate potassium losses. This occurs because very low salt intake markedly increases plasma renin activity and produces very high aldosterone levels.

Spironolactone, which blocks the action of aldosterone, or triamterene or amiloride, which block distal tubule sodium reabsorption, will decrease renal tubule potassium and hypokalemia secretion. Therefore, these diuretics are very helpful adjunctive agents. However, when "potassium-sparing" drugs are used in patients with renal insufficiency, the serum chemistries must be carefully monitored to avoid development of severe hyperkalemia.

Angiotensin converting enzyme inhibitors or angiotensin II receptor (AT1) blockers reduce aldosterone levels by decreasing angiotensin II levels or activity. Therefore, these agents also decrease the incidence and severity of diuretic-

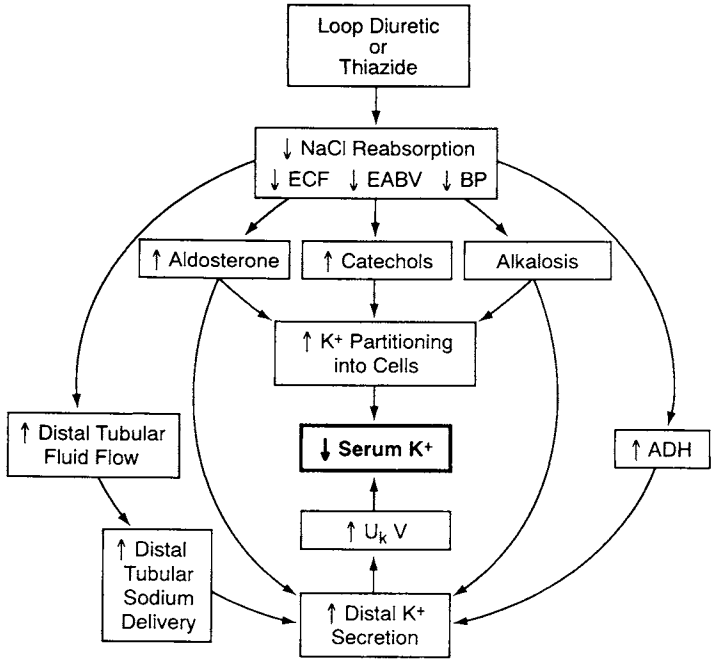

FIGURE 8. Mechanisms which increase renal potassium excretion and generate hypokalemia in patients receiving thiazide and/or loop diuretics. ECV, extracellular volume; EABV, effective arterial blood volume; ADH, antidiuretic hormone. (Adapted from Wilcox, C. S. (1989). Chapter 13. Diuretics and potassium. In: The Regulation of Potassium Balance (eds.) Seldin, D. W., and Giebisch, G., Lippencott-Raven, Philadelphia, p. 339.

induced hypokalemia and potassium depletion. More importantly, such drugs reduce cardiac afterload and thereby improve cardiac function. This will decrease the levels of the neurohormonal mediators which stimulate renal salt and water retention and thereby decrease diuretic requirements and complications.

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CHAPTER VA3

Diuretic Treatment of the Nephrotic Syndrome

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INTRODUCTION

Nephrotic syndrome is caused by an abnormal increase in the permeability of glomerular capillaries to albumin. Increased glomerular filtration of albumin results in albuminuria as well as increased renal albumin catabolism. The increase in catabolism develops because a large quantity of filtered albumin is reabsorbed and degraded by proximal tubule cells. Nephrotic syndrome increases renal retention of salt and water which combines with hypoalbuminemia to produce generalized edema. Hypoalbuminemia and/or decreased plasma oncotic pressure also increase hepatic synthesis of albumin, lipoproteins, and cholesterol. Hyperlipidemia and hyperlipoproteinemia develop as a result of the accelerated hepatic synthesis of lipoproteins and cholesterol, abnormalities of lipoprotein metabolism linked to hypoalbuminemia, and possibly the renal excretion and depletion of poorly defined lipid regulatory factors [21]. In consequence, the hallmarks of nephrotic syndrome include marked albuminuria, usually greater than 3.5 g/day, hypoalbuminemia, edema, hyperlipidemia, and lipiduria.

Many renal abnormalities can increase albumin permeability of glomerular capillaries. Primary glomerular processes, which occur independently of any extrarenal systemic disorders, produce the idiopathic nephrotic syndromes. The pathologies include minimal change disease, membranous nephropathy,

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focal glomerulosclerosis, and various forms of idiopathic proliferative glomerulonephritis. The systemic diseases associated with secondary glomerular disorders producing nephrotic syndrome include diabetes mellitus, collagen vascular diseases, primary and secondary vasculitis, and many bacterial, fungal, rickettsial, viral, and parasitic infections. Nephrotic syndrome can also have an allergic, toxic, or hereditary basis.

PATHOPHYSIOLOGY OF SALT RETENTION AND EDEMA, THE UNDERFILL VS OVERFLOW HYPOTHESES

The accumulation of clinically significant systemic edema generally requires that the kidneys retain salt and water (the acute capillary leak syndromes are exceptions). Renal salt retention certainly develops in patients with nephrotic syndrome. The most proximal signal, or signals, responsible for the renal salt retention of these patients remain uncertain. The classic pathophysiologic explanation for the salt retention of nephrotic syndrome is the underfill hypothesis and follows the sequence shown in Fig. 1. The initial abnormality is the increase in glomerular permeability to albumin which produces albuminuria and accelerates albumin catabolism. The resulting fall in blood albumin concentration increases the hepatic albumin synthetic rate, but the increase is initially inadequate to restore balance so that plasma albumin concentrations continue to fall. As the filtered albumin load decreases both albumin excretion and catabolism also decrease. The plasma albumin concentration eventually stabilizes at a level which permits hepatic synthesis to match the renal excretion and total catabolic rates.

In the systemic vascular beds, hypoalbuminemia shifts the balance of Starling forces to favor filtration of fluid out of capillaries and reduces capillary reabsorption of fluid (see Chapter VA1). The net translocation of fluid from the vascular to the interstitial space simultaneously produces edema and contracts intravascular volume. The reduction in vascular volume increases renal salt and water retention which partially reexpands this space. Otherwise, severe hypovolemia and hypotension would result. This is the underfill hypothesis. It requires contraction of intravascular volume (and effective arterial blood volume (EAVB), see Chapter VA1) to trigger a series of vascular and neurohormonal mediators which stimulate renal sodium reabsorption. They include the sympathetic nervous and the renin–angiotensin systems, aldosterone, and vasopressin. A number of other less well characterized hormone, paracrine, and autocrine factors also participate. The kidney becomes relatively resistant to natriuretic peptides [24].

Renal vascular resistance increases but selective constriction contracts the

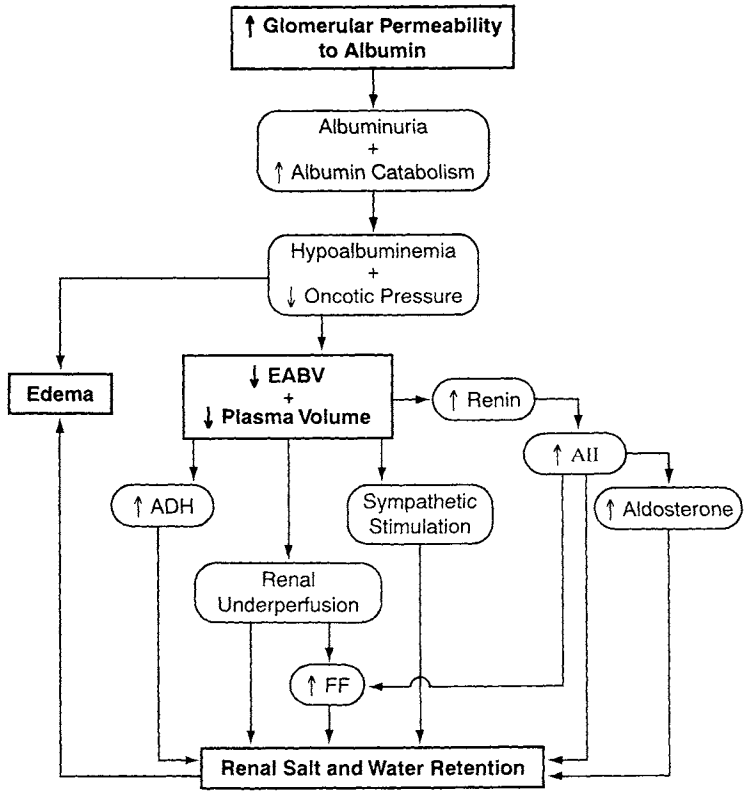

FIGURE 1. The classic underfill hypothesis: renal salt and water retention and edema formation in patients with the nephrotic syndrome. The EABV and plasma volume are reduced.

efferent postglomerular arterioles more strongly than the afferent preglomerular arterioles. This selective constriction will increase the glomerular filtration fraction (filtration fraction = glomerular filtration rate/renal plasma flow rate; FF = GFR/RPF). This hemodynamic profile also stimulates renal salt retention and interacts synergistically with the high levels of salt-retaining hormones. The salt and water retained by the kidneys of nephrotic patients preferentially accumulates in their interstitial spaces, as a result of the Starling force alterations created by the hypoalbuminemia [14].

The accumulation of edema within the interstitial spaces activates local mechanisms which oppose additional edema formation. They include increased hydrostatic pressure within the interstitial space, increased lymphatic drainage out of the interstitial space, and lower interstitial fluid albumin concentrations (oncotic pressure). These mechanisms must be overcome before significant quantities of edema can accumulate (see Chapter VA1).

The basic principles of the underfill pathophysiologic hypothesis, as described above, was proposed over 80 years ago and became widely accepted by 1948 [1]. It requires physiologically and anatomically normal kidneys except for increased glomerular protein permeability. The renal retention of salt and water in this model is a response to systemic hypovolemia and low vascular and EAB volumes. The signals which drive the kidneys to retain salt originate within the systemic circulation. They result from the fluid shifts produced by the altered Starling forces. However, in many clinical and experimental studies of nephrotic syndrome, the underfill hypothesis could not be proven. In those cases it is possible that subtle intrinsic intrarenal alterations also participate in the salt retaining process.

Some disorders which cause the nephrotic syndrome also produce overt structural renal derangements which reduce renal perfusion and glomerular filtration. In such cases, these renal abnormalities may be the principal cause of salt and water retention. This is the obvious explanation for the salt retention which occurs when a proliferative glomerulonephritis produces both the nephrotic syndrome and renal insufficiency. However, in many patients no other apparent functional or structural renal derangements exist. For example, when nephrotic syndrome is due to minimal change disease, this can be considered a "pure" form of nephrosis. In this group underfill pathophysiology is most likely. However, even in many of these pure nephrotic patients, some studies suggest that the salt-retaining signals originate within the kidney itself. If this is correct, an alternative hypothesis to explain the salt retention of nephrosis becomes necessary.

The major alternate pathophysiologic sequence, called the overflow hypothesis, is shown in Fig. 2. The central tenet of the overflow hypothesis is an intrarenal stimulus which causes salt and water retention. This model does not require initial hypovolemia to trigger renal salt retention. Instead, renal salt and water retention develop first and expand the extracellular fluid (ECF), vascular volume, and the EABV. The Starling force derangements secondary to hypoalbuminemia cause the retained salt and water to preferentially accumulate in the interstitial space. The major distinction between the underfill and overflow theories of nephrotic edema formation is the status of the vascular and/or EABV: reduced in the underfill sequence and normal or increased with overfill physiology.

Clinical and Experimental Data

A number of human and animal studies have been undertaken to determine which salt and water retaining hypothesis is most consistent with the observed facts. In 1968, Eisenberg measured the blood volume of nephrotic patients and

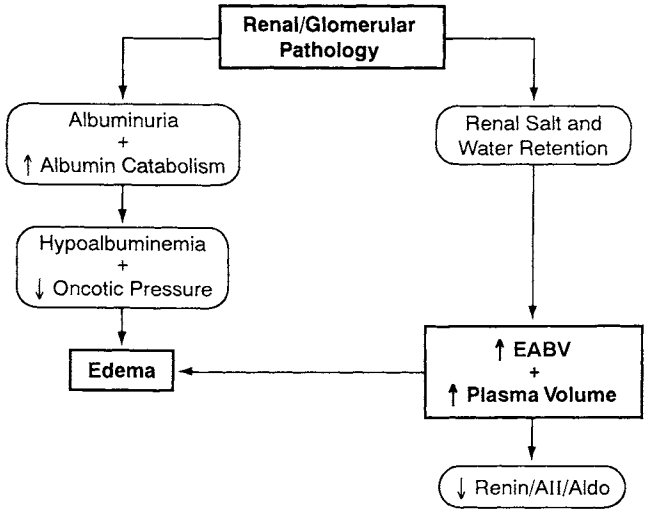

FIGURE 2. The overflow hypothesis: renal salt and water retention in nephrotic syndrome. The pathology which produces increased glomerular permeability also produces intrarenal alterations which directly increase the reabsorption of salt and water by the kidney. Edema under these circumstances is associated with an expanded EABV and plasma volume.

reported that it was usually normal or increased [5]. These findings were consistent with overflow physiology. However, the results of subsequent similar studies were equivocal; the blood volume of some nephrotic patients was reduced, in others it was normal, and in still others expanded [4]. Several factors may account for these conflicting results. First, as discussed, the hypovolemic underfill hypothesis is most likely to explain salt retention in patients with minimal change nephropathy. Many of the aforementioned studies included other forms of nephrotic syndrome. Intrinsic renal abnormalities which may cause renal salt retention are more likely when glomerulonephritis reduces renal perfusion and glomerular filtration. However, studies limited to patients with minimal change disease and normal glomerular filtration rates also often report normal or increased blood volumes. These results suggest that overflow pathophysiology may be operative in many nephrotic patients.

However, subsequent studies have raised a number of issues which confound and may invalidate blood volume measurements in patients with nephrotic syndrome. Total blood volume is usually determined by first measuring the plasma volume with a marker which is restricted to the vascular space, and then dividing this value by (1-Hct). Albumin, labeled with a radioactive molecule or a dye, is the most commonly utilized plasma volume marker. By definition, nephrotic patients have increased glomerular permeability to albumin.

Their systemic capillary beds may also develop increased albumin permeability. This greatly complicates the measurement of plasma volume. Furthermore, the blood volume calculation requires an accurate determination of the hematocrit. The hematocrit of normal individuals varies in different subcompartments of the circulatory system (i.e., the hematocrit in a peripheral vein is not the same as the hematocrit in renal venous blood or in the pulmonary artery). This normal hematocrit variation is greatly exaggerated in patients with nephrotic syndrome [4]. Also, orthostatic pooling of blood can reduce plasma volume when nephrotic patients stand [8]. All of these factors combine to confound blood volume measurements in nephrotic patients.

If all of the above issues could be resolved and the total blood volume of nephrotic patients accurately determined, it would still be difficult to use these results to prove or disprove one of the salt-retaining hypotheses. The underfill hypothesis requires a reduced EABV. It is possible for a low EABV to coexist with a normal or expanded total blood volume. Normally, EABV and total blood volume expand and contract symmetrically, but some pathologic disorders can dissociate changes in the size of these two volumes. For example, although EABV is usually reduced in patients with CHF or hepatic cirrhosis, their total blood volume is generally expanded. This could also be true in some patients with the nephrotic syndrome.

EABV cannot be measured directly, but several indirect markers of the relative size of this "space" do exist. The renin, angiotensin, and aldosterone levels generally reflect the EABV status. The plasma levels of these hormones decrease when the EABV expands and their concentrations increase when the EABV contracts. (The serum potassium concentration can also affect the renin and aldosterone levels.) Another indirect indicator of changes in the size of the EABV is the glomerular filtration fraction which changes in an inverse direction. EABV contraction increases the FF and EABV expansion reduces the FF.

If the underfill theory is operative in a patient with the nephrotic syndrome, then renin, aldosterone, and the FF should all increase. Although high renin and aldosterone levels and an elevated FF do exist in some nephrotic patients, these markers are normal or reduced in many others [16, 23]. Therefore, although the data in some patients is consistent with underfill physiology, in many others they suggest that overflow physiology exists.

Finally, several studies have evaluated changes in salt-retaining hormone levels produced by acute blood volume expansion. If renal salt and water retention is due to an underfilled circulation, then expansion of blood volume (and it is hoped the EABV) should reduce levels of salt retaining hormones and produce a diuresis. Intravenous infusions of colloid containing solutions and head out water immersion (which compresses venous capacitance vessels and expands central blood volume) have been utilized in efforts to expand the EABV

of nephrotic patients. However, the results are again inconclusive. Such volume expanding maneuvers do reduce renin and aldosterone levels and produce a diuresis in some nephrotic patients but in many others salt-retaining hormone levels remain high and antidiuresis persists [9, 10, 15].

In summary, evidence consistent with classic underfill pathophysiology exists in some patients with nephrotic syndrome, but the data is more compatible with the overflow hypothesis in many others. Underfilling may be somewhat more common in patients with minimal change disease. However, even in this most "ideal" subgroup many patients probably have overflow physiology. Consequently, many nephrotic patients may have intrinsic intrarenal alterations which stimulate salt and water retention. It must also be emphasized that the nephrotic syndrome is not a static condition and the salt retaining forces may change over time.

Salt Retention with Severe Renal Failure and/or Acute Glomerulonephritis

Patients with markedly reduced glomerular filtration rates will filter much less salt than normal. Renal tubule salt reabsorption decreases, but if a large quantity of salt is ingested progressive positive salt balance and overload will develop. When salt intake exceeds output, ECF, interstitial and vascular volume all expand. The pattern of distribution of retained salt and water which occurs in patients with severe renal failure is more symmetrical than that which develops in most patients with nephrotic syndrome. All the subcompartments of the ECF expand to produce hypertension, pulmonary congestion, cardiomegaly, and generalized edema. The different salt distribution patterns in nephrotic patients and in patients with renal failure may be due to their different plasma albumin concentrations in these conditions. Hypoalbuminemia favors an accumulation of retained salt and water in the interstitial space. However, some nephrotic patients develop massive edema, without vascular congestion, despite only modest reductions in plasma albumin concentration. Furthermore, many patients with severe renal failure who develop edema, hypertension, cardiomegaly, and pulmonary congestion have marked hypoalbuminemia. Consequently, other factors must also contribute to the differences in fluid distribution which develops in these groups of patients.

Patients with acute glomerulonephritis often develop a "nephritic overflow" form of edema. The stimulus for the salt retention which develops in these patients originates within their diseased kidney and renal vessels. Nephritic overflow edema symmetrically expands the ECF so that hypertension, pulmonary congestion, cardiomegaly, and edema occur frequently.

TREATMENT OF SALT RETENTION AND EDEMA DUE TO THE NEPHROTIC SYNDROME

General and Salt Restriction

Treatment of nephrotic edema should be directed principally at the underlying glomerular process whenever possible. For example, the most effective treatment for the salt retention and edema produced by minimal change nephropathy is a glucocorticoid induced remission. Similarly, the best treatment for edema associated with a toxin or drug induced nephropathy, is elimination of the inciting agent. However, very often the glomerular process cannot be promptly or completely corrected. Weeks or months of treatment may be required to induce a clinical response. Many forms of nephrotic syndrome cannot be effectively treated. In some of these patients symptomatic treatment of the salt retention, ECF expansion, and edema may become necessary.

Salt retention and edema can produce a number of significant medical problems which require aggressive intervention. Tense edema can cause skin breakdown and predispose to the development of cellulitis. Superficial infections which otherwise would be easily treated may progress rapidly as a result of impaired local host defense mechanisms. Generalized edema also contributes to fatigue and immobility, which should be avoided in nephrotic patients who are already susceptible to thromboembolic complications as a result of their hypercoagulable state. Tense ascites can produce marked discomfort and anorexia and contribute to malnutrition. Ascitic fluid can also become infected. Salt retention can exacerbate heart failure and cause pulmonary congestion in patients with coexistent cardiac abnormalities. Edema should not be treated for purely cosmetic reasons. However, if disfigurement produced by edema causes severe psychological or psychiatric problems, treatment may be warranted on this basis. Consequently, therapy of the edema and salt retention of the nephrotic syndrome is often necessary when the underlying renal lesion cannot be rapidly corrected.

Dietary salt restriction is a critically important cornerstone of therapy and should be initiated in virtually all nephrotic patients who develop symptomatic edema. We suggest that sodium intake be reduced to 20 to 50 mmol/day (equivalent to about 500–1200 mg/day of sodium). More aggressive salt restriction may reduce edema more rapidly, but extreme dietary restriction is very difficult to implement, especially in the outpatient setting. Compliance with dietary salt prescription can be approximated by an analysis of the 24-hr urine sodium excretion. The amount of sodium excreted in the urine of patients who are not rapidly gaining or losing weight is similar to the quantity they ingest with their diet (excluding other routes of salt loss, such as diarrhea, etc.).

Patients with nephrotic syndrome have an exaggerated hemodynamic postural response [8]. Upon standing, blood pools in their legs to a degree greater than in normal subjects. The resulting orthostatic fall in blood pressure will decrease renal perfusion. Standing also increases hydrostatic pressures in the veins and capillaries of the legs and thereby increases the formation of dependent edema. Elevation of the legs reduces hydrostatic pressures and permits reabsorption of edema fluid in the extremities. To the extent that underfill physiology exists, bed rest will expand the intravascular space, improve systemic and renal perfusion, reduce levels of salt retaining hormones, decrease sympathetic activation, and sometimes produce a diuresis. Although bed rest is a temporary and partial solution, the improvement produced by a few additional hours per day of leg elevation may be substantial. In some patients increased periods of bed rest can produce sustained improvement. Possibly, the initial diuresis produces some beneficial alterations which persist. However, bed rest also increases the risk of thromboembolic complications in nephrotic patients. Some suggest that nephrotic patients who are confined to bed for a prolonged period should be anti-coagulated unless strong contraindications exist.

Diuretics

When dietary salt restriction with, or without, additional bed rest does not adequately control edema, diuretic therapy is initiated. However, it must be emphasized that moderate dietary salt restriction continues to be an important component of therapy after diuretics are begun. The ingestion of a high salt diet together with diuretics will reduce their efficacy and increase the severity of adverse effects.

The duration of action of many potent diuretics is relatively short. Daily or twice a day administration of loop diuretics produces brief periods of markedly negative sodium balance, followed by periods of avid renal sodium retention as the diuretic effect wanes. Ingestion of a high salt diet results in markedly positive sodium balance during the interdiuretic periods. Thus, the beneficial effect of diuretic-induced natruresis can be entirely offset by intervening periods of sodium retention when a high salt diet is ingested [20].

Diuretic-induced hypokalemia can also be exacerbated by high dietary sodium intake. Diuretic inhibition of sodium reabsorption will initially produce negative salt balance which reduces ECF and vascular volumes and stimulates aldosterone and anti-diuretic hormone (ADH). Later, salt balance is restored because sodium reabsorption increases in those tubule segments unaffected by the diuretic. A larger quantity of sodium salts will be delivered to downstream

tubule segments where sodium is reabsorbed and potassium secreted. Potassium excretion increases as a result of several factors. (i) Increased distal tubule flow dilutes intraluminal potassium concentrations and reduces the gradient against which potassium must be secreted. (ii) Increased distal delivery of sodium combines with secondary hyperaldosteronism to increase distal sodium reabsorption and potassium secretion. (iii) High ADH levels increase distal potassium secretion. In addition, hydrogen ion secretion, stimulated by the increased distal tubule sodium delivery and hyperaldosteronism combines with potassium depletion, hypokalemia, and EABV contraction generate and maintain metabolic alkalosis. Metabolic alkalosis in turn further increases potassium secretion (see Fig. 8, Chapter VA2).

Consequently, hypokalemia and metabolic alkalosis, which are common complications of thiazides or loop diuretics, may be exacerbated by a high-salt diet. Conversely, moderate dietary salt restriction will decrease the severity of these metabolic complications. Paradoxically, extreme dietary salt restriction may also increase urine potassium losses because this diet increases markedly renin and aldosterone levels.

Hypokalemia and metabolic alkalosis can be prevented or ameliorated by coadministration of distal tubule "potassium-sparing" diuretics (see below).

Thiazides

Thiazides are very good first line diuretic agents for the treatment of nephrotic edema. These drugs are well absorbed from the gastrointestinal (GI) tract. In the blood plasma they bind strongly to plasma proteins. To produce a diuresis, the thiazides must be secreted into the proximal tubules by the organic acid secretory pathway and then be delivered to their principle site of action in early distal convoluted tubules where they inhibit the NaCl cotransporters. Thiazides also have modest carbonic anhydrase inhibiting activity in the proximal tubules.

The thiazides can produce a natriuresis of 5–10% of the filtered sodium load. Most are relatively long-acting drugs. Some, such as metolazone, generate almost continuous diuretic effects when taken once per day. Therefore, thiazides are less likely to cause periods of rebound salt retention as discussed above. For this reason, they are sometimes more effective agents than much more potent drugs which have brief periods of action. However, the persistent action of thiazides also increases the incidence and severity of hypokalemia and metabolic alkalosis.

Thiazide diuretics become much less effective when the GFR is below 25–30 ml/min. Organic acids accumulate in plasma of patients with renal insufficiency and compete with the thiazides for proximal tubule secretion. Further, even if thiazides are able to inhibit sodium reabsorption by 5–10% this modest

increment is difficult to discern under these conditions. The fractional excretion of sodium increases as the GFR falls, so that patients with severe renal dysfunction already excrete 5–10% of their filtered sodium load before administration of a diuretic. A further increase of 5% of the low filtered load of sodium may be of little clinical impact.

Although hypoalbuminemia and albuminuria may affect the diuretic action of the thiazides, these drug–protein interactions have not been well studied for this drug class. Protein–diuretic interactions are much better characterized with loop diuretics and probably contribute to the diuretic resistance which develops in nephrotic patients (see below). Similar interactions may affect the thiazide diuretics.

Loop Diuretics

When the response to thiazide diuretics is inadequate, loop diuretics may be successfully utilized. These potent drugs inhibit sodium reabsorption in the thick ascending limb of Henle (TALH) and can deliver up to 25% of the normal filtered load of sodium into the urine. Thus, they are called high ceiling diuretics. Loop diuretics are subclassified into two groups. The most commonly used loop diuretics belong to the furosemide-like group. In addition to furosemide, others in this group presently available in the United States include bumetanide and torsemide. The pharmacologic actions of these drugs are similar although they have differing potencies and rates and routes of metabolism.

Furosemide group diuretics bind to the chloride site of the Na/K/2Cl cotransporter located on the luminal epithelial surface of the TALH cells. To produce a diuresis these drugs must achieve a sufficient concentration within the lumen of the TALH. In plasma all loop diuretics bind very strongly to circulating proteins (90–99%). Therefore, these drugs are poorly filtered by the glomeruli. They reach the tubule lumen primarily via the organic acid (probenecid-sensitive) secretory pathway in the proximal renal tubules. Proximal tubule secretion of these drugs is directly proportional to their plasma concentration and inversely proportional to the GFR. Therefore, high plasma levels of loop diuretics are necessary to produce adequate intratubule concentrations when renal function deteriorates.

Plasma protein binding of loop diuretics has an important impact on their volume of distribution and peak plasma levels. Protein binding restricts and slows the movement of drugs out of the vascular space, which reduces their initial volume of distribution and increases peak plasma levels. The volume of distribution of loop diuretics is normally about 16% of body weight [2]. Marked hypoalbuminemia reduces protein binding of loop diuretics and may enlarge their initial volume of distribution. This decreases peak diuretic plasma levels and can decrease proximal tubule secretion of the drug. Such an effect

has been well documented in animal studies but has not been demonstrated to be clinically significant in most humans with nephrotic syndrome [11, 12]. However, it may become clinically relevant when the serum albumin concentration is reduced below 2 g/100 ml [2, 11]. If a patient with extreme hypoalbuminemia remains refractory to high doses of loop diuretics, premixing the diuretic with concentrated human albumin may improve efficacy. The suggested mixing ratio is 10 gm of albumin for every 40 mg of furosemide [11].

The pathophysiology of nephrotic syndrome may also contribute to loop diuretic resistance via another mechanism linked to the abnormally high albumin concentrations present within the lumen of the renal tubules. Although loop diuretics are >90% protein bound in the blood plasma, these proteins are stripped from the drugs when they are secreted into the proximal tubule. Within the tubule lumen diuretics normally remain free of protein. However, albumin which enters the tubules of nephrotic patients at high concentrations binds intraluminal diuretics and reduces the concentration of free diuretic. Loop diuretic inhibition of sodium transport in the TALH requires that high concentrations of free drug be delivered to this site [13]. Intraluminal protein binding may therefore inactivate the diuretic.

Consequently, nephrotic patients may require large doses of loop diuretics for multiple reasons. (i) Reduced plasma protein binding may increase the diuretic volume of distribution and thereby reduce secretion into proximal tubules (especially if albumin concentrations are less than 2 g/100 ml). (ii) Albumin binding within the lumen of the tubule reduces the luminal concentration of free diuretic within the TALH. (iii) Nephrotic syndrome generates potent antinatriuretic stimuli which must be overcome by diuretics. (iv) Sodium reabsorption beyond the TALH increases in response to the additional sodium load which is delivered and the high levels of aldosterone activity. (v) Proximal tubule sodium reabsorption probably increases. (vi) If the GFR is reduced, diuretic secretion into the renal tubules falls as a result of the smaller renal mass and competition with organic acids which accumulate in patients with renal failure. (This is further discussed in Diuretic Resistance and Synergistic Combinations)

Distal Tubule Potassium-Sparing Diuretics

Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride are very useful adjunctive drugs. When used as single agents these drugs are relatively weak diuretics. Their most important effect is inhibition of distal tubule collecting duct potassium and proton secretion. These three diuretics have different mechanisms of action. Spironolactone is a competitive inhibitor of aldosterone which competes for binding to mineralocorticoid receptors.

Blocking aldosterone activity decreases distal secretion of potassium and protons. Amiloride and triamterene both act principally from within the lumen of the distal tubule but probably via somewhat different mechanisms. These two drugs reduce sodium reabsorption through sodium specific channels in the distal tubules and collecting ducts. This decreases the negative electrical charge which sodium reabsorption normally generates within the lumen of these segments (this is related to the relatively low chloride permeability of these tubule segments). The negative electric charge which normally develops in these segments stimulates secretion of potassium and protons.

When administered together with thiazide and/or loop diuretics these distal tubule diuretics decrease kaluresis and reduce the frequency and severity of hypokalemic metabolic alkalosis. However, "potassium-sparing" distal tubule diuretics can cause severe hyperkalemia when used in patients with renal insufficiency and/or diabetes mellitus or when used together with other drugs which impair potassium secretion (i.e., ACE inhibitors, NSAIDS). Under these conditions electrolytes must be carefully monitored.

Diuretic Resistance and Synergistic Combinations

Patients who are, or become, resistant to high dose monotherapy with loop diuretics will often respond to the addition of thiazide diuretics. Chronic loop diuretic therapy produces structural and functional adaptations in the distal tubule beyond the TALH which increases sodium reabsorption at these sites [7]. This adaptation reduces the natriuresis produced by loop diuretics but actually increases the potential response to thiazides, which inhibit sodium chloride reabsorption in these downstream sites [17]. Therefore, combining a loop and thiazide diuretic may produce a marked synergistic effect [6].

When patients remain refractory to diuretic combinations, it is important to reinforce dietary salt restriction and consider checking the 24-hr urine sodium excretion rate to ascertain dietary compliance. Be certain that the patient is not using nonsteroidal anti-inflammatory drugs which can markedly blunt diuretic efficacy. If the loop diuretic or loop/thiazide combination produces brief periods of diuresis followed by intense antidiuresis, decrease the interval between doses of the loop diuretic. If diuresis remains inadequate, hospitalization may be required. Compliance with both dietary restrictions and medication prescription can then be ensured. It is reasonable to begin intravenous furosemide 40–60 mg. If this dose is transiently effective it can be repeated q 6–8 hr. If ineffective, increase the dose stepwise up to 120–160 mg (equivalent doses of bumetanide are 3–4 mg and torsemide 60–80 mg). If diuresis remains inadequate, begin oral metolazone 5–10 mg once per day together with parenteral loop diuretics 3–4 times/day. If the enteral route is not available or not effec-

tive, intravenous chlorothiazide, 500–1000 mg, should be administered together with high dose parenteral loop diuretics. If severe hypoalbuminemia (<2.0 mg/100 ml) exists and diuretic resistance persists, consider premixing loop diuretics with human albumin concentrate prior to parenteral administration (in a 40-mg furosemide/10-g albumin ratio) [11]. Continuous infusions of loop diuretics (furosemide 80–240 mg/hr or bumetanide 0.5–1 mg/hr) may be more effective and possibly safer than very large dose intermittent bolus infusions [18A].

Albumin infusions of 12.5–25 g q 6–8 hr may help initiate a diuresis in an otherwise refractory patient [3]. If EABV depletion exists, albumin infusions will temporarily expand the intravascular compartment, improve the GFR, and reduce levels of neurohormonal salt retaining mediators. However, most beneficial effects of albumin infusions are short-lived, because higher plasma albumin concentrations will raise the glomerular filtration rate of albumin and thereby increase its excretion and catabolism. This rapidly returns plasma albumin concentration to baseline levels. If vascular volume is not initially reduced, albumin infusions can produce hypertension, congestive heart failure, and pulmonary edema [18]. Hypertension in response to albumin infusion is especially common in nephrotic children. Despite its transient benefit and the potential adverse effects, judicious use of intravenous albumin can establish a diuresis in some nephrotic patients who prove resistant to all other interventions [3, 19]. Synthetic plasma volume expanders such as dextran and hetastarch may have a longer half-life and are less expensive than albumin. However, nonprotein colloid substitutes have been associated with allergic reactions and bleeding disorders. Experience with these substitutes is extremely limited in patients with the nephrotic syndrome.

End Point of Diuresis

When ECF, vascular, and EAB volume are all expanded (classic overflow pathophysiology), aggressive diuresis is clearly indicated and can be continued until these volumes normalize. However, when the EABV status is uncertain, or is clearly reduced, diuresis should be undertaken very cautiously and slowly. The weight, pulse, and blood pressure (both supine and standing) should be monitored frequently. Serum chemistries, including electrolytes, blood urea nitrogen (BUN), and creatinine must be regularly ascertained.

When a pharmacologic diuresis is initiated in an edematous adult nephrotic patient, the weight loss goal should be about 2–3 lb/day. This rate of diuresis can be continued until edema is reduced to tolerable levels. The rate of diuresis should be slowed before edema completely resolves. If clinical evidence of progressive EABV depletion develops, diuretics should be temporarily discontinued.

Successful diuresis will almost invariably cause the BUN to increase. This reflects an inevitable degree of EABV contraction. However, a progressive BUN increase may indicate that negative salt balance is too great, or is developing too rapidly. The BUN/creatinine ratio is also a helpful monitoring parameter. Urea and creatinine are relatively small compounds which are each freely filtered by glomeruli. But their proximal tubule transport properties are different. Urea is reabsorbed by the proximal tubule while creatinine is secreted. Proximal tubule urea reabsorption is principally a passive process. Increased sodium and fluid reabsorption will decrease the volume of proximal tubule fluid and thereby increase the urea concentration of the proximal tubule fluid. This enhances the gradient for urea reabsorption. Therefore, when the kidney is underperfused and proximal filtrate reabsorption accelerates, urea reabsorption also increases. However, creatinine continues to be secreted via the proximal tubule organic acid pathway regardless of volume status. To the extent EABV contraction decreases the GFR, filtration of urea and creatinine will both fall to a similar degree. Increased proximal tubule reabsorption of filtered urea further reduces its renal clearance, while tubule secretion of creatinine increases creatinine clearance above the GFR. In consequence, reduced renal perfusion will cause the BUN to increase disproportionally in comparison with the creatinine concentration and the BUN/creatinine ratio will increase markedly. Other factors which affect the BUN and creatinine concentrations must also be considered. For example, increased dietary protein loads, blood absorbed from the GI tract, parenteral amino acid loads, glucocorticoid therapy, and accelerated rates of catabolism increase urea generation rates and elevate the BUN. Ingestion of a low protein diet and/or severe hepatic disease reduce the rate of urea generation and the BUN. The major site of endogenous creatinine generation is skeletal muscle and at any level of renal function the creatinine concentration will vary directly with muscle mass. Small, poorly muscled individuals have lower creatinine concentrations, while creatinine levels are higher in large muscular men. Rhabdomyolysis causes creatinine release from necrotic muscles and acutely increases creatinine concentrations. Consequently, these variables may also affect the BUN and creatinine concentrations and the BUN/creatinine ratio. Nonetheless, these parameters remain useful indicators of renal perfusion and can help guide the intensity of diuretic therapy.

If progressive renal underperfusion develops or evidence of underperfusion of other vital organs becomes apparent, the diuretic dose should be decreased or stopped. If hypokalemia and/or metabolic alkalosis develop, they may also indicate overdiuresis. Potassium supplements or the addition of a distal tubule potassium-sparing diuretics may prevent or reverse these problems. Recheck the level of dietary sodium ingestion.

Once the edema and ascites have been reduced to tolerable levels, a regular dose of diuretic is usually necessary to maintain the weight and ECF volume at

desired levels. If dietary salt ingestion can be decreased adequately, diuretic therapy may be further reduced or even discontinued in some patients. However, most patients require continued diuretic therapy unless the underlying pathology improves.

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CHAPTER VA4

The Use of Diuretics in the Treatment of Ascites and Edema in Hepatic Cirrhosis

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INTRODUCTION

Cirrhosis of the liver is a major cause of salt and water retention. The tendency for accumulating fluid to localize in the peritoneal cavity is typical of cirrhosis and is far more pronounced than in congestive heart failure or the nephrotic syndrome. Although peripheral edema does occur with cirrhosis, it is generally of lesser magnitude and rarely dominates the clinical picture. In the late stages of cirrhosis, malnutrition and severe hypoalbuminemia may contribute to the development of massive edema.

The pathogenesis of the renal salt and water retention in patients with hepatic cirrhosis remains obscure. Two major fluid-retaining hypotheses have been advanced: (i) the underfill theory and (ii) the overflow theory. In this chapter we review the evidence in support of these two theories, discuss the indications for dietary salt restriction and diuretic therapy, the specific diuretic options which are available, common complications of diuretic therapy, complications specific to the cirrhotic population, and briefly review other therapeutic modalities.

Diuretic Agents: Clinical Physiology and Pharmacology

MECHANISMS OF ASCITES AND EDEMA FORMATION IN HEPATIC CIRRHOSIS [37, 39]

The Classic Underfill Hypothesis

A great deal of clinical and experimental evidence is consistent with the classic underfill hypothesis which is outlined in Fig. 1. Hepatic pathology produces scarring, fibrosis, and nodular hypertrophy of the liver. These anatomic alterations restrict the flow of blood out of hepatic sinusoids producing postsinusoidal venous blockade. Hydrostatic pressure within the sinusoids increases and the higher pressures are transmitted into the splanchnic veins and mesenteric capillary beds. These elevated hydrostatic pressures accelerate the filtration of fluid into the hepatic interstitium (spaces of Disse). The epithelium lining hepatic sinusoids is very permeable to albumin (it has a low albumin reflection coefficient), so that the fluid which accumulates in the hepatic inter-

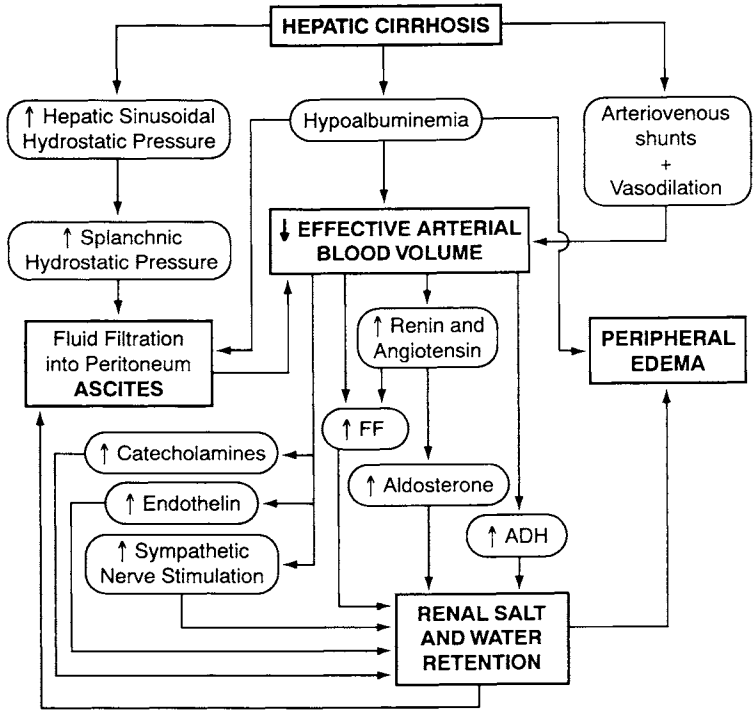

FIGURE 1. Renal salt and water retention and the development of ascites and edema in patients with cirrhosis: the underfill hypothesis. See text for explanation.

stitial spaces has a high albumin concentration. Fluid also accumulates on the surface of the liver and weeps into the peritoneal space. High venous and capillary pressures in other intraabdominal organs produces edema in these locations and some of this fluid also collects in the peritoneal space. Peritoneal fluid derived from these nonhepatic sources has a lower albumin concentration. The ascitic fluid originating from the liver mixes with fluid from other intraabdominal organs and results in ascites with a relatively high albumin concentration. However, in virtually all (~98%) patients with ascites due to portal hypertension, the gradient between the serum and the ascitic albumin concentrations exceeds 1.1 g%, i.e., a serum–ascitic albumin gradient (SAAG) > 1.1 g% [22].

The accumulation of interstitial fluid and ascites markedly increases lymph flow. Lymphatic flow through the thoracic duct can increase 20-fold. During the early phases of cirrhosis, this compensatory response prevents the accumulation of a large quantity of ascites. However, the high rate of fluid filtration eventually overwhelms this compensatory response, resulting in intraabdominal organ edema and progressive ascites. As liver function deteriorates, the albumin synthetic rate falls and combines with malnutrition to produce hypoalbuminemia. The resulting low colloid oncotic pressure increases the transudation of fluid into the abdominal cavity and the peripheral interstitial spaces.

The fluid shift from the vascular to the interstitial and peritoneal spaces reduces the effective arterial blood volume (EABV) (see Chapter VA1), activating multiple counterregulatory responses. The responding mediators include the renin–angiotensin system, aldosterone, antidiuretic hormone, sympathetic nerves, catecholamines, thromboxane, neuropeptide Y, and endothelin. This neurohormonal cascade increases renal salt and water retention and constricts renal blood vessels. However, despite the elevated levels of multiple vasoconstrictors, systemic vasoconstriction does not develop in most cirrhotic patients. In fact, these patients are usually vasodilated and arteriovenous shunting develops in the skin and pulmonary circulations. Cardiac output increases and blood pressure falls. Thus, the circulatory status of cirrhotic patients is "hyperdynamic." The pathogenesis of the vasodilated, shunted circulation of cirrhosis remains unknown.

Under normal circumstances, whenever vasoconstricting and salt retaining cascades are elicited by some stimulus such as hemorrhage, a simultaneous series of counterbalancing modulating systems is also activated. These modulating factors prevent unrestrained systemic vasoconstriction and renal salt retention which would be deleterious. The moderating mediators include vasodilatory prostanoids, atrial and other natriuretic peptides, kinins, nitric oxide, and a number of other less well-defined vasodilating and natriuretic substances including substance P, β-endorphins, and adrenomedulin. In patients with congestive heart failure or the nephrotic syndrome, vasoconstricting and vaso-

dilating forces also develop simultaneously. However, with hemorrhage, heart failure, and nephrotic syndrome the balance generally favors systemic vasoconstriction. In contrast, vasodilation is usually dominant in the systemic circulation of most cirrhotic patients. Recent studies have focused on the potential role played by nitric oxide, a locally generated systemic vasodilator. Cirrhotic patients may develop low grade intermittent endotoxemia which can trigger nitric oxide generation. Excess nitric oxide generation may be one of the features which distinguishes cirrhosis from the other salt-retention disorders [2].

The kidneys of patients with advanced cirrhosis are an exception to this rule—renal vessels usually constrict. The EABV falls as a result of systemic vascular shunting, systemic vasodilation and translocation of fluid into the interstitium and peritoneum. The low EABV increases neurohormonal mediators which produce renal vasoconstriction. Contraction of the glomerular efferent arterioles is more intense than the glomerular afferent arterioles. This pattern of arterial constriction stabilizes glomerular filtration despite the low EABV and/or blood pressure. Renal plasma flow falls to a greater extent than the glomerular filtrate rate and this increases the filtration fraction (FF = GFR/RPF). A high filtration fraction stimulates proximal tubule sodium and fluid reabsorption (see Chapter VA1).

Many of the neurohormonal vasoconstricting responses listed above, including angiotensin II (which stimulates aldosterone), catecholamines, ADH, and activation of adrenergic nerves also increase renal salt and water reabsorption. The fall in EABV may be partially corrected, but a large fraction of the retained fluid accumulates in the peritoneal cavity. This occurs because of the Starling block which exists across the liver due to the restriction to blood flow out of the hepatic sinusoids.

In summary, the underfill hypothesis requires (1). Fluid shifts out of the vascular compartment (as a result of hypoalbuminemia and the restricted blood flow out of hepatic sinusoids) and (2). This stimulates the kidneys to retain salt and water. The retained salt and water is transferred into the peritoneal cavity and this prevents ECF expansion from normalizing the EABV. A-V shunts and generalized vasodilation also contribute to the low EABV and stimulate renal salt retention. Vascular shunting and peritoneal sequestration of fluid may result in unrelenting renal salt and water retention.

The underfill model receives support from studies of cirrhotic patients subjected to head-out water immersion [4]. This maneuver redistributes blood volume from peripheral capacitance vessels to the central circulation and expands EABV. The antinatriuretic and antidiuretic forces described above are often ameliorated and a diuresis frequently ensues. These results are consistent with the inference that cirrhosis is a disorder which produces a low EABV, as a result of peripheral vasodilation and A-V shunting, despite a high cardiac output and an expanded extracellular fluid (ECF). To the extent that the EABV can be normalized the antinatriuretic and antidiuretic stimuli are reduced or eliminated.

The classic underfill hypothesis described above and shown in Fig. 1 requires that ascites and edema develop before the EABV contracts and before renal salt retention occurs. However, it is possible that primary expansion of vascular capacity (i.e., A-V shunts) develops first and that this is the proximal cause of the reduced EABV and renal salt and water retention. If this occurred, then renal salt and water retention could precede development of overt ascites or edema [25]. This modification of the underfill hypothesis has been strongly advanced by Schrier [25, 39]. Ascites and edema formation may then follow rather than precede renal salt retention.

The Overflow Hypothesis

The underfill hypothesis has been challenged on several fronts. Lieberman, Levy, their co-workers, and others have advanced clinical and experimental data which challenge the early sequence shown in Fig. 1 [15,16]. Careful studies of dogs with experimental cirrhosis and patients with early hepatic cirrhosis demonstrate that renal salt and water retention can develop prior to the formation of ascites or edema. The classic underfill hypothesis requires that ascites and/or edema develop first, to reduce the EABV and thereby activate neurohormonal cascades which increase renal salt and water retention. (The modified underfill hypothesis which begins with vasodilation and shunting was discussed above. The data are consistent with that modification.)

In contrast, the overflow hypothesis begins with hepatic abnormalities which in some way cause the kidneys to retain salt and water. This salt retention precedes detectable ascites or edema. This sequence leads to ECF expansion and ascites and edema then follow (Fig. 2). Proponents of the overflow theory believe that cirrhosis and hepatic sinusoidal hypertension activate sensors in the liver which directly, or indirectly, stimulate the kidney to retain salt and water. The retained salt and water are preferentially sequestered in the peritoneal space as a result of hypoalbuminemia and the high hepatic sinusoidal and splanchnic capillary pressures.

The earliest signals for salt retention remain unknown, but they can be blocked or blunted by the creation of a portocaval shunt which prevents the development of portal hypertension [30]. The kidneys of successfully shunted animals with early cirrhosis do not retain salt and water. Closure of the portasystemic shunt promptly increases portal and intrahepatic pressures and quickly leads to salt and water retention and then ascites formation.

Several clinical observations have been used as support of the overflow hypothesis. Spontaneous diuresis and natriuresis occur in some cirrhotic patients in the absence of any measurable change in vascular volume. In these patients, a low vascular volume (?EABV) may not be the proximate cause of salt and water retention [13]. Some cirrhotic patients will diurese in response to intra-

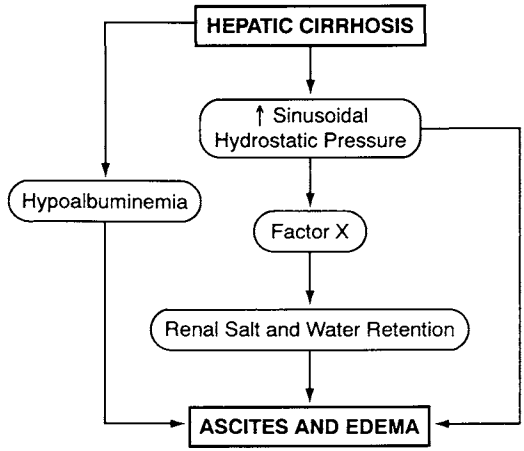

FIGURE 2. Renal salt and water retention and the development of ascites and edema in patients with cirrhosis: The Overflow Hypothesis. Factor X refers to signals from hepatic volume and pressure sensors which are transmitted to the kidney via a neural and/or hormonal mechanism. See text for explanation.

vascular volume expansion, produced either by the infusion of intravenous fluids or head-out water immersion, but many others do not respond to such maneuvers [4, 29]. The absence of a diuretic response indicates that the underfill hypothesis may not be operative in these patients. However, an alternative explanation is that the degree of volume expansion achieved in these individuals may not have adequately expanded the EABV.

It is possible that the overflow hypothesis operates during the earliest phases of cirrhosis, whereas underfill dynamics develop later when hepatic decompensation progresses. The clinical findings in almost all patients with advanced liver disease are most consistent with an underfilled state.

TREATMENT OF ASCITES AND EDEMA IN PATIENTS WITH HEPATIC CIRRHOSIS [35, 37]

Salt restriction and diuretics may be used in patients with cirrhosis to reduce mechanical derangements and enhance patient comfort. However, these treatments do not correct or reverse the underlying hepatic abnormalities. The therapeutic goal of such therapy is the reestablishment of salt and water balance at more clinically acceptable levels of ascites and edema. Complete elimination of detectable edema and ascites is rarely possible or desired. Indeed, attempts to eliminate completely edema and ascites may produce circulatory insuffi-

ciency and precipitate renal failure. Aggressive diuretic efforts are also likely to produce profound electrolyte abnormalities.

Tense ascites and edema do produce significant adverse clinical consequences which can be mitigated by judicious treatment. Ascites can exacerbate gastroesophageal reflux, contribute to anorexia, and possibly increase portal venous pressures, which will heighten the risk of variceal bleeding. Massive ascites in cirrhotic patients commonly becomes infected and the abdominal wall pressure may produce umbilical eventration skin ulceration and necrosis. Elevation of the diaphragms restricts respiration and contributes to development of basilar atelectasis.

Diet and Bed Rest

The safest and most conservative treatment of cirrhotic ascites and edema is the institution of bed rest and a low salt diet. This regimen will produce significant clinical improvement in 20–30% of cirrhotic patients [7]. Bed rest reduces lower extremity venous pooling, shifts some blood from splanchnic to central vessels, and expands the EABV. Although bed rest clearly promotes diuresis and natriuresis, it is only a temporizing maneuver.

Restricting salt intake below the rate of renal excretion will obviously result in negative salt and water balance. However, renal salt excretion may be extraordinarily low in cirrhotic patients, so the required degree of dietary sodium restriction may be difficult or impossible to achieve. Although some investigators suggest that dietary sodium be reduced below 500 mg/day (about 1300 mg of NaCl or 22 mEq of Na^+), this is generally only possible when patients are hospitalized. Moreover, diets with this degree of sodium restriction are generally unpalatable and interfere with efforts to improve nutrition. A more realistic level of outpatient salt restriction is about 2 g/day of sodium (about 5 g NaCl or 87 mEq Na^+). The fact that some cirrhotic patients excrete only 10–20 mEq of Na^+ per day means they will continue to gain weight on such a regimen. When bed rest and dietary salt restriction do not adequately control ascites and edema, diuretics are initiated. However, after initiation of diuretic therapy, a low salt diet remains an important component of the treatment regimen. This will enhance the efficacy of the diuretic and reduce the incidence and severity of diuretic-associated electrolyte complications (see Section on Diuretics, Chapter VA3).

Diuretics [35–37]

Spironolactone and Other Potassium-Sparing Diuretics

Traditionally, the first diuretic used in patients with cirrhosis is the aldosterone antagonist, spironolactone, at an initial dose of 50–100 mg/day. This competi-

tive inhibitor of aldosterone is rapidly metabolized to a number of compounds which undergo slower metabolism and excretion. Several of these spironolactone metabolites also have aldosterone blocking and diuretic activity. In fact, the aldosterone metabolite potassium canreneate is available as a diuretic in Europe. As a result of these metabolites, the biologic diuretic activity of spironolactone is prolonged; hepatic dysfunction causes an accumulation of these metabolites and longer periods of activity [28]. Spironolactone and its active metabolites bind to the mineralocorticoid receptors in the cytoplasm of the cortical and medullary collecting tubule cells (and other mineralocorticoid sensitive tissues) and block the mineralocorticoid effects of aldosterone. In general, 7 to 10 days of spironolactone therapy is required to achieve the maximal effect of a given dose in patients with hepatic cirrhosis. Consequently, it is advisable to wait a week or more before deciding whether a given dose is effective. The maximal therapeutic dose of spironolactone is about 400 mg/day [28].

Many, but not all, cirrhotic patients have a good diuretic response to spironolactone monotherapy [5]. When spironolactone resistance is encountered there are several possible explanations. Spironolactone and its metabolites competitively block the action of aldosterone; therefore, they have little effect when endogenous aldosterone levels are low. Although most patients with decompensated cirrhosis have high aldosterone levels, this is not universally true [24]. Spironolactone will generally be ineffective in this low aldosterone subgroup. Conversely, when aldosterone levels are extremely high, they may not be adequately blocked by a competitive inhibitor. Another potential cause of spironolactone resistance is low distal tubule delivery of sodium salts. Aldosterone can only increase reabsorption of sodium which is delivered to the aldosterone-sensitive distal sites. Avid sodium reabsorption by the proximal tubule, thick ascending limb of Henle (TALH), and early distal tubule will reduce markedly sodium delivery to the late distal and cortical collecting tubules. Under such circumstances even very high aldosterone levels do not produce much sodium reabsorption and blocking aldosterone activity with spironolactone in these patients can only produce a modest diuretic effect. Addition of other diuretics with more proximal effects will deliver sodium to more distal sites where spironolactone acts.

Many spironolactone side-effects result from its potent antiandrogenic activity. Indeed, this side-effect has been effectively employed to treat patients with hyperandrogenic hirsutism and/or acne. This effect can cause painful gynecomastia in many patients receiving this drug. The electrolyte derangements produced by spironolactone include hyperkalemia and hyperchloremic metabolic acidosis. They occur with increased frequency in patients with a reduced renal function.

Amiloride and triamterene are other potassium-sparing diuretics which in-

hibit sodium reabsorption in the cortical collecting tubule (CCT). These are relatively weak diuretics with a 12- to 24-hr duration of action. Unlike spironolactone, amiloride and triamterene are not competitive inhibitors of aldosterone; their diuretic activity is independent of the aldosterone level. The effects of amiloride have been better characterized. The drug acts on the luminal membrane of the CCT to block sodium reabsorption through the sodium channels in this tubule segment. Triamterene has similar transport inhibiting effects, but its mechanism of action may be somewhat different. Like spironolactone, these two drugs can generate a meaningful diuresis only when a significant quantity of sodium is delivered to the CCT.

Both drugs reduce the negative electrical potential difference which sodium reabsorption usually produces in the CCT. This negative charge is critical for distal tubule potassium and proton secretion. Consequently, as with spironolactone, serum electrolytes must be monitored to detect hyperkalemia or hyperchloremic metabolic acidosis.

Triamterene also has several unique side-effects. The drug can precipitate within the distal renal tubules and has been associated with acute renal insufficiency, especially when it is used together with nonsteroidal anti-inflammatory drugs. Clinically significant kidney stones, composed principally of triamterene, have also been reported.

Loop Diuretics

When potassium-sparing distal tubule diuretics do not generate an adequate diuresis, loop diuretics may be substituted or added. Loop diuretics are often required when the GFR is reduced [20]. In general, furosemide pharmacokinetics are similar in patients with cirrhosis and those seen with normal liver function with comparable levels of renal function [32]. However, extrarenal clearance of bumetanide and torsemide are reduced in cirrhotic patients. Therefore, the blood levels and renal delivery of these two loop diuretics are increased in cirrhotic patients [12, 17]. When cirrhotic patients also develop advanced renal insufficiency, high peak plasma levels of loop diuretics are necessary to produce adequate intratubule drug concentrations. Under such circumstances, severe hypoalbuminemia may reduce diuretic efficacy. Less diuretic bound to albumin will increase the drug's volume of distribution and thereby decrease peak diuretic plasma levels (see Section on Diuretics, Chapter VA3 [10]. However, this effect is probably only clinically significant when severe (<2 g/100 ml) hypoalbuminemia and renal failure coexist.

Even when adequate concentrations of a loop diuretic are delivered to the active site of action in the TALH, some cirrhotic patients may remain diuretic resistant. This resistance represents a pharmacodynamic phenomenon of un-

certain mechanism but is probably due to increased sodium reabsorption in the proximal tubules and the distal tubule segments beyond the TALH. Thiazides can be used to overcome this form of resistance (see below).

A reasonable initial oral dose of furosemide in a cirrhotic patient with relatively normal renal function is 40–80 mg. Equivalent doses of bumetanide are 1–2 mg and of torsemide 25–50 mg. If renal function is reduced the initial dose may be doubled or tripled. The two more recently introduced loop diuretics are more completely and reliably absorbed from the GI tract than furosemide. Torsemide also has a longer half-life than furosemide (about 3 hr compared with 1 hr in normal subjects) and its duration of action is further prolonged in patients with cirrhosis.

Once an effective dose of loop diuretic is established, further increases of each dose have minimal additional effect (i.e., the dose–response curve becomes flat once an effective dose is reached). If each dose of loop diuretic is effective but the daily magnitude of diuresis remains insufficient, then periods of avid sodium retention between doses may explain such resistance. The impact of this phenomenon can be reduced by decreasing salt intake, switching to diuretics with a longer half-life (such as torsemide) or increasing the frequency of administration of the diuretic.

Combination Loop and Thiazide Diuretics

Thiazide diuretics rarely generate an adequate diuresis when used alone in cirrhotic patients. However, this class of diuretics has synergistic effects when combined with loop agents [19]. Furosemide is a potent inhibitor of sodium absorption in the TALH. Thiazides have a weak proximal tubule carbonic anhydrase inhibiting effect and more potent effects in the early distal cortical tubule. Combining a thiazide and loop diuretic is often synergistic because the loop diuretic inhibits sodium reabsorption in the TALH and markedly increases sodium delivery to the thiazide-sensitive distal cortical tubule. Combining a long-acting thiazide or thiazide-type drug, such as metolazone, with furosemide is often a successful strategy. If parenteral diuretics become necessary, intravenous chlorothiazide, at doses of 500–1000 mg/day, may be combined with an intravenous loop diuretic. These very potent diuretic combinations can rapidly produce hypovolemia and extreme electrolyte abnormalities, especially hypokalemia. Therefore these patients must be carefully monitored clinically and biochemically.

Other Diuretic Combinations

Patients who remain diuretic-resistant despite use of thiazide/loop diuretic combinations occasionally will respond to the addition of mannitol which ex-

pands the extracellular compartment, increases the GFR, and increases solute delivery out of the proximal tubule. An intravenous bolus of 12.5 to 25 g of mannitol may be administered q 6–8 or 250–500 ml of a 20% mannitol solution may be infused. Although the potent carbonic anhydrase inhibitor acetazolamide will also increase delivery of filtrate out of the proximal tubule, this drug should probably not be utilized in cirrhotic patients because it frequently produces hypokalemia and simultaneously alkalinizes the urine. The potential pernicious effects of these biochemical derangements are discussed under Diuretic Complications, below.

Another therapeutic option which may potentiate diuretic efficacy is expansion of the intravascular space with infusions of salt-poor albumin. Albumin infusions are very expensive and beneficial effects are relatively transient. Nonetheless, markedly hypoalbuminemic patients who are resistant to diuretic combinations may respond favorably to short-term courses of intravenous albumin. Although nonprotein colloids such as hydroxyethyl starch or polymerized gelatin solutions are less expensive, the albumin substitutes may exacerbate bleeding problems in these patients and can also be immunogenic [31].

Low dose dopamine infusions dilate renal arterioles, inhibit renal epithelial sodium transport, and produce a brisk diuresis in normal subjects. On occasion, the addition of dopamine or dopamine agonists will generate a diuresis in otherwise refractory patients with cirrhosis [23]. In general, this is reserved for patients with near end-stage hepatic decompensation.

End Points for Diuresis

The goal of diuretic therapy in patients with cirrhosis is a reduction of the volume of ascites and degree of edema to clinically tolerable levels. Overdiuresis will result in orthostatic hypotension, organ ischemia, metabolic derangements, and progressive cardiovascular collapse. Aggressive diuresis has also been implicated in the development of fatal hepatorenal syndrome. Patients treated with diuretics require careful monitoring and the diuresis must be slowed or stopped when complications develop. Clinical parameters including the weight and the supine and upright pulse rate and blood pressure should be monitored regularly. The BUN, creatinine, and electrolyte concentrations must also be measured at regular intervals.

The BUN of cirrhotic patients may be reduced as a result of their low dietary protein intake and decreased hepatic urea synthesis. Their creatinine concentration is also often reduced because these patients frequently have muscle wasting. Consequently, both the BUN and creatinine concentrations may overestimate the GFR. Acute changes in the BUN and creatinine concentrations and the BUN/creatinine ratio can be very helpful markers of renal perfusion and ischemia (see Section on End Points for Diuresis, Chapter VA2).

Cirrhotic patients with ascites can be divided into two groups on the basis of the presence or absence of significant peripheral edema. Shear and co-workers demonstrated that edema fluid can be mobilized into the vascular compartment much more rapidly than ascitic fluid [26]. This permits a diuresis to more rapidly remove edema than ascites. Peripheral edema can be mobilized at rates up to one liter/day, while ascites returns to the vascular space at only about half this rate. Consequently, cirrhotic patients with generalized edema and ascites can tolerate aggressive diuresis with fewer adverse hemodynamic and biochemical derangements than those without edema. The maximal rate of weight reduction in the cirrhotic patient with ascites and generalized edema should be no more than 1–1.5 kg/day, while it is only about 0.3–0.5 kg/day in those without edema [21, 26].

Diuretic Complications

Renal underperfusion combined with persistently high ADH levels produces continuous concentration of the urine. Therefore, water loads cannot be excreted and hyponatremia is common in cirrhotic patients. The development of hyponatremia indicates that the neurohormonal forces which reduce renal dilation capacity are activated and suggests that the liver disease is advanced. Consequently, spontaneous hyponatremia in cirrhotic patients is associated with a poor prognosis (this is also true in patients with CHF) [1]. The tendency of these patients to develop hyponatremia is exacerbated by aggressive diuresis, especially when thiazides are utilized. The thiazides reduce renal diluting capacity but do not decrease renal concentrating function. Consequently, patients who receive thiazides are still capable of excreting very concentrated urine in response to renal hypoperfusion, increased proximal tubule reabsorption and high ADH levels. Loop diuretics impair both diluting and concentrating mechanisms and are less likely to exacerbate hyponatremia. Water restriction should be initiated when the sodium concentration falls below 130 mEq/liter. In the near future drugs which specifically block the renal effects of ADH should become available for use in patients with persistent hyponatremia.

Thiazide and/or loop diuretics increase delivery of sodium-rich fluid to the aldosterone-sensitive distal nephron. This markedly increases distal renal tubule potassium and hydrogen secretion. Increased distal salt and water delivery will dilute the tubule fluid potassium concentration and improve the gradient for potassium secretion. In addition, distal delivery of sodium salts to aldosterone-stimulated tubules increases distal sodium reabsorption and the secretion of potassium and hydrogen. Hypokalemia and metabolic alkalosis develop. The alkalosis is then be maintained as a result of hypokalemia, decreased EABV, and high angiotensin II levels. High ADH levels will also stimulate distal tubule

potassium secretion. A prospective study of furosemide therapy in cirrhotic patients reported clinically significant hypokalemia developed in 16% [18]. The combination of hypokalemia and metabolic alkalosis has a number of important adverse effects.

The electrolyte abnormalities produced by diuretic therapy can precipitate or exacerbate hepatic encephalopathy. Hepatic encephalopathy is partly due to the accumulation of ammonia and other ionized nitrogenous compounds within the brain. Hypokalemia is a potent stimulus for renal ammonia generation. In part, this is due to movement of potassium out of renal tubule cells and the movement of protons into these cells. This causes relative intracellular acidosis. A low intracellular pH in the renal proximal tubule cells stimulates ammoniagenesis. Ammonia synthesized by renal tubule cells exits the kidney either by entering the urine or via the renal vein. Many factors affect the ammonia partition ratio between urine and renal vein, but one of the most important is the pH of renal distal tubule fluid and urine. An acid pH in the distal tubule fluid shifts tubule fluid ammonia from NH_3 to NH_4^+ as a result of the reaction $NH_3 + H^+ \rightarrow NH_4^+$. NH_3 is much more permeable across cell membranes than ionized NH_4^+. The low pH within the lumen reduces the NH_3 concentration and this increases the gradient for NH_3 to diffuse from renal tubule cells and interstitium into the tubule lumen. Thus, acidification of distal tubule fluid "traps" ammonia in urine and increases the fraction of total ammonia which is excreted rather than transported to the systemic circulation via the renal vein (see Fig. 3). Conversely, an alkaline urine produces the opposite effect, reducing the fraction of ammonia trapped in the urine and this increases the fraction of total synthesized ammonia which enters the renal vein. As a result hypokalemic metabolic alkalosis can increase plasma ammonia levels markedly by (i) increasing total renal production and (ii) favoring its transfer to the systemic circulation.

Hypokalemic alkalosis has additional adverse systemic ammonia effects. The principles of nonionic diffusion trapping discussed above in reference to the kidney and renal tubules also apply at the ECF/intracellular fluid interface. An alkaline blood pH increases the relative concentration of blood NH_3 by shifting the reaction $NH_3 + H \leftrightharpoons NH_4^+$ to the left. A higher NH_3 concentration increases the entry of NH_3 into brain cells. In addition, as discussed, hypokalemia can produce relative intracellular acidosis (potassium moves out of cells into the ECF and protons move in the opposite direction). The lower intracellular pH shifts the above reaction to the right and decreases the intracellular NH_3 concentration. The net effect is a gradient which favors movement of ammonia into cells (see Fig. 3).

Consequently, hypokalemic alkalosis increases the total renal ammonia synthetic rate and elevates the proportion of renal ammonia production which en-

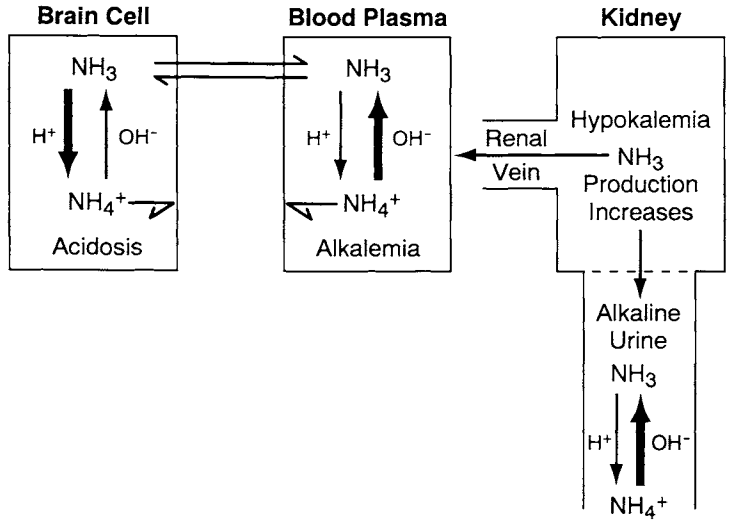

FIGURE 3. The effect of hypokalemic metabolic alkalosis on renal ammonia synthesis and renal and systemic ammonia distribution. Hypokalemia markedly increases renal ammoniagenesis. Metabolic alkalosis increases urine pH which raises the urine concentration of NH_3 and thereby reduces urine ammonia "trapping." Consequently, a larger fraction of ammonia synthesized by the kidney leaves via the renal vein. In the systemic blood, NH_4^+ is the predominant form. However, the very low concentration of NH_3 is critically important because it is this moiety which penetrates into cells. The NH_3 concentration in blood plasma is increased by alkalemia and this increases cell entry of ammonia. Simultaneously, intracellular acidosis, produced by the hypokalemia, shifts the ammonia within cell cytoplasm toward NH_4^+. The lower intracellular NH_3 concentration further increases cell entry of ammonia. These plasma and intracellular effects combine to enhance the movement of ammonia from plasma into brain cells. The net result of hypokalemic metabolic alkalosis is enhanced renal ammoniagenesis, preferential partitioning of the generated ammonia into the renal vein, and an increased gradient for the movement of NH_3 from blood plasma into brain cells. This contributes to hepatic encephalopathy.

ters the renal vein. This raises total plasma ammonia concentrations and the alkaline blood pH also raises the concentration of blood NH_3. Within brain cells intracellular acidosis reduces the concentration of NH_3 and this enhances NH_3 movement into the cells. Because of these effects, the incidence and severity of hepatic encephalopathy is greatly increased by hypokalemic alkalosis. Furosemide therapy has been implicated in the development of hepatic encephalopathy in 19% of cirrhotic patients treated with this drug [18].

Combining thiazide and/or loop diuretics with distal tubule potassium-sparing drugs will reduce the incidence and severity of these electrolyte complications. Potassium supplementation may still be necessary for some patients despite addition of distal tubule diuretics. Others patients may develop severe

hyperkalemia when potassium-sparing drugs are administered. The response of an individual patient to the addition of a potassium-sparing diuretic is unpredictable. Consequently, frequent electrolyte determinations are required whenever diuretics are initiated or doses are changed.

Hepatorenal syndrome represents a state of severe, generally irreversible but functional renal underperfusion associated with intense salt and water reabsorption and progressive azotemia. The kidneys of the patient with hepatorenal syndrome are responding to vigorous salt and water reabsorptive stimuli but remain intrinsically normal. If removed from their cirrhotic environment these kidneys function normally. For example, kidneys donated by patients who die with fatal hepatorenal syndrome will function normally when transplanted into recipients with normal liver function. Hepatorenal syndrome is generally unresponsive to volume expansion and/or administration of high dose diuretics. Indeed, if the urine output and renal function improve in response to such maneuvers, the diagnosis of hepatorenal syndrome was probably incorrect. Full-blown hepatorenal syndrome is fatal unless liver function improves or a successful liver transplant can be accomplished. Occasional cases of the hepatorenal syndrome seem to have been precipitated by aggressive diuretic therapy.

Cirrhotic Patients Refractory to Combination Diuretics

The massive ascites and edema of some cirrhotic patients cannot be reduced despite the above therapeutic interventions. In such patients large volume paracentesis (5–8 liters) can alleviate many of the symptoms associated with tense ascites. In the past, large volume paracentesis was discouraged for fear that it would produce severe intravascular volume depletion and cardiovascular collapse. However, recent studies show that large volume paracentesis can be safely carried out [11]. Indeed, several controlled studies suggest that the complication rate associated with this procedure is lower than that produced by aggressive diuretic therapy. Large volume paracentesis has become a relatively common outpatient procedure [8].

Intravenous expansion with albumin or nonprotein colloids is sometimes combined with paracentesis but the benefit of such adjunctive therapy generally remains unproven. If large volume paracentesis produces hemodynamic instability, or if more than 5 liters of ascitic fluid is to be removed, then postparacentesis azotemia and hyponatremia may be minimized by the administration of 40–60 g of albumin intravenously [9].

Ascites reinfusion simultaneously reduces the ascitic volume and expands the intravascular compartment. For selected patients, ascites reinfusion may

correct the low EABV and reverse diuretic resistance. More recently, internal subcutaneous peritoneovenous shunts have been utilized for this purpose [14]. These internal shunts, inserted under local anesthesia, are associated with a relatively low incidence of infection, permit rapid ambulation and may contribute to earlier hospital discharge. However, peritoneovenous shunts are also associated with a number of complications including disseminated intravascular coagulation, variceal bleeding, and sepsis. Shunt failure due to canula occlusion also occurs commonly. When first introduced, these shunts were considered a major advance and were widely utilized. However, experience has tempered enthusiasm for this approach. Although peritoneovenous shunts reduce certain categories of morbidity, they simultaneously increase other forms of morbidity and have had little impact on overall mortality [27]. Peritoneovenous shunts are now considered a therapeutic option only when end-stage cirrhotic patients have become diuretic resistant.

The transjugular intrahepatic porta-systemic shunt is in an expandable metal mesh intravascular stent used to create a fistula between the hepatic venous and portal venous circulations. The device, inserted percutaneously, reduces portal pressures and was first deployed to treat variceal bleeding [3]. However, it was soon noted that coexistent ascites often improved or resolved after placement of such shunts. Apparently, the reduction in hepatic sinusoidal and splanchnic pressures together with increased cardiac return reduced the ascitic formation rate and increased renal salt excretion [34]. This device has been most often used in patients with end-stage liver disease.

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CHAPTER VA5

Diuretics in Pregnancy

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INTRODUCTION

At one time diuretics were used routinely for edema occurring in pregnancy. Their use became controversial, however, when it was reported that diuretics caused a reduction in the clearance of certain steroids metabolized by the placenta and that pregnant women with edema were noted to have heavier babies than women taking diuretics [8, 16]. However, there is no evidence in any study that diuretics are harmful to the fetus, and given their importance in the treatment of hypertension this chapter will examine their use in pregnancy complicated by hypertension.

EDEMA IN PREGNANCY (TABLE 1)

Edema is a frequent and normal finding in uncomplicated pregnancy, occurring in approximately 35% of pregnant women. It may be generalized or limited to the extremities; in a study of 58,800 pregnant women edema of the lower extremities was noted in 28%, whereas swelling of the face and hands occurred in 10% [5]. Approximately 500–900 mEq of sodium is retained during pregnancy to meet the needs of the fetus and the expansion of maternal blood volume;

Diuretic Agents: Clinical Physiology and Pharmacology

TABLE 1 Proposed Mechanisms for Edema during Pregnancy

1. Sodium retention secondary to sympathetic activation
2. Sodium retention induced by a fall in peripheral vascular resistance and subsequent increased venous capacity
3. Hormonally mediated sodium retention (renin–angiotensin–aldosterone, estrogen, deoxycorticosterone)
4. Inferior vena caval compression
5. Decreased plasma oncotic pressure

300–400 mEq is stored in the maternal extracellular space, and the remainder in the fetus, placenta, and amniotic fluid. A major stimulus for salt retention is the fall in peripheral vascular resistance which occurs with pregnancy. This results in increased vascular capacity, a recognized stimulus to renal sodium reabsorption. Likely causes of the peripheral vasodilation in pregnancy include increased endothelial synthesis of PGI_2 (prostacyclin) and PGE_2, as well as increased levels of estrogen and progesterone. Additionally, the placenta acting as an arteriovenous shunt probably imparts some effect [12]. During pregnancy vessels become refractory to the pressor effects of angiotensin II, probably due to the increased synthesis of PGI_2. Whether this phenomenon plays a major role in vasodilation is uncertain [7]. Although aldosterone secretion increases during pregnancy, its role in the expansion of extracellular volume is unclear [11]. Certainly it is difficult to make a case for aldosterone causing sodium retention in preeclampsia, as aldosterone usually falls from levels seen in normal pregnancy, and preeclampsia with edema has been reported in patients with Addison's disease [3]. Other hormones with sodium retentive properties, including estrogen and deoxycorticosterone, are found in increased amounts in pregnancy and probably contribute to edema formation [6]. The role of ANP (atrial natriuretic peptide), for which normal levels have been measured in the volume-expanded, pregnant state, is unknown [9]. In late pregnancy, additional factors that may contribute to edema include compression of the inferior vena cava by the enlarging uterus and reduction in plasma oncotic pressure.

PREECLAMPSIA

Although edema is common in pregnancy, edema associated with rapid weight gain and a rise in blood pressure are the first signs of preeclampsia [3]. The edema with preeclampsia shares some similarities with angioneurotic edema, with prominence in the hands and face and occasionally laryngeal stridor. One factor causing sodium retention in preeclampsia is the reduction in glomerular

filtration rate (GFR), resulting from both a fall in plasma volume and the effects of the glomerular pathology seen with preeclampsia. The reduction in plasma volume may reflect a loss in venous capacitance with an increase in capillary pressure, thus resulting in a shift in plasma volume from the vascular to the interstitial space. Plasma volume contraction also occurs in renal artery stenosis, pheochromocytoma, malignant hypertension, and essential hypertension; the average contraction of plasma volume in preeclampsia, approximately 9%, is similar to that reported in patients with essential hypertension [15]. Unlike other hypertensive states, however, volume contraction in preeclampsia precedes the onset of hypertension [1]. An increase in capillary permeability to protein may occur as a part of the endothelial cell dysfunction characteristic of preeclampsia. Additionally, a fall in endothelial cell synthesis of PGI_2 increases sensitivity to angiotensin II and probably accounts for the decreased plasma volume due to a diminished vasodilatory effect. Other manifestations of endothelial cell disease include rises in plasma endothelin, cellular fibronectin, and von Willebrand factor, all products of endothelial cell synthesis. Clinically important hemolytic anemia can result from the widespread platelet aggregation [4].

Some have advocated treating the decrease in plasma volume in preeclampsia with volume expansion, but since this decrease in plasma volume is accompanied by normal venous pressure and either a normal or high pulmonary capillary wedge pressure, volume expansion can lead to the development of pulmonary edema.

DIURETIC USE IN PREECLAMPSIA

Thiazide diuretics have been used extensively in pregnancy without ill effect. A review of nine randomized trials of 11,000 women concluded that they lessened the incidence of preeclampsia, with the number of stillbirths reduced by one-third in the diuretic-treated group [2]. In a study of 4000 normal pregnant women given thiazides at the first sign of preeclampsia, severe preeclampsia developed in only 2.3% of the treated women compared with 7.3% of the untreated group. Perinatal mortality was 2.3% in the treated group compared with 4.6% in untreated women [10].

Concern about the use of thiazides in preeclampsia has been based on a fear of further decreasing plasma volume. However, the anti-hypertensive effect of thiazides is not totally dependent on their natriuretic properties. Thiazides have been shown to increase PGI_2 synthesis by endothelial cells, and diazoxide, a most potent arteriolar dilator, is a thiazide without diuretic properties. The effect of a thiazide on plasma volume in preeclampsia depends on the factors causing the decreased plasma volume. Treatment of preeclampsia with

a β-adrenergic blocking agent has been shown to increase plasma volume, and thiazides, by lowering arterial blood pressure and increasing venous capacitance, could similarly cause movement of interstitial fluid into the vascular compartment. Additionally, diuretics can be helpful when used with other antihypertensive drugs in preventing rebound sodium retention.

Pulmonary edema, a serious and potentially life threatening complication of preeclampsia, may be either cardiogenic or noncardiogenic. The former is due to left ventricular failure caused by both hypertension and the cardiac microangiopathy of preeclampsia, and the latter due to alterations in pulmonary capillary permeability. When pulmonary edema does occur in preeclampsia, a Swan–Ganz catheter may be indicated to determine whether a high capillary wedge pressure is present, in which case diuretics would be indicated.

DIURETIC USE IN ESSENTIAL HYPERTENSION DURING PREGNANCY

Hypertension in pregnancy represents a risk factor to the mother and fetus even in the absence of preeclampsia. Women with essential hypertension should continue taking their usual anti-hypertensive medications, including diuretics, during pregnancy. Angiotensin converting enzyme inhibitors are an exception and are contraindicated in pregnancy. In one study of women with essential hypertension, diuretics were stopped and the results compared to women who continued diuretic use throughout pregnancy. There was no difference in fetal survival or birth weight, although maternal plasma volume was found to increase only 18% in the diuretic-treated group compared with 36% in those in whom diuretic use was stopped [14]. In another study of pregnant women with severe essential hypertension, all anti-hypertensives, including diuretics, were stopped and only methyldopa given throughout pregnancy. Half of the women developed preeclampsia with reduction in renal function, one developed malignant hypertension, and the overall perinatal mortality was 25% [13]. This contrasts with the excellent results in women with essential hypertension where antihypertensive drugs, including diuretics, are given throughout pregnancy.

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CHAPTER VA6

Idiopathic Edema

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INTRODUCTION

Idiopathic edema is a poorly understood disorder that affects primarily women and causes salt retention and edema in the absence of cardiac, renal, hepatic, or thyroid disease. Despite many studies of the various factors controlling the renal handling of sodium and water, the disease remains "idiopathic" (see Table 1). It may represent a heterogenous collection of edematous disorders since a variety of abnormalities have been discovered in different subsets of patients. A uniform explanation for its pathophysiology has been lacking and the causes have been postulated to be hormonal, metabolic, or psychologic. The disorder provides a dramatic demonstration of the problem which occurs when fine control of extracellular volume is lost.

CLINICAL FEATURES

Idiopathic edema typically affects women between the ages of 20 and 40; rarely men and prepubertal children have been described who fulfill the criteria for the disorder [7]. The usual complaint is troublesome edema of the legs, hands, and periorbital region, with a sensation of swelling and distention in the abdo-

Diuretic Agents: Clinical Physiology and Pharmacology

TABLE 1 Proposed Mechanisms for the Development of Idiopathic Edema

1. Intermittent fasting and binging
2. Hormonal
   - Prolactin
   - Estrogen
   - Renin–angiotensin–aldosterone
3. Alterations in capillary permeability
4. Decreased plasma oncotic pressure
5. Diuretic abuse

men. The edema may recur intermittently or can be persistent. Although many women gain weight during the luteal phase of the menstrual cycle, premenstrual edema has not been a common complaint in patients with idiopathic edema. A high familial incidence of type II diabetes has been reported in several series and abnormal glucose tolerance has been noted in many patients; however, fewer than 50% of patients are overweight. There are some similarities between idiopathic edema and anorexia nervosa in that both are primarily noted in women and both can be associated with disturbances of body image. A recent survey of a population of college women, in fact, provided evidence for an association between idiopathic edema and eating disorders [3].

PATHOPHYSIOLOGY

An exaggerated diurnal weight gain is a feature of idiopathic edema; normal women gain approximately 0.6 kg during the day, whereas women with idiopathic edema gain more than 1.4 kg [1]. Concern about weight can lead to intermittent fasting and binging in some patients which may be a factor in causing the edema. Fasting suppresses the sympathetic nervous system, and the natriuresis of fasting is in part due to decreased renal sympathetic nerve activity. Carbohydrate feeding results in increased sympathetic activity with subsequent sodium reabsorption. Edema can occur in normal women going from a low to a high carbohydrate diet if sodium intake is high [12].

The possible role of prolactin in the disease was engendered by the report of one patient with galactorrhea and idiopathic edema. Although prolactin is important in salt and water retention in some vertebrates, particularly birds, there is no evidence that it plays a similar role in humans. However, since prolactin secretion is inhibited by dopaminergic receptors in the hypothalamus, bromocriptine has been used to treat idiopathic edema, without uniform success [4]. There is no convincing evidence that estrogen plays a role in idiopathic edema

even though estradiol in high doses, 10–20 mg daily, decreases sodium excretion. Some patients with idiopathic edema are postmenopausal, and normal estrogen and progesterone excretion have been documented in affected patients.

Although angioedema is clinically dissimilar to idiopathic edema in that the episodes of edema are acute and episodic, some have postulated a change in capillary permeability to protein in women with idiopathic edema [11]. In one series comparing normal subjects and patients with idiopathic edema, plasma albumin concentrations were lower in women with the disorder. A greater fractional turnover of albumin was deemed the cause in some, while a lower rate of albumin synthesis was observed in others. However, there is no convincing evidence that the disappearance rate of ^{125}I-labeled albumin is greater in patients with idiopathic edema, although women have greater transcapillary protein flux than men when venous pressure is raised artificially. The decrease in plasma volume reported in some series may reflect obesity, which reduces calculated plasma volume when expressed as milliliters per kilogram of body weight.

Recently a syndrome has been described which may have relevance to idiopathic edema. In approximately 2% of women undergoing induction of ovulation prior to *in vitro* fertilization, the development of ascites with edema of the legs, hands, and face occurs. In some patients this has caused volume depletion with hemoconcentration and renal failure [2]. It has been postulated that endothelial cell damage due to administration of high doses of follicle-stimulating hormone and luteinizing hormone during pituitary suppression with a gonadotropin-releasing hormone analog causes a capillary leak syndrome. However, when a large series of women with this syndrome were studied only half were hemoconcentrated, while all demonstrated increased cardiac output and low peripheral vascular resistance. Elevated plasma levels of renin, norepinephrine, antidiuretic hormone, and atrial natriuretic peptide were noted in conjunction with elevated urinary PGE_2 and 6-keto-$PGF_1\alpha$. The syndrome seems to result from endothelial cell dysfunction which may increase capillary permeability to plasma protein in some women, but cause vasodilation in all, the latter a stimulus to renal sodium absorption. This syndrome provides a striking demonstration of the effect of hormonal stimuli on endothelial cell function.

There is little evidence that a diminished effective blood volume occurs with idiopathic edema since plasma renin, a sensitive indicator of volume perception by the juxtaglomerular apparatus, is not elevated. Moreover, studies in women with idiopathic edema have demonstrated salt retention during normal suppression of renin and aldosterone secretion [9] and with normal increased secretion of atrial natriuretic hormone [1].

DeWardener suggested that idiopathic edema was caused by diuretic abuse based on the observation that when diuretics are discontinued in these women intense salt retention occurs, followed by normalization of sodium excretion

with time [5]. Although chronic diuretic intake may certainly exacerbate sodium retention, this hypothesis would not explain why the women take diuretics initially, nor why many with the disorder have been documented never to have taken diuretics [13]. In trying to wean patients from diuretics, it is important to recognize the role of potassium deficiency in the rebound sodium retention which can occur, perhaps exacerbating edema [10].

TREATMENT

Due to the poorly understood nature of the disorder and its many postulated mechanisms, no single treatment for idiopathic edema exists. Some patients benefit from conservative measures such as the avoidance of prolonged periods of standing and moderate salt restriction. Additionally, the use of elastic stockings may be particularly helpful in patients in whom orthostatic sodium and water retention is excessive. However, diuretics are sometimes required to adequately control edema. Diuretics should be limited to alternate days if possible and potassium supplementation administered appropriately. Given the long held theory that idiopathic edema could result from an exaggerated response of aldosterone to upright posture, some clinicians have suggested that spironolactone, an aldosterone antagonist, is the preferred agent. This is based on anecdotal evidence, however, and it is not clear whether there is any benefit over a thiazide diuretic. Loop diuretics have been avoided by some clinicians in large part due to the findings of worsening renal function in some patients on long-term furosemide therapy [14]. Sympathomimetic drugs such as ephedrine have been employed with some success, perhaps by lowering aldosterone secretion [8]. Likewise, angiotensin converting enzyme inhibitors have shown promising results in some small series [6]. It is important in the treatment of women with idiopathic edema to emphasize the benign nature of the disorder. The patient should be reassured that there are various factors controlling sodium retention that are not completely understood. Likewise, the physician should not be threatened or confused by the failure to understand the pathophysiology of the disorder. To infer that the problem is psychologic or to imply that the disease has been caused by surreptitious diuretic abuse only causes guilt feelings that become counterproductive to proper treatment. As with all chronic diseases, a relationship of trust and confidence between patient and doctor is of utmost therapeutic value.

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CHAPTER VB

Hypertension and Its Treatment: The Place of Diuretics

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THE NATURE OF HYPERTENSION

Hypertension is a raised systemic arterial blood pressure (BP). However, BP is a continuously distributed variable and the numerical boundary between normotension and hypertension is arbitrary and is based on the increasing cardiovascular risk, in particular stroke, as BP rises (Fig. 1) [7]. A WHO-based classification of hypertension is shown in Table 1. Considering end-point trials of cardiovascular risk (more specifically, stroke), it is now widely accepted that maintaining BP below 140/90 mm Hg is beneficial and that a BP of >140/90 mm Hg is therefore considered "abnormal" [10]. However, the level at which pharmacological treatment is used differs between Europe and North America. In North America patients with a diastolic BP of 85 mm Hg or greater are more likely to be given drug treatment to lower BP, but in Europe the criterion for starting antihypertensive drug therapy is approximately 10 mm Hg higher. An isolated numerical definition of hypertension of 140/90 mm Hg or more fails to take into account the normal distribution of BP, its variability, and the contribution of other factors to cardiovascular risk. If rigidly applied it encompasses over 50% of the elderly (>60-year-olds) population, which is an increasing proportion in developed countries [7]. This has significant cost implications, particularly since individual benefit from treatment is so small. Swales [12],

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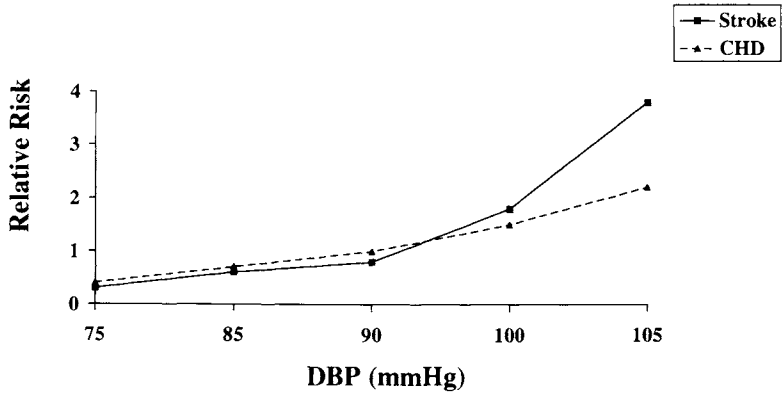


FIGURE 1. Representation of relative risk of stroke and coronary heart disease (CHD) in relation to diastolic blood pressure (DBP).

using data from the recent MRC trial, has compared the number of patients it is necessary to treat for 1 year to prevent one stroke at each of three ranges of diastolic BP: 105–109 mm Hg, 333; 100–105 mm Hg, 666; 95–100 mm Hg, 2000. Another important issue is how BP should be measured. Initial recordings are often unrepresentative and repeated measurements over several months are necessary. "White coat hypertension" must be excluded, although it may not be as benign a condition as originally thought, and could be a prehypertensive state in some individuals. Ambulatory BP recordings are more accurate and reliable, and they correlate better with target organ damage and cardiovascular risk. However, which component of a recording (mean value, variability, diurnal pattern—day *versus* night) is best, and should be the basis of treatment, is unclear.

Both systolic and diastolic BP are related to cardiovascular risk (Figs. 1 and 2), though the emphasis is mainly on diastolic BP, despite epidemiological data

TABLE 1 WHO-Based Classification of Hypertension (1993)

	Systolic blood pressure (SBP) (mm Hg)	Diastolic blood pressure (DBP) (mm Hg)
Normotension	<140	<90
Mild hypertension (Stage 1/2)	140–180	90–105
Moderate-to-severe hypertension (Stage 3/4)	>180	>105
Isolated systolic hypertension	>140	>90

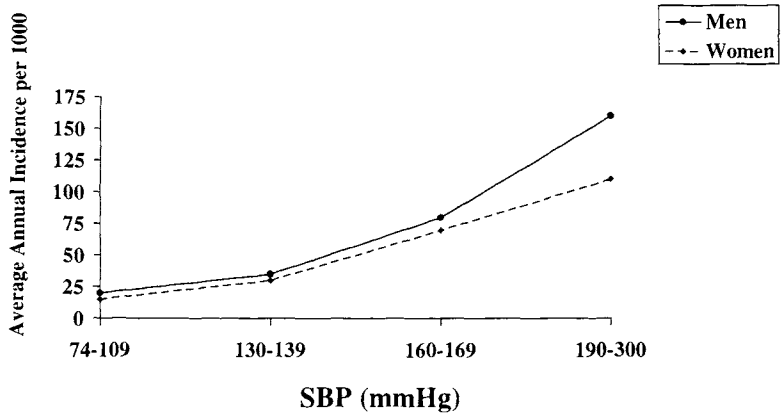


FIGURE 2. Risk of cardiovascular disease related to systolic blood pressure (SBP) at a diastolic blood pressure of <95 mm Hg (based on Framingham 20-year follow-up data).

showing a closer correlation between systolic BP and the risk of cardiovascular events (Fig. 2) [1]. This is particularly relevant to systolic hypertension in the elderly, which is defined as a systolic BP >160 mm Hg and a diastolic BP <90 mm Hg, and which is found in almost 25% of those over 65 years old. It is now evident that treating this form of hypertension and lowering systolic BP significantly reduces the incidence of stroke and myocardial infarction [6]. What is more, there is no specific target level of BP, since any reduction is beneficial in terms of reduced cardiovascular risk. However, this must be balanced against the common side-effects of treatment, especially postural hypotension in the elderly. Moreover, there is some evidence, though highly controversial, that aggressive treatment of hypertension to lower diastolic BP below 80 mm Hg is associated with an increase in mortality, the so-called "J-shaped" curve (Fig. 3).[1]

A BROADER DEFINITION OF HYPERTENSION

Hypertension *per se* must be recognized as a cardiovascular risk factor and considered in the context of other associated risk factors for cardiovascular disease in the individual patient. For example, the patient with a BP of 140/100 mm Hg **and** diabetes mellitus, or who is overweight, a heavy smoker, drinks too much

[1]A low, or declining, diastolic blood pressure has been linked to vessel wall thickening associated with progression of atherosclerosis and therefore may be an indication of widespread arterial disease and increased risk of cardiovascular mortality.

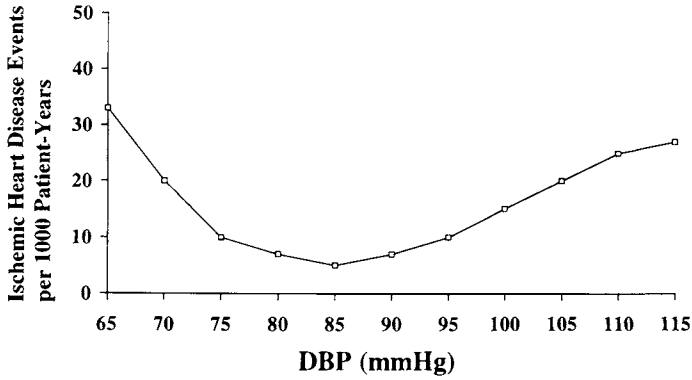


FIGURE 3. The "J-curve" for cardiovascular mortality and diastolic blood pressure (DBP). Low DBP may be a consequence rather than a cause of increased mortality.

alcohol, or has evidence of left ventricular hypertrophy (LVH) (voltage criteria on electrocardiogram, cardiomegaly on chest radiograph, or more reliably, increased LV wall thickness on echocardiogram) has a *higher* risk of stroke or myocardial infarction than the uncomplicated hypertensive with a BP of 170/100 (Fig. 4) [11]. This has implications not only for the target level of BP control, but for the modes of treatment used, which must also address these other risk factors [1]. In the setting of renal impairment and proteinuria, especially in diabetes mellitus, control of BP is essential in limiting the otherwise progressive decline in renal function.

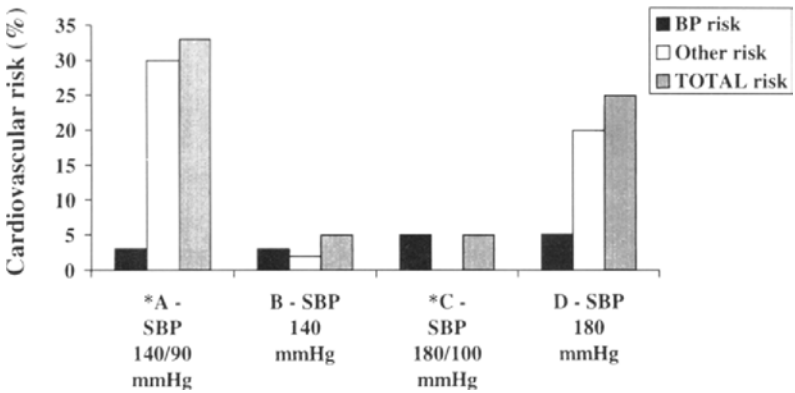


FIGURE 4. Arbitrary representation of cardiovascular risk related to systolic blood pressure (SBP) and additional risk factors (Other), including diabetes, hyperlipidemia, tobacco consumption, and left ventricular hypertrophy.

CAUSES OF HYPERTENSION

Established hypertension, once defined (see above), can be classified as either primary (so-called essential hypertension) or secondary. The latter make up a small proportion, <1%, of hypertensive patients and are those in whom a specific cause can be identified: (1) endocrine-hyperaldosteronism, hypercortisolism, phaeochromcytoma, hyper- and hypothyroidism; (2) renal–parenchymal renal disease (sodium and water retention), renal artery stenosis, and hyperreninism (see Table 2).

Aldosterone and Cortisol Excess

In situations of aldosterone excess causing hypertension, there is usually an adrenal cortical adenoma (Conn's syndrome) or bilateral adrenal hyperplasia. Aldosterone promotes sodium retention and potassium excretion, leading to slight hypernatremia, extracellular volume (ECV) expansion, hypertension, and hypokalemic alkalosis. Unlike secondary causes of hyperaldosteronism, such as renal artery stenosis, in which aldosterone and renin levels are high, in primary hyperaldosteronism, renin is suppressed due to ECV expansion. In states of cortisol excess, caused by either adrenal overproduction (Cushing's syndrome) or pituitary stimulation from an adrenocorticotrophin (ACTH) secreting adenoma (Cushing's disease), high cortisol levels produce aldosterone-like mineralocorticoid effects. Two recently recognized causes of hypertension are apparent mineralocorticoid excess and glucocorticoid suppressible hyperaldosteronism. The first is due to failure to metabolize and inactivate cortisol

TABLE 2 The Main Causes of Secondary Hypertension

Secondary hypertension	Conditions
Endocrine	Hyperadrenalism—cortex and medulla *(aldosterone, cortisol, catecholamines, congenital adrenal hyperplasia)* Hyper- and hypothyroidism Growth hormone excess *(acromegaly)* Oestrogen therapy (HRT)/Oral contraceptive pill
Renal	Parenchymal renal disease Vascular disease *(vasculitis, intra- and extrarenal artery stenoses, diabetes mellitus)* Renin-producing tumors
Other	Neurogenic *(autonomic dysfunction, polyneuropathies, spinal cord trauma and raised intracranial pressure)* Metabolic *(hypercalcemia, toxemia of pregnancy and porphyria)*

to corticosterone in mineralocorticoid-sensitive tissues, like the renal collecting duct and colon. Mineralocorticoid (aldosterone) receptors are not intrinsically selective for aldosterone over cortisol. Normal circulating levels of cortisol are 100–1000 times higher than those of aldosterone and normal mineralocorticoid receptor selectivity for aldosterone is conferred by the enzyme 11β-hydroxysteroid dehydrogenase (11HSD). This enzyme inactivates cortisol by metabolizing it to corticosterone, allowing exclusive binding of aldosterone to its receptor. It can be saturated, as in hypercortisolism (mentioned above), and deficiency results in a hypermineralocorticoid-like state and hypertension. 11HSD can be inhibited by licorice and its derivatives, including the anti-peptic ulcer drug carbenoxolone. The second is a genetic defect (chimeric gene) in which the enzyme aldosterone synthase is abnormally controlled by pituitary ACTH resulting in a form hyperaldosteronism that can be suppressed by dexamethasone treatment, and is therefore known as glucocorticoid suppressible hyperaldosteronism [13]. States of mineralocorticoid excess associated with volume expansion and hypertension, and the corresponding levels of circulating aldosterone and renin, are summarized in Table 3.

Catecholamine Excess

Phaeochromocytomas usually occur in the adrenal medulla, but can arise from any chromaffin tissue along the sympathetic chain. They secrete epinephrine and norepinephrine in varying proportions. Importantly, in this condition the circulating volume is reduced and hypertension is due to a combination of increases in peripheral vascular resistance, heart rate, and cardiac output. Postural hypotension is sometimes observed together with a raised hematocrit, which is also related to an associated increase in erythropoietin production.

Renal Artery Stenosis

Renal ischemia as a consequence of main or branch artery narrowing causes increased renin production by the affected kidney. This in turn leads to high levels of angiotensin II which is a potent arterial vasoconstrictor and also stimulates increased aldosterone production (see Table 3). The degree of associated ECV expansion depends on the function of the contralateral kidney. This is an important and increasingly recognized cause of secondary hypertension in older patients because of widespread atherosclerotic disease. Clues include: (i) hypertension that is severe and difficult to control; (ii) a sudden onset of, or increase in, hypertension; (iii) recurrent left ventricular failure in hypertension; (iv) hypertension associated with peripheral vascular disease; (v) an abdominal bruit; (vi) delayed unilateral excretion on urography or renal asymmetry on

TABLE 3 Syndromes of Mineralocorticoid, or Mineralocorticoid-like, Excess Associated with Hypertension

	Aldosterone	Other mineralocorticoid	Renin
Primary hyperaldosteronism due to Conn's adenoma, adrenal carcinoma (rare), or adrenal hyperplasia (commoner in women)	High[a]	—	Low
Glucocorticoid (dexamethasone)-*suppressible/remediable hyperaldosteronism*	High	—	Low
Hydrocortisone	Low	—	Low
Adrenogenital syndromes (11β- and 17α-hydroxylase deficiences)	Low	DOC[b] excess	Low
Adrenal carcinoma	Low	DOC excess	Low
Liddle's syndrome[c]	Low	—	Low
Gordon's syndrome[d]	Low	—	Low
Licorice ingestion, and apparent minerlocorticoid excess (11HSD inhibition, or deficiency)	Low	—	Low
Glucocorticoid resistance	Low-normal	—	Low
Renal artery stenosis, accelerated (malignant phase) *hypertension and intrarenal vascular disease*	High	—	High

[a] Ambulant aldosterone levels typically fall at midday (3–4 hr after supine sampling) in adrenal adenomas, but not in adrenal hyperplasia.

[b] DOC is the mineralocorticoid deoxycorticosterone.

[c] Liddle's syndrome has recently been shown to be due to an abnormally "open" Na^+ channel in the distal nephron, hence the response to amiloride.

[d] Like Liddle's syndrome, Gordon's syndrome (pseudohypoaldosteronism type II) is an inherited form of hypertension, but unlike the other conditions listed above, it is associated with hyperkalemia, and its cause is unknown.

ultrasound; (vii) a raised serum creatinine and BUN. Despite much discussion and debate, including initial enthusiasm over the screening value of captopril renography, this condition can be excluded only by a high index of clinical suspicion and confirmed by selective renal angiography. Other newer noninvasive methods using color-Doppler ultrasound or MRI angiography are promising developments, but they are less widely available and require more rigorous evaluation. The benefit of diagnosis is the potential for definitive treatment by angioplasty, or surgery, not only to improve BP control and reduce antihypertensive medication, but also to preserve renal function.

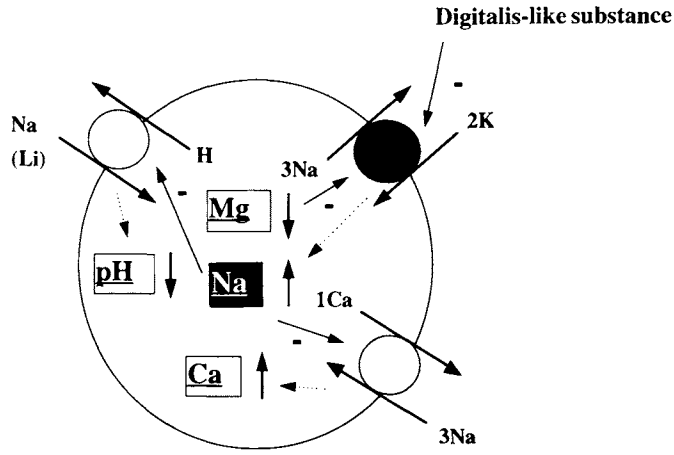


FIGURE 5. Potential cell membrane transport defects and changes in intracellular electrolytes in hypertension.

MECHANISMS OF HYPERTENSION

BP is normally determined by the circulating volume (ECV) and peripheral vascular resistance, although the importance of ECV expansion in essential hypertension is not clear. While no single cause of primary essential hypertension has been identified, there are links with various nutritional factors. The majority of research on the role of diet in the pathogenesis, treatment, and prevention of hypertension has focused on four nutrients [8]: sodium, potassium, and most recently calcium and magnesium. Figure 5 summarizes the currently identified defects of cell membrane ion transport in hypertension and their potential relationship to these cations: increased intracellular concentrations of Na^+ and Ca^{2+} and decreased cytosolic Mg^{2+} and pH. This pattern is exaggerated by salt loading, especially in salt-sensitive subjects (see below). However, so far there is no unifying model for these abnormalities. The reasons for this are in part related to the different cell types in which these defects have been found, in particular in the nonpolarized red cell, leukocyte, and lymphocyte.

SODIUM

Population studies have shown a link between increased dietary sodium intake and the prevalence of hypertension. However, between individuals there is con-

siderable variation in sodium intake and level of BP. There is some evidence that subjects can be divided according to their BP response to sodium into those who are sodium-sensitive and those who are not. Thus, abnormal handling of sodium may be a factor in the etiology of hypertension in salt-sensitive individuals in terms of both enhanced renal absorption and vascular effects through impaired Na^+/K^+ ATPase activity. Inhibition of Na^+/K^+ ATPase by an endogenous digitalis-like factor in response to sodium-induced ECV expansion leads to an increase in cytosolic calcium in vascular smooth muscle, vasoconstriction, and increased peripheral vascular resistance (see Fig. 5) [2]. Patients with low plasma renin[2] activity (blacks and elderly hypertensives) tend to be sodium-sensitive and their BP responds better to dietary sodium restriction [14].

The anion accompanying sodium may be critical in salt-induced hypertension. Studies in animals and humans have shown that salt-sensitive hypertension develops only when the sodium salt is NaCl and not $NaHCO_3$.

Potassium

Low potassium intake and excretion are associated with hypertension and dietary potassium supplementation can lower BP. The antihypertensive effect of potassium may be related to natriuresis, suppression of plasma renin activity, and stimulation of Na^+/K^+ ATPase in adrenergic nerve terminals and vascular smooth muscle (resulting in vasodilatation); all of which have been observed during the administration of potassium. The effect of potassium supplementation on BP may be limited by potassium stimulation of aldosterone secretion. In addition, potassium may protect against stroke, an effect that is not related to its hypotensive action.

Calcium

Dietary intake of calcium has also been implicated in the cause of hypertension. Like potassium, epidemiological studies suggest an inverse relationship between calcium intake and BP. The direct effect of calcium on the vasculature is vasoconstriction, but the antihypertensive action of calcium carbonate probably results from natriuresis. Because the excretion of calcium and sodium are closely coupled, increased calcium intake produces increased sodium excretion. Increased sodium intake also promotes urinary excretion of calcium.

[2]Unless renin is causal, it should normally be suppressed in hypertension. A "normal" or high renin level may also be a risk factor for myocardial infarction and stroke [5].

MAGNESIUM

There is some evidence that dietary magnesium deficiency may be an important factor in the pathogenesis of hypertension and atherosclerosis [9]. Epidemiological data indicate a higher prevalence of hypertension and ischemic heart disease in regions with low water or soil magnesium content. Rats fed magnesium-deficient diets develop significant hypertension and increased vascular contractility in response to angiotensin II. The hypertensive effects of suppressed magnesium levels could be mediated through modulation of cell membrane Na^+/K^+ ATPase activity (see Fig. 5). Additionally, magnesium may also affect cytosolic calcium by influencing calcium flux across cell membranes. Magnesium and potassium deficiencies often coexist and potassium depletion cannot be corrected unless magnesium is also replenished.

TREATMENT OF HYPERTENSION

The goals of treatment are to reduce BP and the risk of cardiovascular events, but to minimize adverse effects and facilitate patient compliance. Treatment can be divided into nonpharmacological and pharmacological [11]. Both forms of therapy rely heavily on patient education and good communication between doctor and patient. Nonpharmacological measures have the advantages of minimal cost and lack of side-effects, although compliance is not necessarily better. Current generally agreed-upon recommendations are [11]: (i) appropriate weight loss; (ii) no tobacco and limited alcohol consumption; (iii) regular moderate exercise; (iv) modest sodium restriction ("no added salt"); (v) diet low in animal fat and high in vegetable fiber. More controversial advice includes dietary potassium, calcium and fish oil supplementation, and reduced stress and caffeine intake. If these recommendations are followed, a significant number of patients with mild hypertension can avoid drug therapy. Even if drug treatment proves necessary, these nonpharmacological measures are an important adjunct to therapy.

The aim of drug therapy in hypertension is to control BP with a drug that best suits the individual patient, taking into account causal factors and the presence of other cardiovascular risk factors. Since hypertension has a high prevalence and treatment is essentially life-long, the economic impact is high. With the ever rising cost of medical care, whatever the national system, drug expenditure is a major consideration and this must be taken into account when prescribing for hypertension. The main classes of antihypertensive drug, excluding diuretics, are listed in Table 4. It is important to recognize that no single class of antihypertensive drug has been established to be superior to another in all respects.

TABLE 4 The Main Classes of Antihypertensive Drug: Their Indications and Side-Effects

Class of drug	Mechanism of action	Advantageous in	Disadvantageous in	Main side-effect(s)
β-Blocker	Reduced cardiac output and heart rate, renin suppression	Angina, postmyocardial infarction (MI), phaeochromocytoma	Asthma, peripheral vascular disease (PVD), diabetes mellitus (DM, especially insulin-dependent), heart failure, bradydysrhythmias	Fatigue, depression, disturbed sleep, impotence
Calcium channel blocker	Vasorelaxant and natriuretic	Black and elderly, angina, asthma, PVD, DM	Heart failure, bradydysrhythmias (depending on type)	Postural hypotension, flushing, ankle swelling
ACE inhibitor	Inhibit AII production and kinin (vasodilatory) breakdown and aldosterone secretion	AII-dependent hypertension, DM (especially if proteinuric) and other proteinuric renal disease (and evidence of hyperfiltration), heart failure, post-MI, LVH	Renal artery stenosis, hyperkalaemia	First dose hypotension, cough, angioedema
α_1-Blocker	Vasodilation	Hyperlipidemia, prostate hypertrophy, DM, heart failure, phaeochromocytoma		First dose hypotension, fluid retention
Vasodilators	Vaso- and venodilation	Heart failure, pregnancy		Postural hypotension, tachycardia, fluid retention
Central sympatholytic	Reduced CO and HR	Pregnancy	Phaeochromocytoma, MAOI use	Postural hypotension, fluid retention, depression

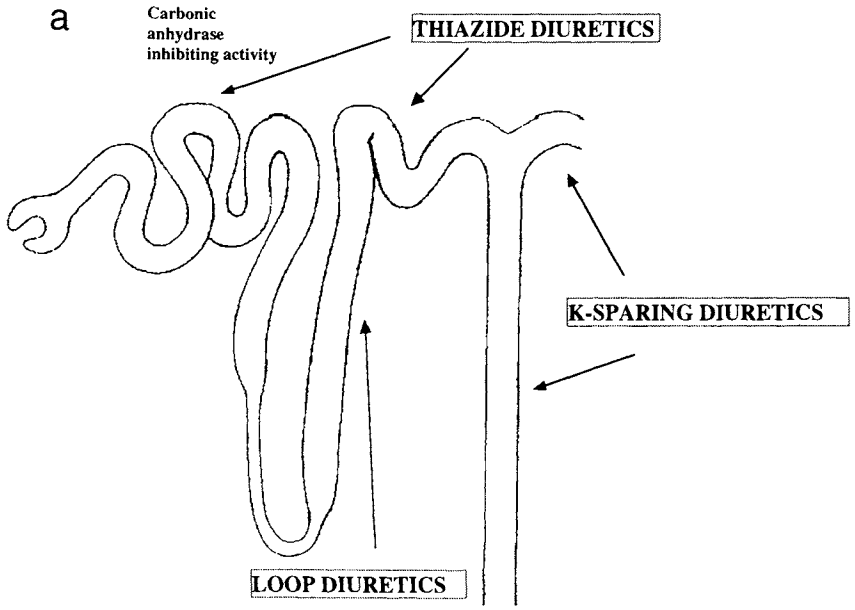
Note. LVH, left ventricular hypertrophy; MAOI, monoamine oxidase inhibitor.

DIURETICS USED IN HYPERTENSION AND THEIR SITES OF ACTION [4]

Mainly three types of diuretic are used in treating hypertension: (i) thiazide; (ii) loop diuretics; (iii) potassium-sparing (antialdosterone and sodium channel blockers). All, except the aldosterone antagonist spironolactone, have a luminal site of action and are secreted into the tubule by an active transport mechanism common to organic anions and cations located along the late proximal tubule. They are highly protein bound in plasma and concentrated several-fold at their site of action in the tubule lumen. Figure 6 illustrates their respective sites of action, which is discussed in greater detail in Section III of this book.

MECHANISM(S) OF ANTIHYPERTENSIVE EFFECT OF DIURETICS [14]

Thiazide diuretics are the most widely used type in hypertension. Their mechanism of sustained action is incompletely understood, but still seems to be related to their natriuretic effect [14]. The initial hypotensive response to a thiazide diuretic is associated with increased urinary loss of sodium, negative sodium balance, ECV contraction, decreased cardiac output, and reflex increases in peripheral vascular resistance and renin release. Over the next several weeks, sodium balance is restored and ECV and cardiac output return toward normal, but hypotension is sustained by a decrease in peripheral vascular resistance. The mechanism of the decline in vascular resistance is unclear. One possibility is that a small (unmeasurable) and persistent *decrease* in ECV sets in motion a series of responses to maintain local tissue perfusion, resulting in decreased peripheral vascular resistance (see Fig. 7). A similar process may explain the rare occurrence of hypertension in patients with renal failure receiving slow and prolonged periods of dialysis and strict maintenance of their dry weight. Another possible effect of thiazide diuretics is to reduce the secretion of and endogenous digitalis-like substance. The presence of a circulating digitalis-like substance is of continuing interest and has been reported in the plasma of hypertensive patients [2]. It is thought to be produced as a result of a persistent positive sodium balance, especially in salt-sensitive hypertension, and to increase intracellular sodium and calcium concentrations, which in vascular smooth muscle would cause vasoconstriction and a rise in peripheral vascular resistance (see Fig. 5). Other speculative effects of thiazide diuretics include reduced vascular smooth muscle and endothelial cell swelling and direct vasodilatation mediated by potassium channel opening, prostacyclin, or nitric oxide release.



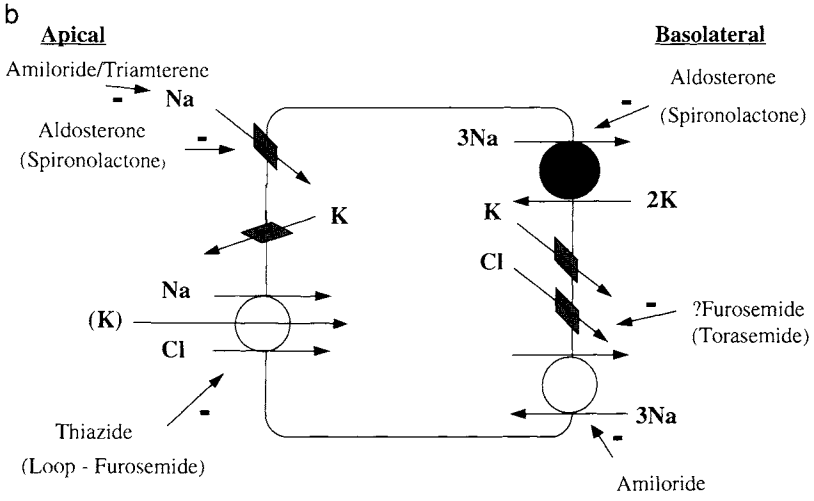


FIGURE 6. Sites and mechanism of action of the three main classes of diuretic (thiazide, loop, and potassium-sparing) on a composite thick ascending limb (TAL) and distal convoluted tubule principal (DT) cell.

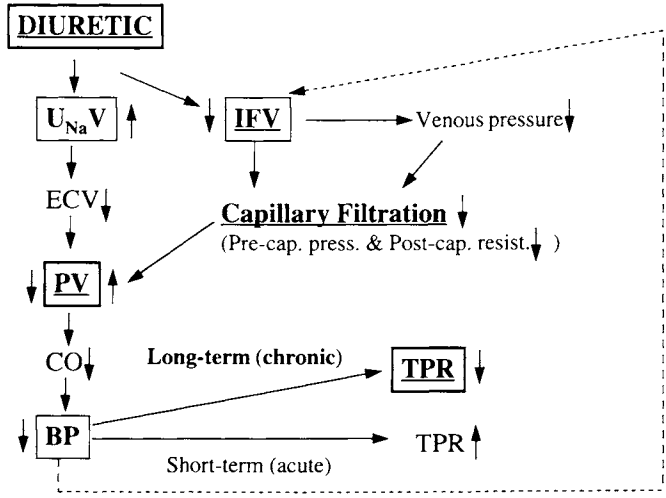


FIGURE 7. Possible mechanism of the long-term anti-hypertensive effect of diuretics.

USE OF DIURETICS IN TREATING HYPERTENSION [14]

THIAZIDE DIURETICS

Thiazide diuretics are the most commonly used diuretics in the treatment of hypertension and most hypertensive patients respond to them. That the response to thiazides depends on sodium intake is emphasized by: (i) their failure to lower BP in advanced chronic renal failure and anephric patients; (ii) persistence of their antihypertensive effect after stopping therapy if sodium intake is restricted; (iii) reduction of their antihypertensive effect by a high sodium intake. Good responders to thiazide diuretics are those patients in whom the compensatory responses to sodium restriction are blunted, i.e., black and elderly, low-renin hypertensives. Unfortunately, in the individual patient, plasma renin measurement is not a reliable predictor of thiazide responsiveness. Non-responders can be converted to responders by sodium restriction or inhibition of the compensatory renin response by combination with a β-blocker or an angiotensin converting enzyme (ACE) inhibitor. One danger of relying on sodium restriction alone as an adjunct to diuretic therapy in controlling hypertension is that it stimulates further the compensatory increases in renin and aldosterone levels and the risk of significant potassium loss and hypokalemia. This is where a potassium-sparing diuretic, or ACE inhibitor, may be a better option if a thiazide diuretic alone is insufficient to control blood pressure.

It is important to remember that the antihypertensive effect of thiazide di-

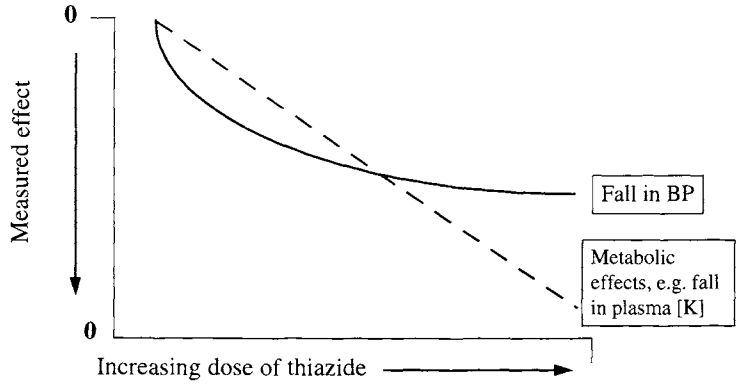


FIGURE 8. Dose–response relationship for the anti-hypertensive *versus* metabolic effects of thiazide diuretics.

uretics has a relatively flat dose–response relationship (Fig. 8), and doses should be kept low and coupled with a "no added salt" diet (80–120 mmol day^{-1}). For example, there is little further lowering of BP with hydrochlorothiazide beyond 50 mg once a day and the optimal dose range is probably 12.5–25 mg daily (Fig. 8). Most patients will respond within 2–4 weeks of starting treatment, but some may take up to 12 weeks. Doses should not be adjusted more frequently than every 2–4 weeks. Higher doses are associated with an increase in adverse metabolic effects (see later). The next step in treatment should be to add another class of antihypertensive, or change the class if monotherapy is still the aim.

Loop Diuretics

These diuretics, such as furosemide, bumetanide, torsemide, and ethacrynic acid, can lower BP acutely because of their potent natriuretic effect and consequent fall in circulating volume. However, when used alone loop diuretics do not have any useful long-term antihypertensive effect. Chronic loop diuretic administration is associated with periods of intense sodium retention once the acute natriuretic effect has worn off. This "braking" response is partially explained by reflex increases in sympathetic nerve activity and angiotensin II production, enhancing proximal tubule fluid and solute reabsorption directly and via changes in peritubule physical factors. In addition, a further compensatory response has been localized to the thiazide-sensitive distal tubule which hypertrophies following chronic loop diuretic treatment, and along which sodium absorption is increased. This adaptive response can be blocked by combining a loop with a thiazide diuretic and this is the basis for using this combination in

severe heart failure and other states associated with resistant edema [4]. These diuretics are particularly effective and often indicated in combination with fluid-retaining antihypertensives, such as sympatholytic (central and peripheral) drugs and vasodilators (e.g., hydralazine or minoxidil), and more specifically with ACE inhibitors, to enhance their hypotensive effect. The potent combination of an ACE inhibitor and loop diuretic must be used cautiously because of the risk of significant volume depletion and prerenal azotemia.

Potassium-Sparing Diuretics

These diuretics are the sodium channel blockers amiloride and triamterene and the antialdosterone spironolactone. They all have weak natriuretic effects and are antikaliuretic (see Fig. 6). Spironolactone is specifically indicated in hypertension due to primary mineralocorticoid excess, although in adrenal hyperplasia and hyperaldosteronism amiloride may prove more effective in maintaining plasma potassium and controlling BP. The main problem with spironolactone is that doses above 100 mg daily are usually poorly tolerated because of nausea and gynecomastia in men, although it does have a useful antiacne and antiandrogen effect in some women (e.g., polycystic ovary disease). Moreover, there is concern that long-term use may be associated with an increased risk of hematological malignancy. These agents are more commonly used to prevent thiazide and loop diuretic induced hypokalemia, particularly in patients on digoxin or with ischemic heart disease and a history of life-threatening cardiac dysrhythmias. It is worth noting that such combination diuretics were used in the trials of hypertension in the elderly (SHEP study, Dyazide; MRC study, Moduretic) and they were associated with significant reductions in the risk of stroke and myocardial infarction. However, they should be avoided in patients with significant renal impairment, because of their accumulation and the increased risk of hyperkalemia; and they must be used cautiously in diabetics in whom hyperkalemia is also a risk, especially in those patients with underlying hyporeninemic hypoaldosteronsism (type IV renal tubular acidosis).

Nonsteroidal antiinflammatory drugs (e.g., indomethacin) antagonize the natriuretic action of thiazide and loop diuretics, and their sodium-retaining effect can impair the antihypertensive effect of thiazides (and other antihypertensives). In combination with potassium-sparing diuretics they may cause hyperkalemia.

METABOLIC AND ADVERSE EFFECTS OF DIURETICS

The metabolic effects of thiazide (and loop) diuretics, many of which are undesirable, are dose-related, whereas their antihypertensive is not (Fig. 8).

TABLE 5 Metabolic and Adverse Side-Effects of Diuretics Used in Hypertension

Class of diuretic	Metabolic side-effect(s)	Other side-effect(s)
Thiazide	Hypokalemia Hypomagnesemia Hypocalciuria (Hypercalcemia) Hyponatremia Hyperuricemia Azotemia Hyperglycemia Hyperlipidemia	Impotence (especially in diabetic patients) Gastrointestinal—rarely pancreatitis Skin rashes and allergic reactions Blood dyscrasias Noncardiac pulmonary edema Muscle cramps
Loop	Hypokalemia Hypomagnesemia Hypercalciuria Hypernatremia Hyperuricemia Azotemia Hyperglycemia Hyperlipidemia	Ototoxic and vestibulotoxic Gastrointestinal Skin rashes and allergic reactions Blood dyscrasias Muscle cramps
Potassium-sparing	Hyperkalemia (Magnesium-sparing)	Decreased libido, impotence and gynecomastia in men Disturbed menstruation in women

Table 5 lists the metabolic and adverse effects of diuretics encountered during the treatment of hypertension.

Hypokalemia and Hypomagnesemia

Mild hypokalemia (Plasma [K] 3.3–3.8 mmol liter^{-1}) and metabolic alkalosis occurs in up to 20% of patients and will appear within the first 6 weeks of starting therapy. Significant hypokalemia (<3.2 mmol liter^{-1}) should not be ignored and warrants further investigation (e.g., underlying hyperaldosteronism) and/or potassium supplementation (especially in elderly patients on digoxin and those with a history of ischemic heart disease and liver cirrhosis). Hypokalemia is thought to predispose to rhabdomyolysis and acute renal failure, especially in young subjects engaged in heavy physical exertion; hypokalemia should be monitored closely in young and physically active hypertensives. While mild hypokalemia is well tolerated and not associated with an increased risk of cardiac dysrhythmias, it may be a factor in diuretic-induced glucose intolerance and hyperlipidemia, and as already mentioned, potassium depletion has been causally linked to hypertension and stroke. Therefore, it is probably advisable to avoid even mild hypokalemia during long-term diuretic therapy. Hypomagnesemia is more likely with a long-term loop diuretic than a

thiazide, because magnesium is absorbed mainly along the thick ascending limb. Moreover, chronic magnesium deficiency prevents correction of associated hypokalemia and this is one reason why potassium-sparing diuretics, which are also magnesium-sparing (particularly amiloride and triamterene), are more effective in treating hypokalemia than oral KCl supplements. Hypokalemia, hypomagnesemia, and hypertriglyceridemia are more likely to be found in hypertension associated with excessive alcohol intake.

Hypercalcemia

A potentially useful effect of thiazide diuretics is increased calcium absorption along the proximal and, more specifically, distal tubules. In the proximal tubule enhanced calcium reabsorption parallels sodium and fluid absorption. The effect of a thiazide diuretic on calcium absorption in the proximal tubule is probably due to mild ECV contraction and associated changes in peritubule physical factors, although this may be limited by any intrinsic carbonic anhydrase inhibiting activity and inhibition of Na^+ reabsorption. Thiazide-induced ECV contraction is also the basis of their use in diabetes insipidus and proximal renal tubule acidosis. In the distal tubule increased calcium absorption is related to inhibition of sodium uptake across the apical cell membrane and consequent activation of basolateral Na^+–Ca^{2+} exchange (see Fig. 6). Since calcium deficiency has been considered to be an etiologic factor in hypertension, and in postmenopausal osteoporosis in women, thiazide-induced calcium retention may be beneficial, especially in elderly female hypertensives. However, it is worth noting that thiazide-associated hypercalcemia may indicate latent primary hyperparathyroidism as a cause of hypertension. A thiazide diuretic would also be useful in a hypertensive patient with idiopathic hypercalciuria and renal calculi.

Hypo- and Hypernatremia

Hyponatremia is an important adverse effect of thiazide diuretics, especially if long-acting like chlorthalidone; hypernatremia is more commonly seen with loop diuretics causing dehydration. Thiazide diuretics induce the excretion of more sodium than water, whereas the impairment of the cortico-medullary osmotic gradient by loop diuretics leads to a larger excretion of water than sodium—loop diuretics are often used in the treatment of hyponatremia. Hyponatremia is also more likely to occur in hypokalemic patients.

Urea and Uric Acid

A rise in blood urea nitrogen (BUN) is commonly seen with diuretic therapy and is a useful warning of excessive dosage, especially when compared with the

plasma creatinine level, which begins to rise only if there is significant ECV depletion and developing prerenal failure. Hyperuricemia is due to a combination of enhanced proximal tubule absorption secondary to ECV contraction and competition between uric acid and diuretic secretion along the proximal tubule. Hyperuricemia is considered by some to be an independent cardiovascular risk factor, but whether this is exaggerated by diuretic therapy is open to question. Thiazide and loop diuretics may precipitate gout, but the risk can be reduced by giving allopurinol. Diuretics are also best avoided in polycythemia, both because of the increased risk of gout and of increasing blood viscosity.

Hyperglycemia and Hyperlipidemia

Thiazide and loop diuretics can precipitate glucose intolerance. This effect has been linked with diuretic-induced hypokalemia, resulting in impaired insulin release and peripheral uptake of glucose. While some studies have reported an increased risk of developing non-insulin-dependent diabetes during long-term administration of thiazide diuretics, a recent large study in elderly hypertensives did not confirm this. However, thiazide diuretics are still best avoided in both insulin- and non-insulin-dependent diabetic patients, because of their tendency to worsen blood glucose control and reports that may increase diabetic proteinuria. In addition to routine urine analysis for glucose and protein, occasional measurement of blood glucose concentration, or glycated hemoglobin level, is worthwhile, especially in obese patients on diuretics. Hyperlipidemia is also seen, at least initially, but does not seem to be sustained.

USE OF DIURETICS IN THE HYPERTENSION OF RENAL IMPAIRMENT AND PREGNANCY

Use of Diuretics in the Treatment of Hypertension in Renal Impairment

Hypertension is a consequence of renal impairment and if untreated accelerates the decline in renal function to end-stage renal failure. Moreover, hyperlipidemia and glucose intolerance are more common in chronic renal failure, and cardiovascular morbidity and mortality are significantly increased, particularly in patients on dialysis in whom BP control is often difficult. The major cause of hypertension in renal failure is sodium retention and ECV expansion, so-called volume-dependent hypertension. Additional factors may include increased sympathetic nerve acuity, hyperparathyroidism, hypothyroidism, increased and decreased production and/or action of endogenous vasoconstrictors (e.g., angiotensin II, endothelin, nitric oxide inhibitors), and vasodilators (e.g., prosta-

cyclin and nitric oxide), respectively. Diuretics should be useful in this setting when there is still residual kidney function, but thiazide diuretics are usually ineffective when glomerular filtration rate is much below 30 ml min^{-1}. Loop diuretics are efficacious in controlling BP in patients with renal failure not yet requiring dialysis, though the dose needs to be very much higher than in patients with normal renal function, e.g., up to 1 g per day orally of furosemide in divided doses (though in more acute situations continuous, rather than bolus, infusion is usually more effective). High (and sustained) peritubule plasma concentrations are necessary to overcome the reduced luminal secretion of diuretic due to competition by increased endogenous organic anions. The thiazide-like diuretic metolazone is still effective in renal failure and can be combined with furosemide to limit diuretic resistance. Other drugs that may be particularly suited to hypertension in renal failure are ACE inhibitors and sympatholytics. The former are especially useful with furosemide in early renal impairment associated with glomerular proteinuria; the best example being diabetic nephropathy, in which meticulous BP control, and other possibly unique actions of ACE inhibitors, can stabilize renal function. It is important to be cautious and aware that in more advanced renal failure this combination can precipitate acute-on-chronic renal failure, which may be the first indication of significant underlying renovascular disease (e.g., bilateral renal artery stenosis). Potassium-sparing diuretics should be avoided in renal failure. Treatment with the immunosuppressive drug cyclosporine A is often associated with significant hypertension. This drug also causes increased urinary losses of magnesium. This should be kept in mind when this drug is used together with loop diuretics in patients following transplantation and when used to treat patients with steroid-resistant nephrotic syndrome. Finally, the issue of hypertension *per se* as a cause of renal failure remains open, but the question of whether particular antihypertensive drugs are renoprotective is beginning to be considered.

Use of Diuretics in the Treatment of Hypertension in Pregnancy

Hypertension in pregnancy can be broadly divided into preexisting hypertension (chronic hypertension), hypertension of pregnancy (usually appearing within the first trimester, but can develop at any time) and preeclampsia/eclampsia (occurring in the third trimester). Preeclampsia is characterized by hypertension, proteinuria, edema, and hyperuricemia, with or without associated liver dysfunction and coagulopathy (HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets). Eclampsia is diagnosed when hypertension is severe and convulsions occur. An early indication of developing hypertension in pregnancy is failure to observe the normal fall in BP during the

first trimester. Patients with preexisting hypertension and hypertension of pregnancy are at increased risk of developing preeclampsia. While there is some debate about diuretic treatment of hypertension in pregnancy, because the plasma volume in pregnant women with hypertension is reduced compared with normotensive pregnancy, especially in preeclampsia, diuretics seem inappropriate and are generally avoided [3]. The mainstay of treatment remains α-methyldopa and hydralazine, although β-blockers are still used during the first trimester and experience with calcium antagonists is increasing. ACE inhibitors cause fetal abnormalities and are contraindicated. Diuretics used postpartum can interfere with normal lactation.

NEW DIRECTIONS IN DIURETIC DEVELOPMENT IN TREATING HYPERTENSION

Recent progress in renal physiology and pharmacology has identified several potential strategies for developing new diuretic agents. These include potentiation of endogenous natriuretic and vasodilator substances, such as atrial natriuretic peptide (ANP) and bradykinin, by inhibiting their degradation by proteases found mainly in the luminal membrane of the proximal tubule [16]. While bradykinin's effects are also potentiated by ACE inhibitors, inhibitors of these neutral endopeptidases are under development, aimed primarily at enhancing the effect of endogenous ANP, but also reducing the breakdown of other natriuretic peptides. Vasopressin antagonists, both V1 and V2, are likely to prove useful both as vasodilators and diuretics. Sulphonylureas, which block ATP-sensitive potassium (K_{ATP}) channels in a variety of tissues, including pancreas and vascular smooth muscle, have been shown to cause natriuresis and diuresis [15]. K_{ATP} channel blockers that affect vascular smooth muscle will cause vasoconstriction, and therefore analogs specifically targeting renal tubule K_{ATP} channels in the thick ascending limb are being developed. Dopamine is natriuretic and vasodilatory, and dopamine agonists lower BP. Endothelin is a potent vasoconstrictor and can cause diuresis or antidiuresis, depending on dose. The diuretic effect is probably mediated via the endothelin B receptor (ETB), since specific ETB agonists are diuretic and increase renal perfusion. Finally, as well as being a strong vasodilator, nitric oxide has recently been shown to be natriuretic by inhibiting sodium absorption along the collecting duct.

WHY DIURETICS?

Thiazide diuretics have been used in the treatment of hypertension for over 30 years. They have been the basis of all major large-scale clinical trials of the

treatment of hypertension, and they are inexpensive and generally well tolerated. Thiazide and loop diuretics are particularly useful in combination with drugs that elicit compensatory fluid retention (see Table 4), such as α-blockers and vasodilators, and as already mentioned, they are very effective antihypertensives in combination with ACE inhibitors, but they are also useful when combined with β-blockers or calcium channel blockers. Despite much recent concern, there is no good evidence that they promote dyslipidemia, at least in the long-term, or cardiac dysrhythmias, often cited as reasons for their failure to reduce the incidence of myocardial infarction to the same extent as stroke. While there are reports linking long-term diuretic use to an increased risk of renal cell carcinoma, the significance of this remains unclear. When used appropriately, and until there is conclusive proof that other agents are superior, thiazide diuretics remain the cornerstone of drug therapy in the treatment of hypertension.

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CHAPTER VC1

Water and Electrolyte Derangements: Overhydration

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Diuretics, especially thiazide diuretics, are a frequent cause of hyponatremia. Paradoxically, loop diuretics can be important adjuncts in the treatment of acute symptomatic hyponatremia, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and diabetes insipidus.

HYPONATREMIA

Hyponatremia is caused by water retention due to a continued water intake more than the ability of the kidneys to excrete electrolyte-free water. The resulting hypotonicity causes water movement into cells, with cell swelling. Swelling of brain cells causes cerebral edema, which results in the neurologic symptoms of hyponatremia. Since brain cells regulate their volume, patients are symptomatic only if the hyponatremia is acute or very severe.

What is the cause of the water retention? Normally, hyponatremia should suppress the secretion of antidiuretic hormone (arginine vasopressin or AVP), decreasing the water permeability of the collecting duct system, allowing the excess water to be excreted. However, AVP release is controlled by both osmotic and nonosmotic stimuli. In the latter case, AVP is released in response to nonosmotic stimuli such as reductions in effective arterial volume, irrespective

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TABLE 1 Etiology of Hyponatremia

Volume depletion	Normal	Volume excess
GI losses Vomiting, diarrhea	Primary polydipsia	Congestive heart failure
Renal losses Diuretics, hypoaldosteronism, salt-wasting	Hypothyroidism	Hepatic cirrhosis with ascites
Skin losses burns, cystic fibrosis	Glucocorticoid deficiency	Nephrotic syndrome with severe hypoalbuminemia
Abdominal sequestration; peritonitis; arsenic or mercury poisoning; pancreatitis, etc.	Drugs (see Table 2)	Renal failure
Potassium depletion	Nausea, pain	
	SIADH	
	Beer potomania	

of whether total extracellular volume (ECF) is reduced as in vomiting or expanded as in heart failure or cirrhosis with ascites, or normal as in pain, nausea or drugs. Indeed, except for patients with psychogenic polydipsia, all patients with sustained hyponatremia have elevated AVP levels. Therefore, it is helpful to categorize the conditions associated with hyponatremia by the volume status of the patients (decreased, normal, or increased; see Table 1). Hyponatremia occurs in beer potomania because the ability to excrete free water is decreased because of poor dietary intake [10]. Beer drinkers may ingest only 250 mOsmol/day or less of sodium, potassium, or protein. Hyponatremia will occur if they ingest more than 5 liters of water a day (since the minimum achievable urine osmolality is 50 mOsm).

Mild hyponatremia is a relatively common complication of diuretic therapy [16]. However, if patients drink large volumes of water, as occurs for unknown reasons in elderly women [6], severe hyponatremia may result. Three mechanisms contribute to the hyponatremia: (i) volume depletion causes increased AVP as discussed above, (ii) potassium depletion causes an intracellular shift of sodium for potassium, and (iii) impaired renal free water formation as a result of diminished delivery of filtrate (increased proximal reabsorption) or inhibition of sodium reabsorption in the diluting segments (loop of Henle and distal tubule). As described in Chapter VC1, most cases of hyponatremia are caused by thiazides, not loop diuretics. This occurs because they act at different sites along the nephron. Thiazides act primarily in the distal convoluted tubule and initial collecting duct to promote hypertonic salt loss. The loss of salt causes volume retention, and AVP induced water retention. The urine sodium + po-

tassium concentrations average about 150 m*M*, while plasma levels were below 110 m*M*. In contrast, loop diuretics act at the medullary thick ascending limb, causing hypotonic or isotonic fluid loss, in part, because they decrease medullary hypertonicity. Thus, hyponatremia is distinctly uncommon.

Hyponatremia generally occurs within the first 2 or 3 weeks of diuretic therapy. After this time, a new steady state is established in which water and solute intake is balanced by excretion. However, hyponatremia can become worse if vomiting, diarrhea, increased water intake, or a new drug is added.

Treatment

The primary treatment of hyponatremia is to correct the underlying cause of the impaired water excretion. For example, glucocorticoid and thyroid deficiencies can be replenished. Drugs that increase AVP release or also increase renal sensitivity to AVP can be stopped (Table 2). Patients with congestive heart failure can be treated so as to improve cardiac performance with unloading agents (captopril), diuretics, and digitalis. Similarly, patients with asymptomatic diuretic-induced hyponatremia can be treated by stopping the diuretic, replacing volume, and potassium losses. If the diuretic needs to be continued, the patient should be placed on water restriction.

TABLE 2 Causes of SIADH

Hypothalamic production of ADH
Neuropsychiatric disorders
Infections, vascular, neoplasms, psychosis
Pulmonary disease
Pneumonia, respiratory failure, asthma
Postoperative patient
Severe nausea
Drugs
Cyclophosphamide, carbamazepine, vincristine, vinblastine, thiothixene, thioridazine, haloperidol, amitriptyline, MOA inhibitors, bromocriptine, lorcainine
Idiopathic
Ectopic production
Carcinoma
Oat cell, bronchogenic, GI, neuroblastoma
Pulmonary TB
Potentiation of ADH effect (also must increase production)
Chlorpropamide, carbamazepine, psychosis, cyclophosphamide, tolbutamide
Exogenous ADH
Vasopressin or oxytocin or DDAVP

The treatment of hyponatremia per se depends primarily on the consciousness of the patient, which is determined by the rate of development of hyponatremia. Thus, mild stable asymptomatic hyponatremia may be left untreated. If it is progressive, the mode of correction depends on the volume status of the patient. Patients with volume depletion caused by diuretics can be treated with sodium chloride, either by mouth or by infusion. The rate of infusion must be carefully adjusted so as to avoid too rapid correction. Patients with volume overload (i.e., heart or liver failure) or normal volume (primary polydipsia or SIADH) are initially treated with restriction of water intake.

In contrast, symptomatic patients who are seizing or obtunded associated with a serum sodium concentration of less than 110 m*M* require more active intervention. The serum sodium should be corrected at a carefully controlled rate (see below) with hypertonic saline. This induces a sodium chloride osmotic diuresis, with a net electrolyte-free water loss from the patient. Hypertonic saline is used because the sodium concentration is greater than that achievable by a maximally concentrating kidney. Often, loop diuretics are added to prevent volume overload. By promoting an osmotic diuresis as a result of copious sodium chloride excretion, they also diminish urinary concentration from a relatively fixed value (say 600 mOsm) to 300 mOsm. This allows excretion of some electrolyte-free water and more rapid correction of the water excess state.

Rate of Correction

The optimal rate of correction depends on the clinical status of the patient. The general rule is that chronic hyponatremia—hypernatremia of a duration greater, say, than 48 hr—should be treated slowly, while symptomatic acute hyponatremia that developed rapidly should be treated more rapidly [3, 7]. Rapid correction of chronic hyponatremia can lead to central demyelinating lesions of central pontine myelinosis.

Thus, asymptomatic patients with chronic hyponatremia should be slowly corrected at such a rate that the serum sodium concentration rises no more than 10–12 mEq/liter for the first day and less than 18 mEq/liter over the first 2 days [13, 17, 20]. Patients with acute symptomatic hyponatremia sometimes present with seizures or neurological deficits caused by cerebral edema. This generally occurs if the hyponatremia develops in less than 2–3 days. These patients should be treated rapidly: while the patient is symptomatic, the plasma sodium can be raised at an initial rate of 1.5–2 m*M*. The rapid correction phase can be maintained for 3–4 hr or longer if the patient remains symptomatic. However, the total correction, in the first 24 hr, should not exceed 12 mEq/

liter. The rapid correction is justified, since the risk of neurologic sequela is greater than the risk of rapid correction. Women are particularly susceptible to injury from hyponatremia. Postmenopausal women may progress rapidly from subtle initial symptoms (headache and nausea) to coma and respiratory arrest within hours. Younger women are at increased risk of death from symptomatic hyponatremia, even if corrected at the above-mentioned rates. In contrast, hyponatremia in men causes fewer symptoms and carries a smaller risk of permanent neurologic injury.

INAPPROPRIATE ADH SECRETION

The syndrome of inappropriate ADH secretion (SIADH) is caused by unregulated nonphysiologic release of ADH instead of in response to the usual stimulus of hypernatremia. Expressed in different terms, ADH secretion is not suppressed by hyponatremia. This causes impaired water excretion. However, the crucial distinction, in contrast to that of volume deletion and volume excess above, is that salt excretion is normal.

The nonsupressed ADH secretion, in the presence of water intake, causes water retention, with resulting hyponatremia and ECF volume expansion [9, 23]. The volume expansion is short-lived, and therefore does not lead to edema, because of the activation of counterregulating mechanisms, including atrial natriuretic peptide (ANP), which cause renal excretion of the sodium chloride. After 1–2 weeks, a new steady state is reached in which sodium excretion equals intake. As a result, the urinary sodium concentration is normal (i.e., above 20 mM). Thus, the plasma sodium is reduced primarily because of water retention, with a small component caused by renal sodium loss. Hyponatremia cannot develop if water intake is restricted. This point is important in understanding the treatment of chronic SIADH. Table 2 shows the common causes of SIADH.

TREATMENT

Water Restriction

As described above, treatment depends on the clinical picture. In asymptomatic patients, water restriction is the primary therapy. Hyponatremia will be corrected if the patient achieves negative water balance. During the correction, the volume depletion may become unmasked unless a sufficient sodium intake is present.

Salt, Diuretic

Patients with more severe hyponatremia, or those resistant to water restriction, may require salt administration. To be effective, the osmolality of the fluid must be greater than the urine osmolality. Patients with severe SIADH can develop worsening hyponatremia even with normal saline infusions. Since renal sodium handling is intact, the patients can excrete the sodium and retain the water, causing worsening hyponatremia. If this occurs, a loop diuretic should be added to the regimen.

Additional Therapies

In the uncommon patient who does not respond to the above therapies, there are several additional lines of therapy: (i) demeclocycline, which indues a nephrogenic diabetes insipidus [11]; (ii) dietary modification to increases the production of urinary solutes (primarily protein, sodium, and potassium), thereby allowing more water to be excreted [15]; (iii) urea infusion to increase solute excretion; (iv) aquatic agents such as V2 AVP receptor antagonists that produce a selective water diuresis. In the past, lithium has been used to produce a nephrogenic diabetes insipidus. However, demeclocycline is preferred because it is more effective and less toxic than lithium [11]. Dietary modification and urea infusions will work in the patient with relatively fixed ADH levels, and hence fixed urinary osmolality, since the main determinant of urine volume is the rate of solute excretion. For example, a patient producing 1 liter of 600 mOsm urine will be excreting 600 mOsmols/day. On a high salt, high dietary protein diet, the patient produces 900 mOsmol/da allowing 1.5 liter/day urine output. This would increase the amount of electrolyte free water excretion by about 50%. However, many patients with SIADH have underlying illnesses that preclude a increased dietary intake. In contrast, the aquatic agents that are currently being tested in humans, may work well in patients with congestive heart failure and hepatic cirrhosis. Of course, the rate of normalization of hyponatremia must be carefully monitored.

DIABETES INSIPIDUS

The hallmark of diabetes insipidus (DI) is polyuria, which means the excretion of a dilute urine of greater than 3 liters a day. Renal concentrating defects, in contrast, only slightly decrease daily urine volumes to about 2 liters/day because of an inability to form a concentrated urine greater than 400–500 mOsm/kg. In contrast, true polyuria is a disorder of water balance, and has a quite limited differential diagnosis which can be caused by either a solute or water

diuresis. Water diuresis can be caused by lack of sufficient AVP release (central diabetes insipidus), destruction of circulating AVP by a circulating vasopressinase sometimes found in the third trimester of pregnancy, primary polydipsia, or inability of the kidneys to respond to AVP (nephrogenic DI). Differentiation between these conditions, described in [18], is critically important, since inadvertent administration of diuretics to patients with primary polydipsia, or solute diuresis can lead to severe hyponatremia or solute depletion.

Treatment

Diuretics have proved useful as second-line therapies in treating both central and nephrogenic diabetes insipidus. They have no role in treating solute diuresis and are extremely dangerous in patients with primary polydipsia.

Central DI

The mainstay of therapy is DDAVP, a long acting V2 receptor agonist that can be given by intranasal spray or im injection [8, 12, 14]. The usual starting dose is 2.5 μg given twice a day. Antidiuresis occurs within 1 hr. The dose is adjusted until the antidiuresis lasts 12 hr. Since DDAVP is the least vasoconstrictive of the vasopressin analogs, adverse side-effects are minimal. However, hyponatremia from water intoxication can occur if water intake is not reduced in patients with damaged thirst centers. In acute medical emergencies, where more shorter acting agents are required, aqueous vasopressin can be used. Vasopressin has a short duration of action of only 4–6 hr. Constantly changing fluid status can be reappraised frequently, and the dose of AVP appropriately adjusted. A dose of 5–10 U is given just as the polyuria reappears, thus reducing the risk of water intoxication. Antibodies to AVP occasionally develop, resulting in secondary resistance to the antidiuretic effect [4, 24]. Since the antibodies do not cross-react with DDAVP, DDAVP can be substituted for AVP. The antibodies only rarely interfere with the diagnosis of diabetes insipidus, but this presence mimics a partial nephrogenic DI.

In patients with partial central DI who have some AVP release, chlorpropamide and clofibrate can be used. They are not used very frequently because of their associated side-effects, such as hypoglycemia in the case of chlorpropamide and gallstones, hepatotoxicity, and rhabdomyolysis from clofibrate.

Paradoxically, hydrochlorothiazide (HCTZ) can decease urine output by 50% in both central and nephrogenic diabetes insipidus [21, 25]. The urine osmolality remains hypotonic, but the decreased urine volume simplifies oral water replacement. The effect is reversed by a high salt intake. The mechanism is likely multifactorial: (i) HCTZ induces a mild volume depletion, which en-

hances proximal tubule salt and water absorption. (ii) Glomerular filtration also decreases, further reducing free water delivery to the collecting ducts and less to the final urine. (iii) HCTZ reduces sodium reabsorption in the distal tubule or initial collecting duct, reducing free water delivery to the collecting ducts. Sodium must be restricted. Otherwise, volume depletion will be reversed, and polyuria will return.

Before HCTZ treatment is started, it is essential to ascertain that the patient does not have primary polydipsia. Institution of an agent that blocks maximal renal water excretion to compulsive water drinkers can lead to life-threatening water intoxication and hyponatremia.

Nephrogenic DI

The first step in treating nephrogenic DI is to attempt to reverse the concentrating defect by removing medications that cause concentrating defects, treating electrolyte disorders (especially hypokalemia and hypocalcemia), and reducing salt intake to reduce free water formation by enhancing proximal reabsorption. Fluid intake must be elevated to prevent the severe neurological complications of hypernatremia. This is especially true in infants and patients with impaired access to water or perception of thirst. Specific therapy is not indicated unless the polyuria is severe or symptomatic.

In congenital nephrogenic diabetes, affected newborn males must be recognized early to prevent the severe neurological complications of hypernatremia. Urine volume can be reduced by limiting solute load by using low solute infant formula. HCTZ can be used as described above. Some female carriers respond to large doses of DDAVP.

Amiloride has been found effective in lithium induced diabetes insipidus [2]. Lithium-induced diabetes insipidus occurs in 19% of patients on chronic lithium therapy [5]. The polyuria generally improves after cessation of lithium, but may persist for months to years.Unfortunately, cessation may not be possible because of severe, life-threatening psychiatric disorders. Treatment of this disorder is very difficult. Diuretics such as HCTZ may cause hypokalemia, which potentiates lithium toxicity and leads to variable lithium blood levels by altering the renal clearance of lithium. In contrast, amiloride has been found to decrease urine volume by 30% in one study. Amiloride acts to block the apical membrane sodium channel in the cortical collecting duct principal cell. This blockade has been thought to prevent entry of lithium in the cell, thereby limiting toxicity.

Other agents used include a combination of DDAVP and indomethacin [1, 19, 22, 26]. While neither agent works by itself, the combination of supraphysiologic concentrations of DDAVP and blockade of renal prostaglandin synthesis by indomethacin is effective. Prostaglandins oppose the action of AVP in

the collecting duct. Thus, indomethacin overcomes the resistance to the action of DDAVP.

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CHAPTER VC2

High Altitude Sickness

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INTRODUCTION

Acute mountain sickness (AMS) encompasses a wide spectrum of ill effects ranging in severity from minor discomfort to life-threatening emergencies. The two major life-threatening manifestations of AMS are pulmonary edema and cerebral edema. These are extremes in a continuum of which milder forms of AMS are common and probably underrecognized. The incidence, severity, and duration of AMS are highly correlated to the speed of ascent, the ultimate height reached, and the level of physical exertion. The syndrome is not seen in normal healthy subjects below an altitude of 2500 m. True incidence is difficult to estimate because the size of the population at risk is not known, but figures as high as 30% of those exposed to 3000 m and 75% at 4500 m have been reported [14]. The incidence of AMS is unrelated to gender or to recent respiratory illness; however, the development of high altitude pulmonary edema (HAPE) is related to strenuous exercise, exposure to cold, and the presence of underlying pulmonary vascular disease. Symptoms vary widely among subjects; common manifestations are illustrated in Table 1. Symptoms usually begin within the first 24 hr of a rapid ascent and improve over 3 to 7 days in most patients. Individual susceptibility varies but severity and duration of illness in a given subject tend to be reproducible upon repeated exposure to high alti-

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TABLE 1 Clinical Manifestations of Acute Mountain Sickness

General	Neuromuscular
Anorexia	Cognitive impairment
Nausea	Muscular weakness
Vomiting	Headache
Lethargy	Dizziness
Insomnia	Ataxia
Peripheral edema	Psychosis
	Coma
Retinal	Cardiopulmonary
Petechiae	Tachycardia
Hemorrhage	Palpitation
Papilledema	Dyspnea
	Cough
	Chest pain
	Periodic breathing during sleep

tude. The overall clinical picture is one of pulmonary and cerebral vascular hypertension, heightened sympathetic activity, and generalized fluid retention accompanied by altered vascular permeability.

ACCLIMATIZATION TO HIGH ALTITUDE

Hypoxia, rather than hypobaria, is the primary stimulus of physiologic changes at high altitude. Alveolar hypoxia causes pulmonary vasoconstriction and hypertension, arterial hypoxemia, and, if uncompensated, tissue hypoxia. As a compensatory response, various processes of acclimatization are elicited in order to alleviate tissue hypoxia. These processes include:

(i) Early sympathetic hyperactivity to increase cardiac output and O_2 delivery.
(ii) Early increase in cerebral blood flow to preserve O_2 delivery to the brain.
(iii) Progressive rise in ventilation to increase alveolar P_{O_2}.
(iv) Progressive rise in hematocrit to increase O_2 carrying capacity of blood.

Changes (i) and (ii) occur immediately and tend to aggravate pulmonary hypertension, raise cerebral vascular pressures, and predispose to both pulmonary and cerebral edema during the initial period of exposure to high altitude. Changes (iii) and (iv) occur more slowly over the course of several days and tend to raise alveolar O_2 tension, reduce hypoxic pulmonary hypertension, and

raise arterial O_2 content. These in turn lower cardiac output and cerebral blood flow requirements. Therefore as changes (iii) and (iv) become more effective, there is a gradual return of cardiac output and cerebral blood flow toward normal levels, reducing the risk of pulmonary and cerebral edema. Acute mountain sickness can potentially develop when the early increases in sympathetic activity and cerebral blood flow are exaggerated or when the augmentation of ventilation and hematocrit response becomes blunted or ineffective.

VENTILATORY ACCLIMATIZATION AND ACID–BASE HOMEOSTASIS AT ALTITUDE [11]

Upon exposure to high altitude, a drop in arterial P_{O_2} or O_2 saturation stimulates peripheral chemoreceptors and produces an immediate increase in ventilation which raises alveolar P_{O_2} (P_{AO_2}) back toward normal. The beneficial effect of hyperventilation on oxygenation is offset by the rapid development of hypocapnia and respiratory alkalosis which in turn blunts further ventilatory response. A biologic compromise is quickly reached where P_{AO_2} is only partially restored and the changes in arterial pH and P_{CO_2} are less severe than if a full ventilatory response is allowed to occur. Subsequently three mechanisms may be elicited to overcome the feedback inhibition of ventilation due to the initial respiratory alkalosis and to allow a continued increase in ventilation during the first week at high altitude:

(i) Active HCO_3^- and H^+ transport in the brain to lower pH
(ii) Enhanced lactate production in the brain
(iii) Renal compensation by HCO_3^- excretion.

Active transport of HCO_3^- out of the cerebrospinal fluid (CSF) has been postulated to begin within the first 24 hr at high altitude [21], with the effect of rapidly lowering pH and HCO_3^- concentration in the CSF, stimulating central respiratory drive and counteracting the inhibition of peripheral chemoreceptors by alkalosis. Both carbonic anhydrase and the Na^+/K^+ ATPase pump mediate HCO_3^- and H^+ transport between blood and the CSF; however, the importance of active transport in enhancing the rate of ventilatory acclimatization at different altitudes is unclear [7]. Another source for the rapid fall in pH of the CSF during early ventilatory acclimatization is increased lactate formation in the brain in response to hypoxia and alkalosis [27]; although this mechanism alone could not entirely account for the fall in CSF HCO_3^- concentration. In the periphery, the acute alkalemia induced by hyperventilation is partially ameliorated by the release of H^+ from nonbicarbonate buffers in the intracellular and extracellular fluid compartments; this acute compensation is complete within 15 min and does not involve changes in renal handling of bicarbonate.

Further reductions in plasma HCO_3^- concentration involve renal excretion of HCO_3^- which commences within a few hours after onset of hypocapnia and reaches a new steady state in 2 to 3 days at a lower set point of plasma HCO_3^- concentration. Bicarbonaturia as well as a reduction in ammonium excretion accounts for the reduction in net acid excretion and subsequent fall of plasma HCO_3^- concentration.

VASCULAR RESPONSE TO HYPOXIA AT ALTITUDE [11, 12, 28]

In the central nervous system hypocapneic hypoxia leads to a net fall in cerebral vascular resistance and increase in cerebral blood flow. The resultant increase in hydrostatic capillary pressure may contribute to fluid leakage and the development of cerebral edema. In the lung hypoxia causes vascular smooth muscle constriction and an increase in pulmonary vascular resistance. Uneven pulmonary vasoconstriction may lead to uneven distribution of perfusion and an uneven rise in microvascular pressures in different regions of the lung. This vasoconstrictive response is mediated locally and can be inhibited by calcium channel blockers such as nifedipine [2]. Hypoxia also increases sympathetic nerve activity which can increase cardiac output leading to systemic arterial hypertension as well as exacerbation of pulmonary vascular hypertension. Sympathetic hyperactivity also contributes to a lower peripheral vascular resistance, leading to an increased peripheral capillary pressure.

FLUID AND ELECTROLYTE BALANCE AT ALTITUDE [3, 4, 10]

Studies of the regulation of plasma and extracellular fluid volume at high altitude have yielded conflicting results; discrepancies are in part due to the variability in experimental protocols in terms of speed of ascent, ultimate altitude, duration spent at high altitude, degree of exertion, dietary solute and caloric intake, methods used to measure volume compartments, and the usually small number of subjects involved in each of the studies. Some of the more reproducible, clinically relevant data are summarized. Blood hematocrit rises acutely upon ascent to high altitude prior to any increase in red blood cell mass. This acute hemoconcentration is due to a shift of fluid from the intravascular to the extravascular compartment, a shift of fluid from the extracellular to the intracellular compartment, an absolute reduction of the extracellular fluid volume and total body water, or a combination of all of the above. A number of studies have described a natriuresis during acclimatization that is associated with reduced plasma and urinary aldosterone levels as well as renal potassium reten-

tion. These data suggest that a low aldosterone bioactivity may contribute to the negative sodium balance at high altitude. Despite a suppressed aldosterone activity, plasma renin activity is variable. When paradoxically high plasma renin levels were reported, they were associated with low angiotensin converting enzyme activity. Water homeostasis is also altered at high altitude, but despite a water diuresis and a higher plasma osmolarity, plasma antidiuretic hormone (ADH) levels are not increased. The mechanisms of the homeostatic reset of extracellular fluid volume and total body water are largely unknown. Body weight generally declines during the first week at high altitude due to a loss of protein, fat, and water.

PATHOGENESIS OF AMS [11, 14]

It is highly likely that the pulmonary, peripheral, and cerebral forms of high altitude sickness share similar pathogenic mechanisms of impaired acclimatization (Fig. 1). Patients susceptible to AMS tend to demonstrate less weight loss than normal, do not diurese adequately and may actually gain weight; they

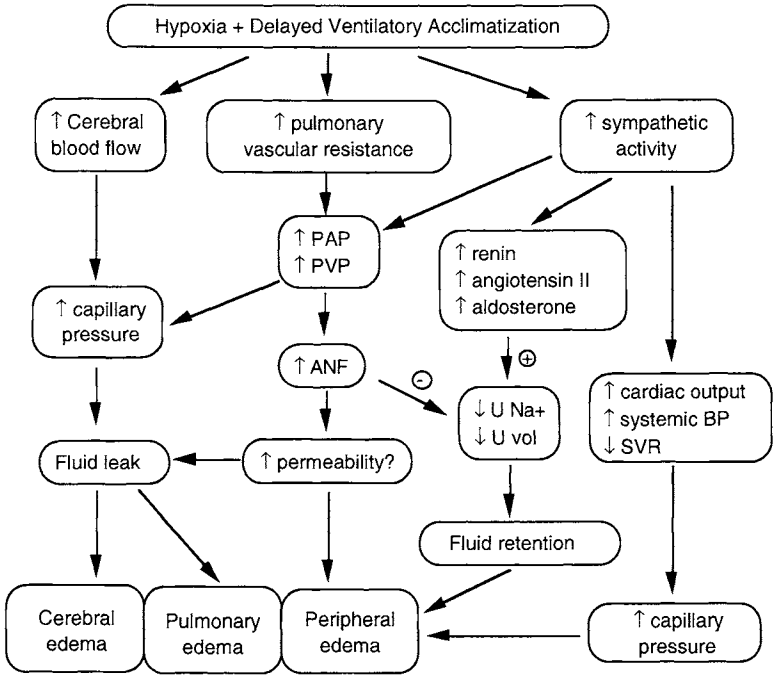

FIGURE 1. Pathogenesis of AMS. PAP, pulmonary artery pressure; PVP, pulmonary venous pressure; ANF, atrial natriuretic factor; U Na^+, urinary sodium concentration; U vol, urinary volume; SVR, systemic vascular resistance.

generally show higher plasma levels of renin, angiotensin II, aldosterone, and ADH at altitude than control subjects [3]. They may also show higher levels of atrial natriuretic factor (ANF) associated with a larger right atrial diameter as a result of a higher extracellular fluid volume. In animals exposed to chronic hypoxia, the administration of ANF is associated with a dose-dependent reduction in pulmonary artery pressure [17], but this beneficial effect may be partially offset by its direct effect in causing fluid shift to the extravascular compartment [3, 26]. Increases in plasma aldosterone, ADH, norepinephrine, and ACTH during exercise which occur in most subjects are greater in individuals who develop AMS than in those who do not. Individuals who fail to lower their extracellular fluid volume during acclimatization are at a higher risk for developing AMS. In addition, susceptible subjects are more hypoxemic in part due to a reduced ventilatory response to hypoxia; hence they tend to develop a higher pulmonary vascular resistance. A higher circulating fluid volume in conjunction with the increased pulmonary vascular resistance may render them particularly prone to pulmonary edema.

The abnormal fluid retention is not evenly distributed throughout the body, but produces edema in specific sites depending on local conditions. Both hydrostatic pressure and altered vascular permeability have been postulated as mechanisms of edema formation. According to the hydrostatic edema theory, nonuniform regional hypoxic vasoconstriction in the lung leads to nonuniform regional increases in pulmonary blood flow and pressure that may be sufficiently high (particularly after exercise) to cause stress failure of thin walled arterioles and the alveolar epithelium or to stretch the alveolar pores so that large molecules leak out of the vascular space [1, 25]. This theory is consistent with the observation that patients with a restricted pulmonary vascular bed from any etiology are more susceptible to developing HAPE and may develop the syndrome at a lower altitude than in normal subjects. Similarly, cerebral vasodilation combined with systemic hypertension would predispose to cerebral edema which is believed to underlie the generalized symptoms of AMS (Table 1). Cutaneous vasodilation would in turn predispose to peripheral edema. On the other hand, hypoxia may alter capillary membrane permeability either directly or through the local release of specific vasoactive and inflammatory mediators [22]. This permeability theory is supported by the finding of a similar cerebral blood flow in subjects with or without AMS [12], a normal pulmonary capillary wedge pressure in patients with florid HAPE, an increased pulmonary lymph flow and microvascular fluid filtration rate observed in animals exposed to hypoxia, and the finding of numerous microvascular thrombi in the lung at postmortem. The edema fluid in HAPE is highly proteinaceous containing an elevated neutrophil count, fragments of complements, and other mediators of inflammation. It remains unclear whether the release of inflammatory mediators is the cause or result of the fluid leak.

PREVENTION AND TREATMENT OF AMS [11, 14]

Effective steps for the prevention and treatment of AMS are summarized in Tables 2 and 3. The definitive prevention is slow ascent with adequate time spent at intermediate altitudes to allow gradual acclimatization. The definitive treatment is immediate descent and administration of oxygen; even a modest descent by 300 m may result in rapid and dramatic clinical improvement. Despite generalized fluid retention, aggressive diuresis should be avoided in patients suffering from AMS. High altitude pulmonary or cerebral edema is not due to cardiac failure although severe myocardial hypoxia can depress cardiac contractility. Vigorous diuresis may be harmful by further impairing cardiac output and oxygen transport. Furosemide and other potent diuretics do not prevent the development of AMS, do not accelerate normal acclimatization, and can be associated with undesirable side-effects such as hypovolemia, potassium wasting, exaggerated polycythemia, and pulmonary thromboembolism. In animal studies, furosemide-treated animals became volume contracted and had a higher death rate from high altitude sickness than animals given placebo [15]. Furthermore, symptoms of AMS and HAPE typically improve with rest alone; therefore anecdotal reports of clinical improvement after administration of furosemide cannot be solely attributed to the diuretic.

TABLE 2 Treatment of Acute Mountain Sickness

Mild to moderate symptoms
Rest
Acetaminophen
Acetazolamide (250 mg q8h)
Severe symptoms
Descent
Oxygen
Dexamethasone (4 mg q6h)
Acetazolamide (250–500 mg q8h)
Nifedipine (10 mg sublingual × 1 + 20 mg po q6h)
Inhaled nitric oxide (40 ppm)
Positive pressure breathing
Compression chamber

EFFECTIVE DRUGS IN THE TREATMENT OF AMS

Mild symptoms of AMS can be alleviated with rest and analgesia. The only diuretic routinely administered for both prevention and treatment of AMS is the carbonic anhydrase (CA) inhibitor acetazolamide. The primary action of acetazolamide is to hasten the rate of ventilatory acclimatization by:

(i) accelerating the renal loss of bicarbonate. The resulting mild metabolic acidosis enhances ventilatory response to hypoxia.
(ii) increasing the P_{CO_2} gradient between brain tissue and alveolar air by preventing the equilibration of CO_2 between cerebral tissue and capillary blood as well as between pulmonary capillary blood and the alveolar air. The resultant relative respiratory acidosis in the brain further stimulates ventilation.

Inhibition of renal CA is considered the main action of the drug that accelerates ventilatory acclimatization. However, acetazolamide can also directly induce generalized tissue CO_2 retention. In the pulmonary capillaries, CA inhibition of the red blood cells and the pulmonary endothelium produces an alveolar–arterial CO_2 gradient which accentuates stimulation of the chemoreceptors to increase ventilation [13]. Although CA is present in the cerebral glial cells and the formation of HCO_3^- in the CSF is likely CA-dependent, it has not been clearly shown whether CA inhibition can cause direct acidification of the CSF independent of systemic acidosis. Nonetheless such a direct action seems plausible. Cerebral blood flow may or may not increase significantly in response to administration of acetazolamide but the production of CSF is reduced. Acetazolamide augments the ventilatory response to hypoxia by elevating the relationship of ventilation to arterial O_2 saturation without changing the slope of the relationship [23]. In patients with established AMS, acelazolamide has been shown to ameliorate symptoms as well as increase ventilation, improve oxygenation, and lower arterial P_{CO_2}; the increase in resting alveolar ventilation occurs without any change in CO_2 chemosensitivity [6]. Acetazolamide reduces the wide fluctuations in arterial O_2 saturation associated with periodic breathing during sleep at altitude. The action of acetazolamide is superior to that of other respiratory stimulants such as almitrine. In acclimatized normal subjects studied at high altitude, both acetazolamide and almitrine improve oxygenation during sleep; however, the duration of periodic breathing during sleep is reduced in subjects given acetazolamide but increased in subjects given almitrine [9]. Subjects taking acetazolamide during acclimatization demonstrate significantly better preservation of body weight, muscle mass, and total body fat than subjects given placebo and similar dietary intake [5]. In addition to stimulation of ventilation, acetazolamide also causes a mild diuresis which may augment the hypoxia-induced increase in hematocrit and further improve oxygen transport.

Although earlier studies have utilized high doses of acetazolamide (e.g., 1500 to 2000 mg orally in a single dose) which inhibit renal, red blood cell, pulmonary, and cerebral CA, lower doses (e.g., two to three doses of 250 to 500 mg orally 8 hr apart) which predominantly inhibit renal CA also result in significant clinical improvement within 24 hr in patients suffering from AMS. Benzolamide, a more impermeant CA inhibitor that acts on luminal CA in the renal tubules with relatively little effect on red cell and tissue CO_2 transport, is effective in reducing periodic breathing and improving daytime O_2 saturation in subjects exposed to high altitude [24].

Other medications effective in the treatment of high altitude sickness include dexamethasone, nifedipine, and inhaled nitric oxide. Dexamethasone suppresses the inflammatory mediators associated with altered capillary permeability; it is often given concurrently with acetazolamide to treat severe cases of AMS [8,16]. By blocking calcium influx in pulmonary artery smooth muscle cells, nifedipine effectively relieves pulmonary hypertension and improves arterial oxygenation in mountaineers who develop HAPE [18]. Nifedipine may also block the calcium-mediated steps of the inflammatory response, including the activation of phospholipase A_2, leading to a lower permeability of the capillary membrane. Acute inhalation of the endothelium-derived smooth muscle relaxing factor nitric oxide at a concentration of 40 ppm produces a greater decrease in systolic pulmonary artery pressure at high altitude in subjects prone to HAPE than in subjects resistant to HAPE and improves arterial oxygenation in subjects with active HAPE [20]. These changes result from the redistribution of pulmonary blood flow away from edematous segments toward nonedematous segments, thereby improving ventilation–perfusion matching (see Table 3).

TABLE 3 Prevention of Acute Mountain Sickness

Identify individual susceptibility
Previous history
Cardiopulmonary disease
Slow ascent
<300 m per day above 3000 m
Avoid alcohol, sedatives, and excessive exertion
Acetazolamide
250–500 mg qhs up to 250 mg q8h × 3 to 5 days starting on day before ascent
(Nifedipine)
20 mg qd × 2 days before ascent
20 mg q8h × 3 days starting on day of ascent
(Dexamethasone)
4 mg q12h starting on day of ascent
Continue for 3–5 days with taper

EFFECTIVE DRUGS IN THE PREVENTION OF AMS

Prophylactic administration of acetazolamide at 10 mg per kg given in two to three oral doses 8 hr apart beginning prior to ascent significantly improves arterial P_{O_2} upon acute exposure to high altitude. Lower doses (250–500 mg qhs) are also effective and the minimum dose should be established individually. After drug administration the greatest increase in arterial P_{O_2} is seen after 24 hr at high altitude, suggesting that cerebrospinal fluid alkalosis is corrected first before ventilatory augmentation occurs. In prospective trials, prophylaxis significantly reduces the frequency and severity of symptoms of AMS but does not clearly improve exercise performance at high altitude. The duration of treatment or prophylaxis is highly individualized but the drug may be continued for 5 to 7 days if necessary. Side-effects are frequent but generally mild, including paresthesia of the face and extremities, gastrointestinal upset, somnolence, and altered taste of carbonated beverages. For subjects allergic to sulfa drugs, or for circumstances where an urgent rapid ascent is unavoidable, dexamethasone may be administered as an alternative or adjunct prophylactic agent. Although dexamethasone is effective in preventing AMS [19], the drug has not gained widespread usage. Dexamethasone does not accelerate ventilatory acclimatization, and symptoms of recurrent AMS as well as adrenal suppression can occur after discontinuation of the drug. Nifedipine has recently been shown as an effective prophylaxis against the development of HAPE in susceptible subjects [2] but its major side-effect, systemic hypotension, requires close medical supervision and precludes its routine use. The efficacy of nifedipine in preventing or treating other manifestations of AMS has not been established.

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CHAPTER VC3

Diuretics in the Treatment of Metabolic Alkalosis

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INTRODUCTION

After correcting the underlying cause, the initial goal in the treatment of metabolic alkalosis is to remove those factors that are responsible for maintaining the alkalosis. In some circumstances, diuretic therapy may be the preferred method of achieving this goal. When utilizing this approach, however, one needs to consider carefully both the type of diuretic to be used as well as the underlying condition that gave rise to the metabolic alkalosis. For example, use of mercurial, thiazide, or loop diuretics in the setting of metabolic alkalosis that is associated with decreased extracellular fluid volume would be expected to worsen the alkalotic state. On the other hand, the potassium sparing diuretics are well suited to treating metabolic alkalosis that occurs in the setting of primary increases in mineralocorticoid activity. As a result, it becomes of paramount importance to be able to distinguish between those causes of metabolic alkalosis in which diuretic therapy is contraindicated and those conditions in which diuretics may be of clinical benefit. This chapter will briefly review the pathogenesis of metabolic alkalosis. Following this review, a categorization of clinical syndromes associated with metabolic alkalosis will be presented which will provide a rational basis by which to determine if and when diuretic therapy

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is indicated. The remainder of the chapter will focus on those conditions in which diuretic therapy has proven to be of therapeutic benefit.

GENERATION AND MAINTENANCE OF METABOLIC ALKALOSIS

The pathogenesis of metabolic alkalosis involves both a generation and a maintenance phase. In the generation of metabolic alkalosis new bicarbonate must be added to the blood as a result of either a loss of acid or a gain of alkali. This gain in new bicarbonate may be generated by either renal or extrarenal mechanisms. Because the kidneys have an enormous capacity to excrete bicarbonate, even vigorous bicarbonate generation may not be sufficient to produce sustained metabolic alkalosis. To maintain a metabolic alkalosis, the capacity of the kidney to reclaim bicarbonate must be enhanced. On the other hand, increasing the capacity for bicarbonate reclamation in the absence of bicarbonate generation will also not result in metabolic alkalosis. Thus, the two ingredients required for the pathogenesis of metabolic alkalosis are the generation of new bicarbonate combined with an augmentation in the capacity of the kidney to reclaim the filtered bicarbonate.

Renal Generation of Metabolic Alkalosis

Bicarbonate may be generated from renal or extrarenal sources (Table 1). The renal generation of bicarbonate involves, in general, three features: (1) relatively high distal delivery of sodium salts; (2) persistent mineralocorticoid ex-

TABLE 1 Generation of Metabolic Alkalosis

I. Excessive loss of acid
Extrarenal
Loss of acid into gastric juice: vomiting, nasogastric suction
Intestinal acid loss: villous adenoma, congenital chloridorrhea
Translocation of acid into cells: K deficiency
Renal
Coupling of high mineralocorticoid activity and high distal Na delivery
Persistent mineralocorticoid excess
Potassium deficiency
II. Excessive gain of bicarbonate
Oral or parenteral intake of bicarbonate (usually in setting of impaired renal function)
Metabolism of lactate, ketones, or other organic anions to bicarbonate

cess; and (3) potassium deficiency. For these processes of bicarbonate generation to initiate metabolic alkalosis, enhanced bicarbonate reclamation also is usually necessary to hasten removal of bicarbonate in the proximal portions of the nephron. Bicarbonate removal in the proximal nephron allows longer segments of the distal tubule to be exposed to a bicarbonate-free urine. Instead of expending its comparatively limited hydrogen ion secretory capacity in bicarbonate reabsorption, the distal nephron can generate new bicarbonate, depending on the stimuli to which it is subjected and the composition of the fluid reaching it.

A simple increase in distal delivery of sodium salts without an increase in mineralocorticoid activity does not lead to an increase in net acid excretion and results only in the increased urinary excretion of administered sodium. Similarly, increased mineralocorticoid activity in the absence of distal sodium delivery fails to increase net acid excretion. In order to augment net acid excretion, and thus generate a metabolic alkalosis through renal mechanisms, delivery of sodium salts to the distal nephron must be in the setting of increased mineralocorticoid activity. Aldosterone directly stimulates electrogenic Na reabsorption in the cortical collecting tubule by stimulating both apical membrane Na permeability, mitochondrial enzymes, and the Na/K ATPase. This leads to an increased negative voltage of the tubule lumen that secondarily increases the rates of K and H secretion. For every hydrogen ion secreted into the lumen a bicarbonate is returned to the blood. In the absence of distal Na delivery, aldosterone cannot stimulate Na reabsorption and thus cannot change the voltage of the lumen. As a result, H and K secretion are not stimulated. While aldosterone has been shown to have a direct stimulatory effect on H secretion in the distal nephron, the observation that mineralocorticoids do not stimulate K or H excretion by the kidney in subjects on a low-salt diet implies that this direct effect is quantitatively of lesser importance that the voltage effect.

Potassium depletion has several effects on renal acidification mechanisms which contribute to the maintenance and generation of metabolic alkalosis. Potassium depletion can lead to a decrease in glomerular filtration rate, which would lower the filtered load of bicarbonate and secondarily help to maintain metabolic alkalosis. In addition, potassium depletion has been demonstrated to stimulate rates of proximal and distal tubular hydrogen ion secretion. In the proximal tubule, increased rates of hydrogen ion secretion are associated with decreased cell pH and increased activities of the apical Na/H antiporter and the basolateral membrane $Na/3HCO_3$ cotransporter. Last, potassium depletion leads to an adaptive increase in the enzymes that synthesize ammonia, causing increased rates of ammoniagenesis in the proximal tubule. While all of these effects contribute to the generation and maintenance of metabolic alkalosis, potassium deficiency also inhibits aldosterone secretion, an effect that will inhibit acidification. The net result is that potassium deficiency alone has

been shown to have only a variable effect on overall acid–base balance when examined in different species. In humans, potassium deficiency alone will generally not cause significant metabolic alkalosis. However, a few patients have been described where severe potassium depletion (concentrations less than 2 mEq/liter) is associated with maintenance of metabolic alkalosis. By contrast, if potassium depletion occurs in the setting where mineralocorticoid secretion is nonsuppressible, then the stimulatory effects on renal acidification dominate and metabolic alkalosis will develop. Indeed, in patients with primary hyperaldosteronism, patients with the most severe potassium depletion have the most marked metabolic alkalosis.

Extrarenal Generation of Metabolic Alkalosis

Extrarenal factors may also be responsible for the generation of metabolic alkalosis (Table 1). Acid loss, as in vomiting, can be a source of new bicarbonate added to the blood. Alkali gain, as in the milk–alkali syndrome or use of injectable $NaHCO_3$ during cardiopulmonary resuscitation, may also generate metabolic alkalosis. Acid may also be translocated within the body, producing acidosis in one compartment and alkalosis in the other. This may occur with severe potassium deficiency. Finally, relative bicarbonate generation (increased concentration) may be induced by extracellular volume contraction. In order for metabolic alkalosis to be sustained in any of these circumstances, the capacity of the kidney to reclaim bicarbonate must also be enhanced.

Maintenance of Metabolic Alkalosis

Reduced effective arterial blood volume is the mechanism responsible for the maintenance of metabolic alkalosis in the majority of patients (Table 2). The mechanisms by which volume contraction maintains metabolic alkalosis have

TABLE 2 Maintenance of Metabolic Alkalosis

Increased proximal bicarbonate reabsorption
Reduced effective arterial blood volume
Potassium deficiency
Increased pCO_2 concentration
Increased distal bicarbonate reabsorption
Persistent mineralocorticoid excess
Potassium deficiency
Reduced glomerular filtration rate

been recently reviewed and will be only briefly summarized. In some settings volume contraction is associated with a decrease in the glomerular filtration rate. A decrease in glomerular filtration rate would tend to maintain metabolic alkalosis by decreasing the filtered load of bicarbonate presented to the tubules. In addition, volume contraction increases the capacity of the proximal tubule to reabsorb HCO_3 by two mechanisms. First, volume contraction leads to a decreased permeability of the pericellular pathway to HCO_3 and thus inhibits the backleak of HCO_3 from the blood into the tubular lumen. Second, chronic decreases in extracellular fluid volume lead to an adaptation in the proximal tubule which is associated with enhanced Na/H antiporter activity and tubular hypertrophy. These effects increase the capacity of the proximal nephron for bicarbonate reabsorption. Last, volume contraction decreases distal Cl delivery to the cortical collecting tubule. Since HCO_3 secretion in the collecting tubule requires luminal Cl to exchange for HCO_3, the rate of HCO_3 secretion will be decreased.

Factors which reduce the steady state pH of the proximal tubule, notably hypercapnia and potassium deficiency, will also contribute to the maintenance of metabolic alkalosis. Under these conditions total hydrogen ion secretary capacity is increased, resulting in enhanced bicarbonate reabsorption. In states of chronic metabolic alkalosis the pCO_2 concentration increases due to hypoventilation as a compensatory response to the alkaline pH. The resultant decrease in cell pH stimulates hydrogen ion secretion in the proximal nephron and therefore contributes to the maintenance of metabolic alkalosis. This stimulatory effect is small in magnitude since the rise in pCO_2 is accompanied by a fall in arterial pO_2 concentration which acts to stimulate respiration, thus limiting the rise in pCO_2.

Since hypercapnia ordinarily is not very severe in metabolic alkalosis, potassium deficiency is usually the principal determinant of augmented hydrogen ion secretion. As discussed earlier, isolated potassium deficiency is generally not sufficient to generate metabolic alkalosis but is an important factor in the maintenance of metabolic alkalosis. The principal site where potassium deficiency enhances bicarbonate reclamation is the proximal nephron. Potassium deficiency also augments distal hydrogen secretary capacity, since, in the presence of potassium deficiency, distal sodium delivery will preferentially elicit hydrogen rather than potassium secretion, thereby serving to reclaim the sodium bicarbonate that escapes proximal reabsorption. Although expansion of volume can override the effects of moderate potassium deficiency, a severe degree of potassium depletion will serve to maintain metabolic alkalosis even in the face of sufficient volume expansion to produce copious chloruresis. For example, in the setting of primary mineralocorticoid excess where extracellular fluid volume is expanded, potassium deficiency is the main factor responsible for the perpetuation of the alkalosis. Correction of the potassium deficit will return the plasma bicarbonate concentration toward normal in this setting.

Mineralocorticoids contribute to the maintenance of metabolic alkalosis by stimulating hydrogen ion secretion in the distal nephron. As discussed earlier, mineralocorticoids are important in the generation and maintenance of metabolic alkalosis only when high levels are associated with increased distal delivery of sodium. This will occur with primary increases in mineralocorticoids where mineralocorticoid-induced volume expansion ensures high distal delivery of sodium. Diuretics may also cause this picture, with volume contraction leading to high aldosterone levels and the diuretic maintaining distal delivery. Only diuretics which act proximal to the cortical collecting tubule would be expected to have such an effect. Bartter's syndrome and magnesium deficiency are in many respects similar to diuretic ingestion in that these patients have high renin and aldosterone levels, hypokalemic alkalosis, and are not hypertensive. Distal delivery of sodium is high in these disorders as a result of impaired reabsorption of NaCl in the loop of Henle. In patients with extrarenal generation of alkalosis, filtered loads of HCO_3 may exceed the capacity of the proximal tubule, leading to distal delivery of Na and HCO_3 and thus allowing high mineralocorticoid levels to play a role by increasing hydrogen ion secretion and decreasing the magnitude of bicarbonaturia.

CLINICAL SYNDROMES ASSOCIATED WITH METABOLIC ALKALOSIS

Table 3 lists the clinical syndromes associated with metabolic alkalosis. The two major categories of metabolic alkalosis are those associated with volume contraction and volume expansion.

Volume Contraction with Mineralocorticoid Excess

These conditions are characterized by a contraction of effective extracellular fluid volume, a circumstance usually associated with reduced distal delivery of Na salts and a volume mediated stimulation of the renin–angiotensin–aldosterone system. Ordinarily, this would not produce alkalosis. However, if distal sodium delivery is inappropriately increased as with use of diuretics or secondary to the presence of a poorly reabsorbable anion, then net acid excretion will be stimulated and alkalosis may result. In addition, extrarenal loss of acid (vomiting) will generate an alkalosis which is maintained because the combination of extracellular fluid volume contraction and varying degrees of hypokalemia stimulate bicarbonate reabsorption.

TABLE 3 Syndromes of Metabolic Alkalosis

Effective volume contraction, secondary increase in aldosterone, blood pressure normal or low
Gastrointestinal or dietary origin
Vomiting or nasogastric suction
Chloride wasting diarrhea
Villous adenoma
Renal origin
Diuretics (mercurial, loop or thiazide diuretics)
Volume depletion with increased distal delivery of poorly reabsorbable anions
Bartter's syndrome
Magnesium deficiency
Posthypercapnic state
Extracellular fluid volume expansion with mineralocorticoid excess, increased blood pressure
Increased renin, increased aldosterone
Renal artery stenosis
Accelerated hypertension
Renin secreting tumor
Decreased renin, increased aldosterone
Primary aldosteronism
Adrenal adenoma
Bilateral adrenal hyperplasia
Dexamethasone-responsive adrenal hyperplasia
Carcinoma
Decreased renin, decreased aldosterone
Cushing's syndrome
Exogenous mineralocorticoid
Congenital adrenal enzyme defect
Extracellular fluid volume expansion, suppressed mineralocorticoid, increased blood pressure
Liddle's syndrome
Exogenous bicarbonate load in setting of decreased glomerular filtration rate
Milk alkali syndrome
Miscellaneous
Compartmental shift: potassium deficiency
Contraction alkalosis

Volume Expansion with Mineralocorticoid Excess

These conditions are associated with a primary increase in mineralocorticoid activity. Increased mineralocorticoid activity is considered primary in that it persists in the face of activation of the control system normally responsible for its suppression, an expansion of the effective extracellular fluid volume. As long as dietary sodium is normal, distal delivery of sodium salts will be plentiful and, as a result, urinary potassium and net acid excretion are increased, result-

ing in potassium deficiency and generation of metabolic alkalosis. As discussed earlier, the resulting hypokalemia further increases net acid excretion in the presence of nonsuppressible mineralocorticoid activity.

A variety of stimuli may be responsible for the excessive mineralocorticoid activity. Increased activity may be caused by aldosterone, the hypersecretion of which results from increased renin–angiotensin activity. Increased renin production may result from conditions such as renal artery stenosis, accelerated hypertension, or a renin-secreting tumor. Hypersecretion of aldosterone also may be associated with suppressed renin. Conditions which can give rise to primary hyperaldosteronism include an adrenal adenoma, bilateral adrenal hyperplasia, and dexamethasone-responsive adrenal hyperplasia. A third group of patients display evidence of excessive mineralocorticoid activity attributable to some agent other than aldosterone. Examples of these syndromes would include the various causes of Cushing's syndrome, in which secretion of hydrocortisone is increased, and oversecretion of deoxycorticosterone, as found in some adrenogenital syndromes.

Volume Expansion with Mineralocorticoid Suppression

In the setting of significant renal disease bicarbonate clearance will be decreased and severe metabolic alkalosis may occur following exogenous bicarbonate administration. Similarly, renal insufficiency is a critical event in the pathogenesis of milk–alkali syndrome. In this syndrome consumption of large quantities of milk and calcium containing antacids will result in hypercalcemia and metabolic alkalosis.

Liddle's syndrome has all the clinical features of primary mineralocorticoid excess and yet all endogenous mineralocorticoids are suppressed. Recent data would suggest that this disorder results from a genetic defect in the amiloride sensitive sodium channel such that its activity is constituatively increased.

DIURETIC USE IN THE TREATMENT OF METABOLIC ALKALOSIS

It is important to be able to distinguish between the various clinical syndromes associated with metabolic alkalosis before considering the use of diuretics as treatment. In some conditions use of certain diuretics may actually worsen the alkalotic state while in other circumstances certain diuretics may be the preferred mode of therapy (Table 4). In general, the mercurial, thiazide, and loop diuretics have no place in the treatment of metabolic alkalosis. In fact, one of the most common causes of metabolic alkalosis is the use of these diuretics.

TABLE 4 Diuretic Use in the Treatment of Metabolic Alkalosis

Acetazolamide	
	Patients with volume overload and reduced effective arterial blood volume who cannot tolerate further NaCl: congestive heart failure, cirrhosis
	Chronic respiratory acidosis and cor pulmonale
Spironolactone, triamterene, amiloride	
	Primary increase in mineralocorticoid activity
Triamterene, amiloride	
	Liddle's syndrome

Note: Mercurial, loop, and thiazide diuretics are all associated with the development of metabolic alkalosis and, in general, are not used in the treatment of metabolic alkalosis.

The mechanism by which these agents give rise to metabolic alkalosis is discussed in detail in Chapter VC1.

Volume Contraction with Secondary Mineralocorticoid Excess

In these conditions volume depletion is the principal factor responsible for maintaining the metabolic alkalosis. Administration of isotonic saline to restore volume will correct the alkalosis in most situations. As a result, diuretic therapy is mostly contraindicated in these clinical syndromes of metabolic alkalosis. However, in certain patients with metabolic alkalosis administration of NaCl may be poorly tolerated. This situation arises in edematous patients whose metabolic alkalosis is maintained by decreased effective arterial blood volume but whose cardiovascular system cannot tolerate further addition of NaCl. The most commonly used approach toward correcting alkalosis in these difficult patients is use of the diuretic, acetazolamide.

The mechanism by which acetazolamide leads to inhibition of bicarbonate reabsorption is directly related to its ability to inhibit luminal carbonic anhydrase. This enzyme normally catalyzes the dehydration of carbonic acid (produced when filtered bicarbonate reacts with secreted hydrogen ions) to water and CO_2, thereby maintaining a favorable concentration gradient for further hydrogen ion secretion. The uncatalyzed dehydration of carbonic acid occurs very slowly. By inhibiting the activity of this enzyme, acetazolamide allows for the concentration of luminal carbonic acid to increase. The resultant increase in hydrogen ion concentration creates an unfavorable concentration gradient for further hydrogen ion secretion. Due to the lipid solubility of acetazolamide, inhibition of intracellular carbonic anhydrase may also contribute to the impairment in proximal bicarbonate reabsorption. Inhibition of the intracellular

enzyme will decrease the supply of hydrogen ions available for the secretory process. In either case, decreased secretion of hydrogen ions will inhibit reabsorption of filtered bicarbonate and thus cause the kidney to at least partially correct the metabolic alkalosis. The magnitude of the bicarbonaturia is directly related to the serum bicarbonate concentration. As the bicarbonate concentration falls, the clinical effectiveness of the drug declines in a parallel fashion. As a result, only rarely does the plasma bicarbonate concentration return to normal.

Acetazolamide may also be used in patients with chronic respiratory acidosis who develop a metabolic alkalosis. Normally, in patients with chronic respiratory acidosis the capacity of the kidney to reabsorb bicarbonate increases. This increased capacity to reabsorb bicarbonate is a compensatory response and is the result of increased hydrogen ion secretion by the proximal tubule mediated by a decrease in cell pH. The rise in plasma bicarbonate concentration serves to attenuate the fall in systemic pH that would otherwise occur as a result of hypercarbia. Use of loop diuretics in such patients, as in the treatment of cor pulmonale, can result in further increases in the serum bicarbonate concentration. In this setting, the induction of a metabolic alkalosis can depress ventilation, aggravating both the hypoxemia and the hypercapnia. Normally the metabolic alkalosis can be treated by discontinuing the diuretic and administering NaCl. In the patient who is significantly edematous, however, this approach may not be practical. In this circumstance, acetazolamide can be used to inhibit bicarbonate reabsorption and thus lower the serum bicarbonate concentration.

A potential problem that is associated with use of carbonic anhydrase inhibitors in patients with lung disease is a worsening of hypercapnia. Carbonic anhydrase is normally present within red blood cells and is involved in CO_2 movement into red cells in peripheral tissues and movement from red cells into the alveoli in the lungs. Thus carbonic anhydrase inhibition can prevent red cell uptake of pCO_2 in peripheral tissues and can prevent pCO_2 release in the lung. The latter can lead to an increase in pCO_2 of the arterial blood, while the former leads to an even further increase in pCO_2 in peripheral tissues. Generally, patients with normal lungs can respond to this by increasing respiration and preventing the increase in the pCO_2 of the arterial blood. However, patients with lung disease cannot respond adequately and further increases in arterial pCO_2 as well as even larger increases in tissue pCO_2 may be dangerous to the patient.

Volume Expansion with Primary Mineralocorticoid Excess

In these syndromes, nonsuppressible mineralocorticoid activity is the underlying factor in the generation and maintenance of metabolic alkalosis. The pre-

ferred treatment of these syndromes is to remove the underlying cause of the persistent mineralocorticoid activity. When this is not possible, then therapy is directed at blocking the actions of the mineralocorticoid at the level of the kidney. The potassium sparing diuretics are effective agents in blocking the actions of mineralocorticoids in the kidney and are commonly used in the treatment of these disorders.

The potassium sparing diuretics block the mineralocorticoid-induced increases in hydrogen and potassium secretion. The mechanism by which these drugs impair distal hydrogen ion and potassium secretion is related to their ability to decrease the luminal electronegativity of the collecting duct. The potassium sparing diuretics decrease the luminal electronegativity of the collecting duct by inhibiting the reabsorption of Na in this segment. The manner in which this is accomplished, however, differs between the various agents. Amiloride and triamterene directly inhibit Na reabsorption by blocking the Na channel located on the luminal membrane. Spironolactone inhibits sodium reabsorption indirectly by blocking the binding of aldosterone to its cytoplasmic receptor, thereby inhibiting aldosterone-induced sodium reabsorption. The decrease in luminal electronegativity impairs distal acidification as a result of the decrease in driving force for hydrogen ion secretion into the tubular lumen. Spironolactone can further limit distal hydrogen ion secretion because this drug not only inhibits aldosterone-stimulated Na reabsorption but also blocks the direct stimulatory effect of aldosterone on the hydrogen ion secretory pump.

Either the mineralocorticoid receptor blocker (spironolactone) or the sodium channel blockers (triamterene and amiloride) will be effective in treating the metabolic alkalosis and hypokalemia associated with primary increases in mineralocorticoid activity.

Volume Expansion with Mineralocorticoid Suppression (Liddle's Syndrome)

As discussed earlier, this syndrome is characterized by hypokalemic metabolic alkalosis and volume expansion but is not due to mineralocorticoid excess. Rather, this disorder results from overactivity of the Na channel in the distal nephron. Predictably, use of spironolactone to block the mineralocorticoid receptor is without effect in this disorder. By contrast, the electrolyte abnormalities and hypertension are normalized by use of the sodium channel blockers, triamterene and amiloride.

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CHAPTER VC4

Use of Diuretics in Disorders of Calcium Metabolism

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SITE AND MECHANISM OF ACTION OF DIURETICS ON RENAL CA HANDLING

Figure 1 indicates the sites of action of various diuretics on Ca transport in the nephron. It represents a composite of data from several investigators [37, 39]. The mechanism of action of the different classes of diuretics on renal Ca transport will now be reviewed in the order of their respective sites of action in the tubule.

OSMOTIC DIURETICS

Osmotic diuretics such as mannitol increase both Na and Ca excretion in the urine. The mechanism probably involves parallel inhibition of Na and Ca reabsorption in both the proximal tubule and the loop of Henle, overwhelming the more distal Ca reabsorptive mechanisms.

ACETAZOLAMIDE

Although acetazolamide inhibits both Na and Ca reabsorption in the proximal tubule, in the final urine only Na excretion is increased, while Ca excretion is

Diuretic Agents: Clinical Physiology and Pharmacology

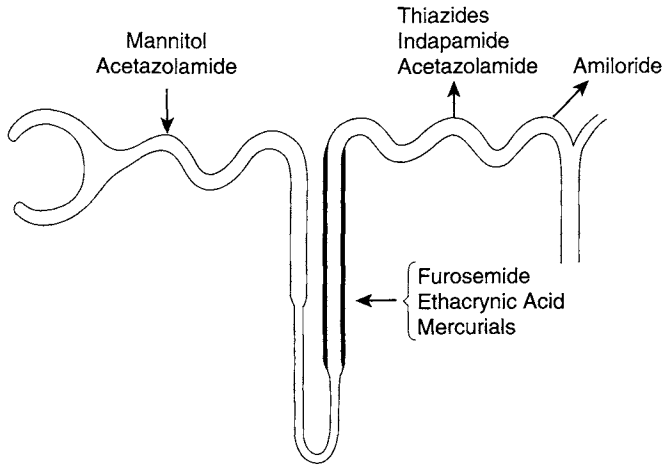

FIGURE 1. Sites of action of various diuretics on Ca transport in the mammalian nephron. Arrows pointing toward a nephron segment denote inhibition of Ca reabsorption; arrows pointing away from a nephron segment denote stimulation of Ca reabsorption. Modified with permission from Ref. [37].

either unchanged or reduced. This observation clearly suggests a preferential reabsorption of Ca in the distal nephron. Postulated mechanisms include a direct thiazide-like effect on distal Ca reabsorption or a distal inhibitory effect on Na reabsorption with consequent reduction in lumen electronegativity and parallel reduction in potential difference (PD)-driven Ca reabsorption. Since acetazolamide also inhibits proximal bicarbonate reabsorption, the consequent increase in distal delivery of this molecule may increase Ca reabsorption similar to that observed in metabolic alkalosis.

Loop Diuretics

Loop-active diuretics such as furosemide, ethacrynic acid, and the mercurial diuretics produce a large increase in Na and Ca excretion. The primary action is the inhibition of Na and Cl transport in the thick ascending limb, which in turn, would dissipate the lumen-positive PD, the force responsible for the reabsorption of Ca in this nephron segment [34,16]. The increase in Ca excretion is relatively greater than that of Na. This has been attributed to a greater inhibitory effect of the loop diuretics on the reabsorption of Ca than on the reabsorption of Na [29]. Alternately, this may be a reflection of greater reabsorption of Na than Ca in the more distal nephron segments. With replacement of the urinary losses other than Ca, high Ca excretion rates can be maintained with

furosemide treatment. This regimen is used therapeutically to lower serum Ca levels acutely in severe cases of hypercalcemia [36].

Thiazides

Acute administration of thiazide diuretics is associated with a marked natriuresis but only a small increase or a decrease in Ca excretion [4]. Based on *in vivo* microperfusion studies in the rat, Costanzo and Windhager demonstrated that chlorothiazide, in addition to its known inhibitory effect on Na reabsorption, also exhibited an acute stimulatory effect on Ca reabsorption in the distal convoluted tubule [14]. Although thiazide diuretics enhance the ratio of Ca to Na reabsorptions, the tendency for absolute hypocalciuria can be overridden initially by the large natriuretic response to these drugs. Volume contraction, which minimizes the natriuretic response to diuretics, allows a more immediate and pronounced hypocalciuric response to thiazides [4]. The hypocalciuric effect of thiazides appeared to be mediated through a parathyroid hormone (PTH)-independent mechanism [13, 5].

Long-term administration of thiazide diuretics produces frank hypocalciuria that can be reversed by salt replacement [12]. This observation suggests that the long-term effect on urinary Ca excretion involves enhanced proximal reabsorption in response to extracellular fluid volume contraction. The latter property forms the basis for the treatment of patients with idiopathic hypercalciuria [40] and hypoparathyroidism [27]. With salt restriction and long-term therapy with thiazide agents, the potential for hypercalciuria and stone formation is reduced and serum Ca can be normalized.

The Potassium-Sparing Diuretics

The potassium-sparing diuretics, amiloride, triamterene, and spironolactone, cause a greater increase in Na than Ca clearance, i.e., reducing the ratio of Ca clearance to Na clearance [37, 39]. Amiloride, like the thiazides, has been shown to cause absolute reduction in Ca clearance. The mechanism, however, appears to be different from that of the thiazides since the effect of the two diuretics is additive [15]. In perfusion studies, the effect of amiloride is mainly observed in the latter half of the distal convoluted tubule (DCT), while the effect of thiazides is observed in the first portion of the DCT [15]. Unlike chlorothiazide, amiloride reduced distal tubule and collecting duct negative potential difference (PD) and may thus reduce Ca back flux into the lumen and thereby increase net Ca reabsorption [13]. Spironolactone may act primarily by inhibiting the mineralocorticold effects on the distal nephron [35].

USE OF DIURETICS IN MANAGEMENT OF HYPERCALCEMIA

Hypercalcemia of any cause may result in a syndrome consisting of intractable nausea and vomiting, dehydration, stupor, coma, and azotemia that, unless recognized and promptly treated, is accompanied by a high mortality [36]. Hypercalcemia occurs most commonly in association with malignant disorders and primary hyperparathyroidism. Together, malignancy-associated hypercalcemia and primary hyperparathyroidism constitute over 90% of the hypercalcemia likely to be encountered. In the approach to the management of the hypercalcemic patient, it is very important to establish the diagnosis expeditiously and accurately. This is done readily by considering these two most common causes first, distinguishing between them on clinical grounds and by measuring the circulating level of PTH. In primary hyperparathyroidism, an assay that measures intact, circulating PTH will be elevated in approximately 90% of patients whereas in hypercalcemia of malignancy, PTH levels are invariably suppressed [25]. The seriousness, and hence the approach to management of hypercalcemia, depends on whether it is mild, moderate, or severe [2].

Management of Hypercalcemia Based on Severity

Management of the Patient with Mild Hypercalcemia

The most common cause of calcium levels within 1 mg/dl above the upper limit of normal is primary hyperparathyroidism. If the normal range of serum Ca concentration is 8.5–10.5 mg/dl, most patients with primary hyperparathyroidism will show Ca levels between 10.6 and 11.5 mg/dl. Even with mild hypercalcemia, if such a patient suffers from any of the adverse consequences of hyperparathyroidism such as kidney stones, recurrent ulcers, or fractures, or if underlying physiologic derangements are present such as hypercalciuria or markedly reduced bone mineral density, the appropriate recommendation would be parathyroid surgery. However, approximately 50% of patients with primary hyperparathyroidism will not demonstrate any of these complications and, thus, will not be clear surgical candidates.

In patients who do not meet any of the above surgical criteria, management becomes focused on a more conservative approach, namely addressing the mild hypercalcemia. The patients are encouraged to consume a moderate diet with respect to Ca-containing foods, to remain mobile, and to keep well-hydrated. Loop diuretics to promote renal Ca excretion are not required and might even have negative consequences such as predisposition to nephrolithia-

sis and stimulation of further parathyroid growth. Thiazide diuretics would also be ill-advised because they would worsen the hypercalcemia [26]. Indeed, a short course of thiazide diuretics has sometimes been used as a "challenge test" to provoke hypercalcemia in patients with borderline serum Ca levels who are suspected of having hyperparathyroidism [26].

Other options available for managing mild hypercalcemia in patients with asymptomatic primary hyperparathyroidism include estrogen therapy in postmenopausal women, oral phosphate therapy and the use of bisphosphonates. Other causes of mild hypercalcemia, besides primary hyperparathyroidism, are approached best by dealing directly with the underlying etiology. For example, the hypercalcemia of hyperthyroidism is best handled by treating the hyperthyroidism. The hypercalcemia of granulomatous diseases such as sarcoid and tuberculosis is best handled by treating the disorder itself.

Management of the Patient with Moderate Hypercalcemia

Moderate hypercalcemia is considered to be between 11.5 and 13.5 mg/dl. One does not ordinarily use a full-scale aggressive approach when the serum Ca is less than 13.5 mg/dl. Sometimes one uses an approach similar to that described for patients with mild hypercalcemia. In patients with moderately elevated serum Ca levels, however, the approach is dictated by the extent to which the patient is symptomatic. Some of these patients will be relatively asymptomatic and thus one's approach, besides hydration and ambulation, is focused primarily upon the underlying etiology. If the patient has primary hyperparathyroidism, plans should be made for parathyroidectomy because the level of the serum Ca defines that patient as a surgical candidate. Any other etiology of the hypercalcemia should be addressed directly.

Hypercalcemia in the moderate range may be associated with symptoms such as polyuria, polydipsia, anorexia, constipation, and various degrees of obtundation. In this setting, it is prudent to embark upon a more aggressive approach to the hypercalcemia as described below. The therapy, however, has to be adapted to the actual level of the serum Ca and is not ordinarily as vigorous as it is when the serum Ca is much higher.

Management of the Patient with Severe Hypercalcemia

Serum Ca levels greater than 13.5 mg/dl are usually associated with symptoms and can constitute a life-threatening medical emergency. Consideration of this value for the serum Ca concentration assumes that any correction for hypoalbuminemia has been made. For every 1 g/dl reduction in the serum albumin, the total serum Ca should be adjusted upward by 0.8 mg/dl. The most common etiology of severe hypercalcemia is cancer, but one must also consider acute

primary hyperparathyroidism. PTH levels would be markedly elevated in acute primary hyperparathyroidism, but suppressed in malignancy-associated hypercalcemia. If the diagnosis of malignancy can not be made readily, other causes of severe hypercalcemia associated with suppressed PTH levels should be considered such as vitamin D intoxication or milk–alkali syndrome. Whatever the cause of the hypercalcemia, prompt efforts to reduce the serum Ca are indicated whenever the serum Ca is greater than 13.5 mg/dl, particularly if the patient is symptomatic. We will next consider the pathophysiology of severe hypercalcemia as this governs the principles of treatment.

Pathophysiology of Severe Hypercalcemia

Most causes of severe hypercalcemia are associated with increased osteoclastic bone resorption. The osteoclast is activated by substances like PTH, PTH-related protein, and other osteoclast activators. The activated osteoclast leads to excessive bone resorption and the release of Ca from bone into the extracellular fluid. Excessive absorption of Ca from the gastrointestinal tract is not usually an important mechanism although it can play a role in states of vitamin D excess. Hypercalcemia develops when the entry of Ca from the skeletal compartment into the extracellular space overwhelms the normal homeostatic mechanisms that help maintain normal serum Ca levels. The kidney is crucial in this regard and if renal mechanisms can lead to the excretion of the enhanced filtered load of Ca, the tendency to marked hypercalcemia would be ameliorated. Unfortunately, in this setting, renal tubular reabsorption of Ca is often stimulated, worsening the disposition to hypercalcemia. This is due, in part, to dehydration, which results from the interference of high Ca with the renal concentrating mechanism and from the anorexia and nausea associated with hypercalcemia. Dehydration reduces the extracellular fluid volume which would decrease GFR and stimulate proximal tubular reabsorption of sodium and Ca. Moreover, PTH and PTH-related protein directly stimulate distal tubular Ca reabsorption. The tendency to dehydration worsens the hypercalcemia, thus setting up a vicious cycle.

Goals of Therapy for Severe Hypercalcemia

There are four basic goals of therapy for severe hypercalcemia:

Restore Adequate Hydration

The initial approach to all severely hypercalcemic individuals is hydration with saline. Rehydration alone will reduce serum Ca by 1.5 to 2.0 mg/dl. Expansion

TABLE 1 Goals of Therapy in Severe Hypercalcemia

1. Hydration
2. Loop diuretics
3. Inhibit osteoclasts
4. Treat underlying disorder

of intravascular volume also leads to increased renal Ca clearance. The choice of saline enhances renal Ca clearance further by virtue of the obligatory link, in this situation, between sodium and calcium excretion. Isotonic saline is administered at a rate of between 2.5 and 4 liters daily. The rate of fluid administration is guided by the severity of the patient's dehydration as well as by any concerns about cardiovascular tolerance to vigorous fluid therapy. Although useful and always indicated, hydration alone does not usually lead to normalization of markedly elevated Ca levels.

Use of Loop Diuretics

Once volume deficits have been corrected with isotonic saline, the use of loop diuretics like furosemide may further enhance sodium and Ca excretion [36]. Using a combination of saline and furosemide, the mean fall in serum Ca is 3.1 mg/dl. Greater than 1000 mg of Ca per day is excreted in the urine. The careful replacement of water and electrolyte losses (sodium, potassium, and magnesium) is essential if this therapy is to be safe. When this therapy was first introduced, large doses of furosemide [80 to 100 mg iv every 1–2 hr) were recommended, but currently, a dosage schedule of 10–20 mg furosemide iv every 6–12 hr is considered safe and effective [2]. In addition to facilitating urinary Ca excretion, the loop diuretics help to prevent volume overload. This may be particularly important in patients with compromised cardiac reserve or with moderate renal insufficiency.

Inhibit Osteoclast Action in Bone

Bisphosphonates have become one of the mainstays of therapy for severe hypercalcemia. These drugs are effective osteoclast inhibitors and thus influence one of the most important pathophysiological mechanisms for hypercalcemia. Pamidronate seems to be the preferred agent because of its potency, wide experience, formal FDA approval as a single iv therapy, and efficacy. The effective dosage of pamidronate is 30–90 mg (generally 60 mg is used) given iv over 4 hr. Peak effect takes 2–3 days and lasts about 2 weeks. Normalization of the serum Ca occurs in 70–100% of patients.

Calcitonin is another important therapeutic approach to acute hypercalcemia. Like the bisphosphonates, calcitonin inhibits osteoclastic bone resorp-

tion. Calcitonin also facilitates urinary Ca excretion. It is administered sc or im in a dosage of 4–8 MRC U/kg every 12 hr. The major advantage of calcitonin is its rapidity of action with reduction in the serum Ca of about 2 mg/dl occurring within hours of administration. The effect does not usually last more than 1–2 days. Combination therapy with calcitonin and pamidronate provides a rapid and sustained reduction in serum Ca levels.

Glucocorticoids can be effective in patients with hematological malignancies, and with hypercalcemias associated with vitamin D excess or sensitivity. Myeloma, lymphoma, sarcoidosis, and other granulomatous diseases are conditions for which glucocorticoids might be particularly effective. In these disorders glucocorticoids inhibit production of various osteoclast-activating factors including calcitriol [7]. In general, patients with nonhematological malignancies and primary hyperparathyroidism do not respond. A dosage of 200–300 mg of hydrocortisone iv or prednisone 50 mg po is given daily for 5–7 days.

Treat, if Possible, the Underlying Disorder

If hyperparathyroidism is present, then parathyroidectomy should be performed. If a tumor is detected, then resection and/or appropriate radiotherapy and chemotherapy should be provided. Any other etiology of the hypercalcemia should be addressed directly.

USE OF DIURETICS IN IDIOPATHIC HYPERCALCIURIA AND HYPOPARATHYROIDISM

The association of hypercalciuria with Ca nephrolithiasis has long been recognized [11]. It continues to be the most common metabolic derangement encountered in stone-formers, occurring in over 60% of the patients. Hypercalciuria could cause or contribute to Ca stone formation by two mechanisms. First it increases the saturation of the urine with respect to stone-forming salts. Second, hypercalciuria may facilitate stone formation by reducing the inhibitor activity in urine against the crystallization of stone-forming Ca salts. For example, negatively charged inhibitors such as citrate and chondroitin sulfate may be bound by Ca and inactivated. The causal role of hypercalciuria in stone formation is further supported by the amelioration of stone disease on correction of hypercalciuria with thiazide diuretics [40].

The term "idiopathic hypercalciuria" was introduced by Albright *et al.* in 1953 [1] to describe a group of patients with hypercalciuria, normocalcemia, and a history of recurrent passage of Ca-containing renal stones. Today, idio-

pathic hypercalciuria denotes the urinary excretion of Ca above normal levels for which there is no readily apparent cause, such as hypercalcemia, sarcoidosis, excessive vitamin D ingestion, glucocorticoid excess, thyrotoxicosis, or immobilization. Reasonable upper limits for 24-hr urinary Ca excretion on an ab lib diet are 250 mg per day in women, 300 mg per day in men, or 4 mg/kg/day in patients of either sex. A more rigid definition of hypercalciuria is a urinary Ca excretion of more than 200 mg/day after 1 week's maintenance on a diet restricted in calcium and salt (400 mg Ca, 100 mEq Na daily).

There is now ample evidence that idiopathic hypercalciuria is a heterogeneous disorder comprised of at least two distinct pathogenetic subsets: absorptive hypercalciuria and renal hypercalciuria [10]. In absorptive hypercalciuria, by far the most common type, the primary abnormality is the intestinal hyperabsorption of Ca. The pathogenetic scheme for renal hypercalciuria originates with impaired tubular Ca reabsorption, i.e., "a renal Ca leak." Although both forms of hypercalciuria may be treated with thiazide diuretics, the responses are not exactly alike (*vide infra*). In addition to patients with idiopathic "normocalcemic" hypercalciuria, patients with hypoparathyroidism may be considered to suffer from a form of "hypocalcemic hypercalciuria." In the absence of PTH, these patients are characterized by high urinary Ca losses when treated with vitamin D and Ca supplements and are prone to nephrolithiasis. The usefulness of thiazide diuretics in the management of normocalcemic and hypocalcemic hypercalciurias will be examined in more detail in the following sections.

Asorptive Hypercalciuria (AH)

The primary abnormality in AH is the intestinal hyperabsorption of Ca. The consequent increase in serum Ca (within the normal range) increases the renal filtered load and suppresses parathyroid function. Hypercalciuria results from both the increased filtered Ca load and reduced tubular reabsorption of Ca that results from the reduced PTH level. The enhanced excretion of Ca contributes to keeping the serum Ca within the normal range.

Thiazide diuretics have been widely used to treat AH because of their hypocalciuric action [40]. Urinary Ca excretion may be reduced by as much as 50%. Previous studies of the short-term effects of thiazides have demonstrated that while this treatment is effective in reducing urinary Ca initially in patients with AH, it does not produce any decrease in intestinal Ca absorption (Fig. 2) [41, 28]. Since thiazide diuretics do not correct the primary defect of hyperabsorption of intestinal Ca in AH, this raises questions as to the fate of the retained Ca and regarding the long-term effectiveness of thiazide therapy in the treatment of this condition.

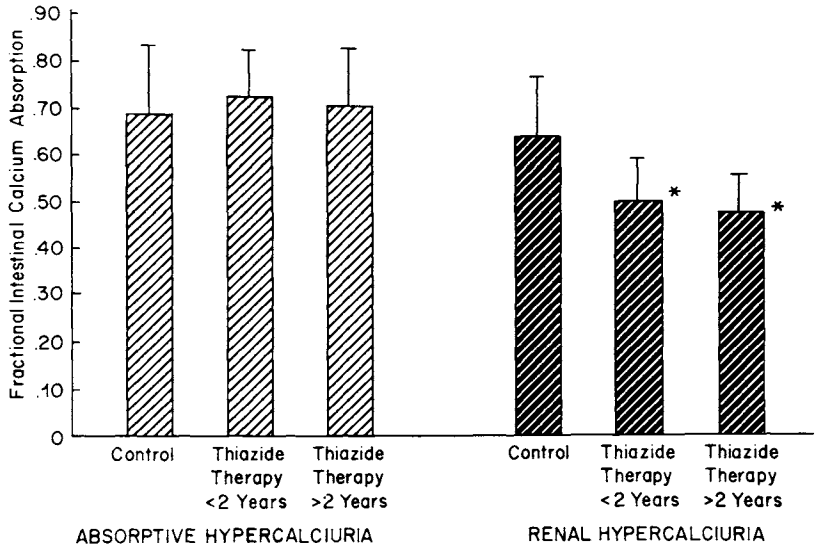

FIGURE 2. Effect of hydrochlorothiazide on fractional intestinal Ca absorption in absorptive and renal hypercalciuria. In each group of patients values were obtained during control phase and short-term (less than 2 years) and long-term (greater than 2 years) thiazide therapy. Asterisk shows significant difference from control period produced by thiazide treatment ($P<.05$). With permission from Ref. [28].

Indeed, thiazides may have a limited long-term effectiveness in patients with AH (Fig. 3) [28]. These agents are usually effective in reducing urinary Ca excretion during the first 2 years of treatment. Thereafter, urinary Ca generally returns to the pretreatment range. In contrast, intestinal Ca absorption remains persistently elevated throughout thiazide treatment (Fig. 2) [28]. During the first 2 years of therapy, radial bone density increases about 1.5% yearly, but then plateaus [28]. It is at this point that the hypocalciuric effect of thiazide becomes attenuated. Conceivably, thiazide treatment may eventually cause a low turnover state of bone, which interferes with continued calcium accretion in the skeleton. The rejected calcium would then be excreted in the urine.

Renal Hypercalciuria (RH)

The primary abnormality in RH is thought to be an impairment in the renal tubular reabsorption of Ca [11, 10]. The consequent reduction in serum Ca concentration (within the normal range) stimulates parathyroid function, with a secondary increase in the renal synthesis of $1,25\text{-}(OH)_2D$. The increased PTH

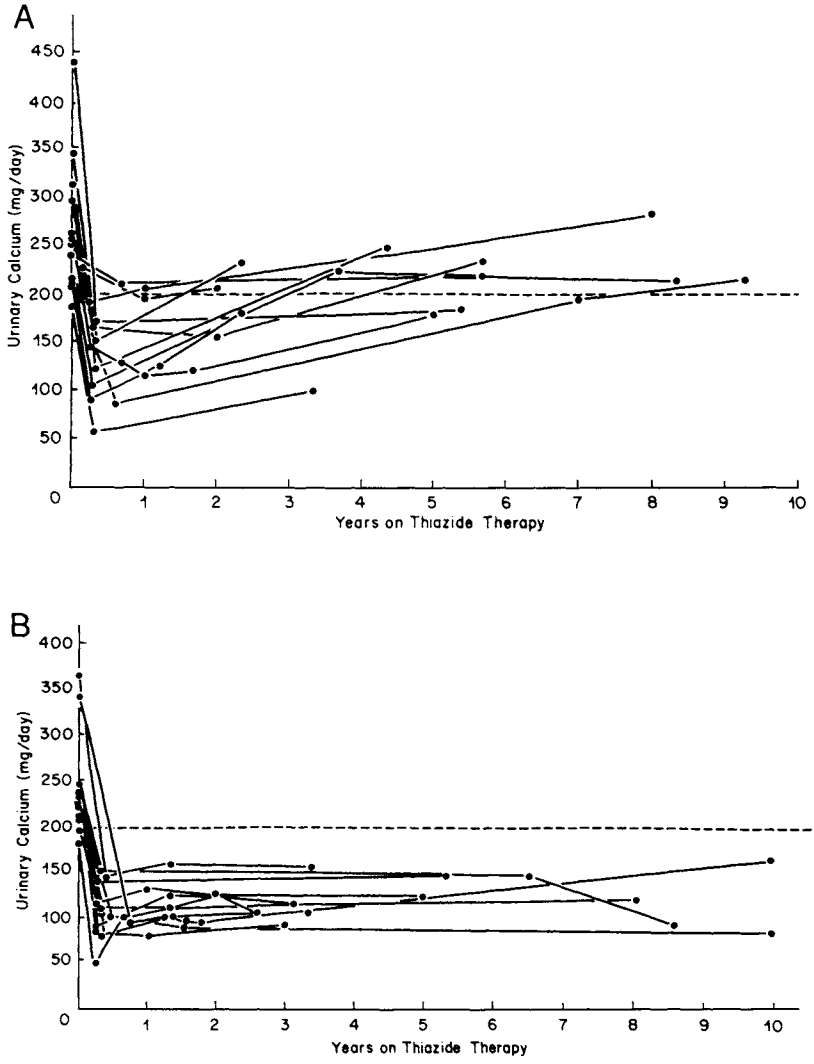

FIGURE 3. (A) Effect of hydrochlorothiazide therapy on urinary Ca in 12 patients with absorptive hypercalciuria. Each line represents study in separate patient. Note that at all time points, patients were studied while on a 400-mg Ca, 100 mEq Na per day diet. Although nearly all patients reduced urinary Ca excretion after short-term treatment, 50% of patients became overtly hypercalciuric (urinary Ca greater than 200 mg per day) with long-term hydrochlorothiazide therapy. (B) Effect of hydrochlorothiazide therapy on urinary Ca excretion in 10 patients with renal hypercalciuria. Each line represents a study in a separate patient. None of these patients had hypercalciuria with long-term hydrochlorothiazide therapy. With permission from Ref. [28].

and 1,25-$(OH)_2D$ then increase, respectively, the mobilization of Ca from bone and the intestinal absorption of Ca. These effects restore serum Ca toward baseline. Unlike the situation in primary hyperparathyroidism, serum Ca concentration is normal, and the hyperparathyroidism is secondary. The frequency of RH, rigidly defined by fasting hypercalciuria in the presence of secondary hyperparathyroidism, is much less than that of AH (<5% of stone formers).

Thiazide therapy is ideally indicated for the management of RH [41]. By correcting the renal Ca leak, thiazide reverses secondary hyperparathyroidism and restores a normal serum 1,25-$(OH)_2D$ level and intestinal Ca absorption. Thiazide has been shown to produce a sustained correction of hypercalciuria commensurate with a restoration of normal serum 1,25-$(OH)_2D$ levels and intestinal Ca absorption (and stability of bone density) during up to 10 years of therapy (Figs. 2 and 3) [28]. Thus, thiazide action in RH differs from that previously described for AH.

Overall Effectiveness of Thiazide Treatment of Idiopathic Hypercalciuria and Practical Guidelines

Thiazide diuretics have proven effectiveness in reducing the likelihood of stone formation. In two double-blind, placebo-controlled trials lasting 3 years, chlorthalidone and chlorothiazide reduced the rate of stone recurrence from 40–50% to 10–20% [17, 22]. This matches the results of previous prospective, open trials in which thiazides reduced stone recurrence by 80–90% [40, 11].

Side-effects of thiazide therapy include fatigue, dizziness, hypokalemia, hyperuricemia, and exacerbation of lipid disorders and diabetes mellitus. Another problem with thiazide is the induction of hypocitraturia, which can be overcome by the coadministration of potassium citrate.

In persons weighing more than 60 kg, recommended dosages are hydrochlorothiazide 50 mg twice daily, trichlormethiazide 4 mg daily, or chlorthalidone 50 mg daily. In smaller individuals, one-half of these dosages might be used. Potassium citrate (15–20 mEq twice daily) should be added to prevent hypokalemia and attendant hypocitraturia. Sodium restriction (100 mEq/day) is critical, since a high sodium intake could blunt the hypocalciuric action of thiazide.

Hypoparathyroidism

The traditional treatment of hypoparathyroidism consists of vitamin D and dietary Ca supplements [6]. This therapy increases intestinal absorption of Ca,

resulting in a return of the serum Ca level to normal. As serum Ca increases toward normal, however, marked hypercalciuria results. This effect gives rise to one complication of vitamin D therapy, i.e., nephrolithiasis. A second complication of this therapy is transient hypercalcemia, with its attending manifestations, which include nephrocalcinosis and renal failure.

In an effort to maintain normal serum Ca levels without inducing hypercalciuria, Porter *et al.* treated seven hypoparathyroid patients for up to 25 months with chlorthalidone, a thiazide-like sulfonamide diuretic, plus a salt-restricted diet, without added vitamin D [27]. Mean 24-hr urinary Ca excretion decreased from 179 to 88 mg ($P < .001$) and mean serum Ca increased from 8.2 to 9.3 mg/dl ($P < .05$). Beneficial effects were sustained for as long as therapy was maintained. It was felt that the rise in serum Ca could not be due entirely to reduced excretion, and potential effects of thiazides on bone or intestine were invoked. Thus, oral chlorthalidone plus a low salt diet appeared to be an effective alternative to vitamin D in the maintenance therapy of at least some patients with hypoparathyroidism [27]. It should be emphasized that most of the patients who responded to the above therapy probably did not have severe hypoparathyroidism, since the mean serum Ca level prior to treatment was 8.2 mg/dl. However, as adjunctive therapy for hypoparathyroid patients that do require vitamin D and Ca supplements, thiazide diuretics often permit the attainment of a more comfortable serum Ca level at lower vitamin D dosages and without incurring significant hypercalciuria.

Unlike the thiazide diuretics, furosemide may augment renal Ca excretion and reduce serum Ca concentration in patients with hypoparathyroidism [18]. Loop diuretics such as furosemide should be avoided.

Nonthiazide Hypocalciuric Diuretics

In addition to the thiazides, certain nonthiazide diuretics such as amiloride or indapamide have been shown to have hypocalciuric effects. These agents may also be of use in the management of idiopathic hypercalciuria or hypoparathyroidism.

Amiloride

Amiloride, an antikaliuretic diuretic agent, is a pyrazine–carbonyl–guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. Compared to thiazide, it is a weak diuretic agent. Amiloride is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone. In the rat, luminal application of amiloride simultaneously depressed sodium

reabsorption and enhanced Ca reabsorption in the late distal convoluted tubule [15]. Similar results had already been reported in dogs [13]. Consistent with the known K-sparing activity of amiloride, it caused a dramatic reduction in fractional K excretion due to diminished K secretion in the distal tubule [15].

There is evidence for a hypocalciuric effect of amiloride in humans [23]. Seven patients with renal stones were evaluated before and after 1 month of treatment each with amiloride (2.5 mg twice daily), hydrochlorothiazide (25 mg twice daily), and both drugs at the same dosages. Although amiloride alone reduced urinary Ca in only two patients, it caused a slightly more prominent decline in urinary Ca when added to hydrochlorothiazide treatment in five patients. The amiloride treatment caused an additional 15–20-mg decline in 24-hr urinary Ca values when added to thiazides. Although serum K was significantly reduced during combined treatment with amiloride and hydrochlorothiazide, this reduction was not as prominent as that occurring during treatment with hydrochlorothiazide alone. The results suggested that the addition of amiloride to hydrochlorothiazide treatment in calcium nephrolithiasis may be advantageous because of its stimulation, though slight, of the thiazide-induced reduction in urinary Ca and because it may avert the development of severe hypokalemia.

Indapamide

Indapamide (Lozol) is the first of a new class of oral antihypertensive/diuretics, the indolines. In a randomized, prospective study, 75 patients with calcium nephrolithiasis and hypercalciuria were randomly assigned to three different therapies: diet and fluid, diet and fluid + indapamide 2.5 mg/day, and diet and fluid + indapamide 2.5 mg/day + allopurinol 300 mg/day [3]. During 3 years of treatment, indapamide caused a 50% drop in urinary Ca excretion. Thus, its hypocalciuric effect was as potent as that of the thiazide diuretics. Relative supersaturations of Ca oxalate and Ca phosphate also decreased by 50%. During the treatment period, the stone rate decreased by 95% in the indapamide group (significantly better than the 64% drop in the diet and fluid group). During indapamide treatment, there were no significant changes in serum glucose, total cholesterol or triglycerides. Serum uric acid increased by 1.0 mg/dl and serum K decreased by 0.4 mEq/liter after 3 years of treatment with indapamide. In contrast to the action of thiazide diuretics (without K supplementation), the citrate excretion was unaffected. If additional studies confirm that indapamide has fewer side-effects than thiazide diuretics, indapamide would be an interesting alternative to thiazides in the prevention of Ca stones in hypercalciuric patients.

BONE-PROTECTIVE EFFECTS OF THIAZIDE DIURETICS IN IDIOPATHIC HYPERCALCIURIA AND OSTEOPOROSIS

Idiopathic Hypercalciuria

It has become increasingly clear that many stone formers with idiopathic hypercalciuria have reduced bone density, particularly at the spine [10, 11]. The cause of the osteopenia is not yet established, but considerations include prolonged dietary Ca restriction, excessive production of or sensitivity to 1,25-$(OH)_2D$, and excessive production of bone resorptive cytokines by marrow cells, e.g., IL-1. Despite the widespread use of thiazide diuretics in the management of various forms of idiopathic hypercalciuria, there have been few longitudinal studies of the effect of these agents on markers of bone turnover or bone density. In one recent study, Rico *et al.* randomized 14 patients with idiopathic hypercalciuria to treatment with chlorthalidone 50 mg/day and 10 such patients served as untreated controls over a 1-year period [32]. The treated patients had a significant decrease in 24-hr urine Ca and tartrate resistant acid phosphatase (a marker of bone resorption), whereas the control group showed no changes. The thiazide-treated group showed an increase of bone mass in the arms, trunk, and total body by DEXA (Norland) of about 3%, whereas the untreated group lost about 2.5%. Thus, it appeared that thiazide diuretics decreased bone remodeling and improved bone mass in patients with idiopathic hypercalciuria.

Osteoporosis

In particular settings where there is evidence of a renal calcium leak contributing to the development of osteoporosis, thiazide diuretics appear to be useful. For osteoporosis, in general, while thiazide therapy might serve as an adjunctive anti-resorptive measure, its usefulness is not yet proven.

Renal Ca Leak Osteoporosis

There is a subset of osteoporotic patients who have fasting hypercalciuria and secondary hyperparathyroidism compatible with a renal calcium leak, but who are unable to compensate by increasing calcitriol synthesis and intestinal Ca absorption [33, 9]. A similar state may be induced in elderly subjects by salt loading [8]. Moderating salt intake and using thiazide diuretics can reduce urinary Ca excretion and thereby reverse secondary hyperparathyroidism and increased bone resorption [33].

Patients on glucocorticoids often develop hypercalciuria because of direct tubular effects of the steroids and because accompanying treatment with vitamin D and Ca supplements may suppress PTH levels. In this setting, anticalciuric thiazide diuretic therapy is generally recommended [24]. Whether thiazide therapy actually contributes to maintenance of bone mass in steroid-treated patients is not known.

General Osteoporosis

Fracture of the proximal femur (hip) is the osteoporotic fracture with the most pronounced adverse medical and economic consequences. This injury takes its greatest toll among persons 65 years of age or older, a group that in the United States incurs more than 200,000 hip fractures annually [31]. Insufficient Ca intake or excessive salt-driven urinary Ca losses, together with sluggish ability to augment renal 1,25-$(OH)_2D$ synthesis and raise intestinal Ca absorption, has been hypothesized to cause proximal femoral bone loss (1% per year) [31]. The bone loss is believed to occur through a long-term negative calcium balance or indirectly through a mild secondary hyperparathyroidism. Supplementation with vitamin D and calcium has been demonstrated to have some protective effect in reducing the hip fracture rate, and there is also evidence that thiazide diuretics, because of their hypocalciuric effect, might retard the rate of bone loss and prevent hip fractures.

Cross-sectional studies have shown that thiazide users have greater bone mass at several skeletal sites than do nonusers and that their effects may be additive to those of estrogens [38]. Longitudinal studies have shown that thiazide users have lower rates of bone loss [31]. Numerous epidemiologic studies have indicated that thiazide therapy reduces the hip fracture rate by 30–50% [21, 30]. However, the negative study of Heidrich and colleagues which found a 60% increased risk for hip fractures [19] underscores that it is still premature to prescribe thiazides for all osteoporosis patients. A recent metaanalysis involving 13 studies and 29,600 subjects found that thiazide users have a 20% reduction in fracture risk and that long-term use may reduce fractures by a similar amount [20]. Clearly, randomized, controlled clinical trials are needed to examine the risk/benefit ratio of using thiazides to prevent hip fractures. In the absence of a suitably designed, large randomized, controlled trial, thiazides should be considered as part of an approach to osteoporotic fracture prevention, particularly in hypertensive or hypercalciuric subjects.

Unlike thiazides, furosemide is a diuretic agent that promotes calcium excretion by the kidney; it therefore may place users at an increased risk for osteoporosis. In a case–control study of 462 elderly patients hospitalized because of hip fracture and an equal number of age- and sex-matched control patients, the adjusted risk for hip fracture for current furosemide use was 3.9 (CI, 1.5 to 10.4) [19].

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CHAPTER VD

Indications for the Use of Diuretics in Patients with Renal Impairment

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INTRODUCTION

In discussing the indications for the use of diuretics in patients with renal impairment it is well to remember that these drugs are composed of five groups with different mechanisms and sites of action which determine their desirability and usefulness.

The *osmotic diuretics* act to limit water absorption in the proximal tubule, the loop of Henle, and the collecting tubule and in so doing produce a modest sodium diuresis. Their renal actions result in increased blood flow (including medullary) and increased tubule pressure. Extrarenally, by virtue of their hyperosmolarity, they shift water out of body cells and so expand the extracellular and intravascular spaces. This efflux of cellular water is accompanied by efflux of potassium and a resulting increase in the serum $[K^+]$, an effect that is also due, in part, to the resulting dilutional acidosis, i.e., the dilution of extracellular buffers by water derived from the cellular compartment.

The *carbonic anhydrase inhibitors* act in the proximal convoluted tubule to inhibit bicarbonate absorption. They are dependent for their effect on the presence of a normal (or elevated) serum $[HCO_3^-]$. By delivering $NaHCO_3$ to the distal nephron they augment K^+ secretion and loss of K^+ in the urine. However, they produce only a modest loss of NaCl.

Diuretic Agents: Clinical Physiology and Pharmacology

The *loop-acting diuretics,* the most potent of the diuretics with the steepest dose–response relationship, inhibit Na^+, K^+, Cl^-, Ca^{2+}, and Mg^{2+} absorption in the thick ascending limb. They produce renal vasodilatation and a vigorous diuresis of an essentially isotonic urine. Protracted use of these agents, by increasing the load of salt delivered to the distal convoluted tubule, results in hypertrophy and compensatory increased transport capacity of this segment (see Chapter IVB).

The *thiazide diuretics,* unlike the loop-acting diuretics, exert their effect in the distal convoluted tubule, a site where the fraction of filtered salt reabsorbed is limited. Their dose–response relationship, therefore, is considerably flatter than that of the loop-acting agents. The thiazides also cause renal vasoconstriction and decrease glomerular filtration rate (GFR). A few members of this family of diuretics have been found to be more potent than others, and an additional site of action in the proximal tubule has been invoked.

Finally, the *potassium-sparing diuretics* inhibit sodium absorption and potassium secretion in the initial and cortical collecting tubules, either by inhibiting aldosterone action or by directly blocking the apical sodium channel. The diuresis that results is very modest, and hyperkalemia and acidosis are frequent side-effects following their use.

With this brief review of actions as background, the appropriate indications for the use of diuretics in patients with renal impairment can be more clearly developed. Four types of renal impairment will be dealt with: acute renal failure, chronic renal failure, renal transplantation, and renal tubular acidosis.

ACUTE RENAL FAILURE

Acute renal failure is characterized by the sudden deterioration of renal function with a rapid decline of GFR to near 5 ml/min, often associated (in approximately 75% of cases) with oliguria ($<$ 500 ml of urine/day or $<$ 20 ml/hr). Acute renal failure may result from numerous causes that may be divided into prerenal, renal, and postrenal. *Prerenal causes* are generally associated with diminished renal perfusion caused by decreased cardiac output, hypovolemia, hypotension, or severe renal vasoconstriction. *Postrenal causes* involve conditions in which intrarenal or extrarenal urinary passages become obstructed. Our emphasis shall be on *renal causes* of acute renal failure, especially those resulting from severe and sustained renal hypoperfusion (such as cardiovascular surgery) or those resulting from noxious substances: intrinsic nephrotoxins such as those released during hemolysis or rhabdomyolysis or extrinsic nephrotoxins such as certain antibiotics and radiocontrast agents.

PREVENTION

Two major aspects of acute renal failure will be considered: prevention and treatment. In a number of experimental models either osmotic diuresis induced by mannitol or diuresis induced by use of loop-acting diuretics (primarily furosemide), have been found to mitigate the development of acute renal failure. Both mannitol and furosemide vasodilate the kidney, increase intratubular pressure and produce a diuresis. These effects would serve, respectively, to ameliorate renal ischemia, expel intraluminal detritus, and maintain the tubules patent in the face of increased interstitial pressure. Furosemide also inhibits transport and reduces O_2 need in the cells of the thick ascending limb of Henle, known to be the most sensitive to ischemic injury [19].

The evidence for *prevention* of acute renal failure in humans by the use of mannitol is less well established than in experimental animals. A number of uncontrolled studies have claimed a beneficial effect of mannitol in preventing acute renal failure in clinical settings where there is a likelihood of developing this complication: patients receiving radiocontrast agents and nephrotoxic drugs such as amphotericin B and patients with acute muscle injury or undergoing major cardiovascular surgery such as aortic aneurysm repair. However, from controlled randomized studies no clear evidence for a beneficial effect of mannitol has emerged. For example, in a randomized study of patients with obstructive jaundice undergoing surgery, Gubern *et al.* [18] found that kidney function was worse and more patients died with acute renal failure in the group receiving preoperative mannitol than in the nonmannitol group. Similarly, in a randomized study by Solomon *et al.* [42], renal function of patients with renal insufficiency undergoing cardiac angiography worsened in only 11% of patients receiving 1 ml/kg body weight/hr of 0.45% saline alone, but it worsened in 28% of patients who received, in addition to the saline solution, 25 g of mannitol infused intravenously during 60 min prior to angiography. It is fair to conclude, therefore, that mannitol has not been proven efficacious for the prevention of acute renal failure.

In fact, physicians should be cautioned that mannitol itself can cause acute renal failure. Dorman *et al.* [12] reviewed both previously reported cases of mannitol-induced acute renal failure and eight cases from their own study. Renal failure developed within 3.5 ± 1.1 days of receiving daily mannitol resulting in a cumulative dose of 626 ± 270 g (peak osmolal gap of 74 ± 39 mOsm/kg). In these quantities, used usually in the setting of intracranial hypertension, mannitol may induce renal vasoconstriction either directly or by activation of tubuloglomerular feedback. Moreover, mannitol may induce severe vacuolization and swelling of tubular cells, which may then be shed in the urine and seen in the urine sediment.

There is no more evidence for a preventive role of furosemide than there is for mannitol. In a prospective randomized study of patients with renal insufficiency undergoing cardiac angiography and receiving 0.45% saline, 80 mg furosemide infused intravenously during 30 min prior to the procedure was associated with worsening of renal function in 40% of patients, whereas only 11% of those receiving the saline solution exhibited deterioration of renal function [42]. These data suggest that with exception of hydration with saline solution little else has been shown convincingly to prevent acute renal failure.

With respect to the remaining three classes of diuretics there is no place for them in the prevention of acute renal failure. If anything, these agents may be harmful or may themselves induce acute renal failure. Tubular obstruction by crystals resulting in acute renal failure has been reported with acetazolamide, a carbonic anhydrase inhibitor. [36]. Acute renal failure has also been reported to be caused by triamterene, a potassium-sparing agent, given either in combination with hydrochlorothiazide [15] or with a nonsteroidal anti-inflammatory agent [48]. In any condition with more than a trivial risk of developing acute renal failure these agents must be avoided.

Treatment

In the patient with developing or established acute renal failure there are at least three indications for the use of diuretics: the correction of oliguria, the hastening of the recovery of renal function, and the alleviation of some of the complications of oliguric acute renal failure. A number of small and uncontrolled studies have claimed a beneficial effect of mannitol and/or of a loop-acting diuretic in attaining one or more of the three benefits enumerated above. Mannitol and $NaHCO_3$ have been used together in patients with myoglobinuria: in 45% of patients such treatment resulted in increased urine output and improved renal function [13]. Furosemide alone in either moderate or very high doses has been reported to convert oliguric acute renal failure to nonoliguric acute renal failure in 35% [29] to 85% [8] of patients. In patients who fail to respond to furosemide alone, combined treatment with dopamine results in diuresis and stabilization or improvement of renal function [26, 27]. Clearly, increased urine output alleviates congestion, facilitates fluid management, and allows the administration of parenteral nutrition; it might even preclude the need for dialysis [29]. Even in patients who remain oliguric, intravenous furosemide has been shown to correct pulmonary ventilation–perfusion mismatch and to increase P_{O_2} without measurable hemodynamic changes [2].

All the above benefits notwithstanding, mortality is not changed by the use of diuretics [8, 29]. This, however, is more likely to be the consequence of the severity of the underlying disease and has little to do with the course of acute

renal failure whether or not modified by diuretics. Nevertheless, a nonoliguric patient is an easier patient to care for.

CHRONIC RENAL FAILURE

The common denominator in chronic renal failure, irrespective of its cause, is reduced renal blood flow and glomerular filtration rate. To maintain the proper milieu interieur the kidney, responding to hemodynamic, neural, and humoral signals, undergoes some very significant alterations in its reabsorptive and secretory functions. In order to continue excretion of the ingested sodium in the diet, the diseased kidney with a reduced number of functioning nephrons, reabsorbs less of the filtered sodium in each of the remaining functioning nephrons. To illustrate, an individual with a GFR of 100 ml/min and a serum [Na^+] of 150 mEq/liter (of plasma water) who excretes 150 mEq of Na^+/day reabsorbs all but 0.69% of the filtered sodium (99.31%): [filtered Na^+ = 150 mEq/liter × 100 ml/min × 1440 min/day = 21,600 mEq/day; % fractional excretion of Na^+ = (150 mEq/ day ÷ 21,600 mEq/day) × 100 = 0.69]. A patient excreting 150 mEq of Na^+/ day with a GFR of 10 ml/ min excretes as much as 6.9% of the filtered sodium and reabsorbs only 93.1%. This inhibition of tubular reabsorption of Na^+ is achieved by a variety of mechanisms including osmotic diuresis per nephron, intravascular volume expansion, renal hemodynamic changes, and the elaboration of humoral factors which suppress tubular Na^+ absorption. The expansion of intravascular volume and the subsequent release of humoral natriuretic substances are probably the factors most likely responsible for the development of *systemic hypertension. Fluid overload* and hypertension can culminate in congestive heart failure and pulmonary and peripheral edema.

A somewhat different situation obtains for K^+. When a subject, with a GFR of 100 ml/min and a serum K^+ of 4.0 mEq/liter, excretes 80 mEq of K^+/day, 13.89% of the filtered K^+ is excreted. A patient with a GFR of 10 ml/min excreting the same amount of K^+ will have a fractional excretion of K^+ of 138.9%. Stated differently, the patient excretes an amount of potassium approximately equivalent to 1.4 times the total filtered K^+—dramatic evidence of net tubular secretion of K^+. Such K^+ secretion is achieved by increased delivery of Na^+ from the proximal nephron to more distal nephron segments where, in the presence of increased blood level of aldosterone, K^+ secretion is maximally activated. Body K^+ homeostasis is further maintained by increased rectal K^+ secretion [37]. With progressing decline in renal function, excessive dietary K^+ intake, the development of acidosis and, in certain diseases, the development of hyporeninism and hypoaldosteronism, or of tubular resistance to aldosterone (e.g., diabetic nephropathy, obstructive uropathy), *hyperkalemia* may supervene.

Acidosis is another frequent accompaniment of chronic renal failure. Despite increased production of NH_3 by individual nephrons, the total amount of NH_3 produced may become insufficient to buffer the amount of H^+ that needs to be secreted. Certain systemic or tubulointerstitial diseases as well as hyperkalemia may result in further impairment in NH_3 production and/or in H^+ secretion and hasten the development of acidosis.

Efficacy of Diuretics

For the abnormalities of homeostasis recounted above, diuretics have been used with varying degrees of success. Almost all diuretics are highly protein bound, gain access to the nephron lumen by means of tubular secretion, and act on specific transporters located in the luminal membrane. To bind effectively to these transporters, however, the diuretics must be in free solution.

Chronic renal failure poses some significant challenges to therapy with diuretic agents. First, renal blood flow is reduced and, therefore, the delivery of diuretics to the kidneys may be reduced. Second, the number of nephrons is diminished and, consequently, the amount of diuretic actually secreted declines. This problem is compounded by the presence, in the circulation of chronic renal failure patients, of organic acids which compete with diuretics for the tubular secretory sites. Finally, the lower filtered load of sodium severely limits the absolute amount of sodium excreted under the influence of diuretics even though, in fractional terms, the degree of Na^+ diuresis may be actually quite substantial.

To illustrate, let us return to the normal subject discussed earlier, with a GFR of 100 ml/min, and the patient with chronic renal failure, whose GFR is 10 ml/min. These two individuals are filtering Na^+ at a rate of 15 and 1.5 mEq/min, respectively. If they were both given a thiazide diuretic which, at the peak of its action, were to induce a loss of Na^+ equivalent to 10% of the filtered load, the healthy individual would lose 1.5 mEq/min, whereas the patient in renal failure would lose 0.15 mEq/min. After 1 hr, the normal subject would have lost 90 mEq of Na^+, while the patient would have lost only 9 mEq. Accordingly, for the patient with chronic renal failure to develop a significant Na^+ diuresis, several doses of the thiazide diuretic would be required to be given in the span of a day. The use of a diuretic several-fold more potent than the thiazide diuretic (e.g., a loop-acting diuretic which could cause a Na^+ loss equivalent to 30% of the filtered load or greater) or the concurrent use of both drugs would be necessary to achieve significant natriuresis [50].

One might speculate that the reduced renal excretion of a diuretic would result in its delayed excretion and, consequently, a more protracted diuresis. Unfortunately, for many diuretics their half-life ($t^{1/2}$) is essentially unchanged

when renal function is compromised (e.g., torasemide [43]), because of the compensatory increase in the hepatic clearance. This process is mediated by the known decrease in protein binding of diuretics in chronic renal failure [17]. Conversely, an agent with lower hepatic clearance would be expected to prolong the $t^{1/2}$ of diuretics and to produce a greater cumulative natriuresis. For instance, at intravenous doses that produce similar maximal FE_{Na}, furosemide produced a 52% greater cumulative natriuresis than bumetanide [47].

Following oral administration bioavailability of loop diuretics varies greatly: torasemide is most bioavailable, followed by bumetanide and furosemide [35].

Management of Hypertension

Hypertension in chronic renal insufficiency has been shown to respond to treatment with loop diuretics, either given alone or in combination with thiazide diuretics. A number of authors report success with the combined use of furosemide and hydrochlorothiazide [3] or metolazone [32]. Whether these agents exert their hypotensive effect exclusively by inducing natriuresis and are thereby useful in patients with advanced renal failure and in patients undergoing dialysis is a matter of controversy. Several investigators have found indapamide effective in lowering blood pressure in patients with chronic renal failure and in patients undergoing dialysis [1, 24]. These effects were thought to be mediated by reduction of the pressor response to norepinephrine and angiotensin II [24]. Others, however, using hydrochlorothiazide or metolazone in patients undergoing maintenance hemodialysis, affirm that "a functioning kidney with the ability to respond to diuretics with a natriuresis is necessary for the antihypertensive action of diuretics" [5]. If diuretics were to be used in the setting of advanced renal failure it is prudent to avoid large doses which may have toxic effects on cardiac and central nervous system (CNS) functions [51].

Management of Vascular Congestion

As discussed under Management of Hypertension (above) loop diuretics such as furosemide, bumetanide, and torasemide are useful in controlling vascular congestion and hypertension in patients with chronic renal failure, when used alone or in combination with a thiazide diuretic, especially metolazone. Comparing the daily urinary losses of electrolytes with the weight lost by individual patients, it was observed that the patients lost more weight than could be accounted for by the urinary fluid losses. This discrepancy raises the interesting possibility that the fluid balance may have been achieved by an additional extrarenal route such as the gastrointestinal tract [49].

Another example of extrarenal effect of diuretics is a report of the immediate hemodynamic response to furosemide in patients undergoing chronic hemodialysis. It was observed that within 5 min after injection there was a 13% decrease in central blood volume, together with a fall in stroke volume and cardiac output [39]. These data suggest that intravenous furosemide may be useful in relieving heart failure in dialyzed patients by inducing peripheral venous dilatation and decreasing preload until a more permanent therapy such as ultrafiltration can be implemented (see also Chapter VA2).

Potassium Homeostasis

The modest natriuresis induced by diuretics in chronic renal failure patients is often accompanied by a similarly modest kaliuresis. However, a significant drop in serum potassium concentration has been reported in anuric patients maintained by chronic hemodialysis after oral chlorothiazide administration (15 mg/kg) [14]. These observations point to an extrarenal action which may prove useful in the management of the hyperkalemia that is not infrequently encountered in these patients.

The use of the potassium-sparing diuretics in patients with compromised renal function is problematic. In the first place, these drugs appear to be capable of blocking extrarenal sites of K^+ disposition and inducing hyperkalemia as has been demonstrated with spironolactone [30]. Second, the actions of these drugs in patients with chronic renal failure may be prolonged because of the compromised renal excretion of amiloride and of triamterine and its active metabolites [21, 22].

Acid–Base Balance

Nonvolatile acids derived from food and metabolism in chronic renal failure are buffered by extracellular protein and HCO_3^-, by intracellular phosphate, protein, and other organic buffers and also by the skeleton where hydroxyapatite provides a rich source of buffer. Buffering by bone is enhanced by parathyroid hormone, which is one of the beneficial effects of hyperparathyroidism in chronic renal failure. Acetazolamide, a carbonic anhydrase inhibitor used in the treatment of glaucoma, has been reported to induce marked metabolic acidosis in virtually anuric hemodialysis patients when used in a dose of 500 mg/day for 7 days [28]. Accordingly, these drugs appear to be capable of inhibiting skeletal buffering and their use should be avoided in patients with impaired renal function.

Complications

In addition to the problems of cardiac and CNS toxicity, hyperkalemia and acidosis that may occur during the use of diuretic drugs in patients with impaired renal function, other side-effects must be considered:

1. *Acute pancreatitis* is observed with increased frequency in this patient population particularly following administration of thiazide and loop diuretics [44]. This diagnosis must be considered in every renal patient receiving a diuretic who presents with nausea, vomiting, and abdominal pain.
2. *Azotemia* often follows the use of diuretics in patients with impaired renal function. This is due to extracellular fluid volume depletion which enhances tubular absorption of urea and decreases its excretion [10].
3. *Hyperlipidemia,* consisting of increased total, VLDL, and LDL triglycerides and decreased HDL triglycerides has been reported in patients with chronic renal failure [31]. Furosemide treatment in these patients resulted in further increase in VLDL triglycerides and in VLDL cholesterol. In view of the accelerated atherosclerosis in renal patients it would be well to remember hyperlipidemia as a potential complication when using diuretics in these patients.

TRANSPLANTATION

Delayed Graft Function

Transplantation of cadaveric kidneys is beset with a significant problem with the potential of adversely affecting transplant outcome. Difficulties derive from the periods of warm and cold ischemia that precede transplantation. The incidence of delayed graft function (defined as failure of the graft to function promptly following transplantation), usually requiring dialysis, varies widely. It may be encountered in as few as 10% of patients in some programs, but in as many as 50% of patients in others. When the effects of delayed graft function are analyzed it can be shown that it usually reduces 1-year graft survival by 10% or more and reduces the half-life of the graft by nearly 3 years. A number of regimens designed to ensure prompt graft function have been employed by various organ harvesting and transplant teams, usually involving the use of vasodilators such as calcium channel blockers, blood volume expanders such as saline solutions and hyperoncotic albumin, and diuretics such as furosemide and mannitol. Despite the many papers written on the subject there have been few that report prospective and randomized studies. Two of the best studies were authored by the same group [45, 46], who first investigated the importance of hydration in a prospective trial examining the effects of restricted fluid

TABLE 1 Effects of Moderate Hydration and Mannitol on Graft Function[a]

Group	n	V (ml ± SD)	ATN (%)
1	21	1059 ± 371	43
2	19	1548 ± 622	53
3	21	2529 ± 675	4.8

[a] Data from Tiggeler [45].

infusion (Group 1), restricted fluid infusion along with 250 ml of 20% mannitol (Group 2), and moderate hydration together with 250 ml of 20% mannitol [45]. The results, showing the volume of fluid infused (V) and the incidence of acute tubular necrosis (ATN) are shown in Table 1. It can be seen that hydration with 2.5 liters of fluid and administration of mannitol, 250 ml of 20% immediately before the release of the vascular clamps, greatly reduced the incidence of ATN. The authors reported that this treatment also decreased the number of dialyses, radionuclide scans, ultrasound studies, transplant biopsies, and rejection episodes in the first 3 months post-transplantation.

In a subsequent study the same authors [46] investigated whether hydration alone, without mannitol, was sufficient to prevent ATN in the setting of either cyclosporine (CS) or azathioprine (AZ). Patients were randomly allocated to treatment with moderate hydration (2.5 liters) with or without mannitol (patients not receiving mannitol received glucose instead). The results are shown in Table 2, wherein the hydration and the hydration plus mannitol groups are designated H and H+M, respectively. It is clear from these studies that hydra-

TABLE 2 Effects of Moderate Hydration, with or without Mannitol, on Graft Function[a]

Group	n	ATN (%)
CS		
H	32	54
H + M	32	19*
AZ		
H	34	44
H + M	33	18**

[a] Data from van Valenberg [46].
*$P < 0.01$.
**$P < 0.05$.

tion *and* mannitol, but not hydration alone, produced a highly significant reduction in the incidence of ATN. When the two immunosuppression groups are combined the difference in ATN becomes even more significant ($P < 0.001$).

The foregoing studies demonstrating the usefulness of mannitol in renal transplantation are in sharp contrast to those discussed under Prevention above. The reason(s) for this discrepancy is (are) elusive. One important difference between the transplanted kidney and the native kidney is the fact that the former is denervated. Whether mannitol can induce a neurally mediated injury in the intact kidney but fails to do so in the denervated transplanted kidney remains to be determined.

The experience with furosemide in preventing ATN in the transplanted kidney has been disappointing. Infusion of 200–400 mg furosemide just before restoration of renal circulation in kidney transplant recipients given mannitol did not prevent acute renal failure nor did it reduce the need for dialysis [23]. Our own observations strongly suggest that the intraoperative infusion of furosemide significantly complicates the postoperative care since it may cause massive diuresis which requires massive fluid replacement and careful and frequent monitoring of the serum electrolytes, especially K^+ and Mg^{2+}. Finally, the potential for developing pulmonary edema should be considered when using OKT3 for induction of immunosuppression. This monoclonal antibody is known to precipitate noncardiogenic pulmonary edema in overly hydrated patients.

Efficacy of Diuretics

The pharmacokinetic and pharmacodynamic behavior of several diuretics has been studied in renal transplant recipients and found to be similar to that of nontransplant patients with comparable renal function [16]. Certain drugs often prescribed to transplant recipients, such as sulfisoxazole, may decrease the protein binding of diuretics [41], but this does not seem to alter significantly either the amount of drug excreted or its efficacy. Of note is a defect in K^+ excretion that was observed despite a similar degree of natriuretic response to furosemide. This did not appear to be due to failure of the kidney to respond appropriately to renin or aldosterone, suggesting a tubular defect.

The indications for the use of diuretics in renal transplant recipients are primarily two: edema and hypertension. *Edema* is not infrequent in renal transplant recipients, especially those receiving calcium channel blockers for the treatment of hypertension. Although not usually accompanied by expanded plasma volume, this edema is often the source of enough discomfort to warrant the use of a thiazide or loop-acting diuretic.

Hypertension in kidney transplant recipients not receiving cyclosporine is not thought to be volume dependent. Therefore, there is little to indicate the use of diuretics in these patients other than to enhance the efficacy of converting enzyme inhibitors. Cyclosporine, on the other hand, causes salt retention by a variety of mechanisms which include altered renal hemodynamics, direct renal tubule effect, and activation of the sympathetic nervous system. Diuretics, therefore, are especially indicated in patients whose immunosuppressive regimen includes cyclosporine. Unlike patients receiving azathioprine, cyclosporine-treated patients do have volume-dependent hypertension which responds to salt deprivation.

Complications

The complications of diuretics use are numerous, but only few that are especially relevant to the renal transplant recipient will be discussed.

Hyperlipidemia

In comparing a large number of renal transplant recipients to the general population, Bittar *et al.* [7] found high total cholesterol and triglyceride levels in all age groups, most strikingly in women. HDL cholesterol was similar or slightly lower in transplant recipients than in the general population. Using multiple regression analysis they found cholesterol associated with age, sex, urinary protein, and diuretic therapy which consisted of loop diuretics in 95% of patients. Plasma triglyceride was independently associated with age, urinary protein, plasma albumin, beta-blocker therapy, and diuretic therapy. In view of the known accelerated atherosclerosis in renal transplant recipients it would be prudent to monitor the plasma lipid levels in these patients and to use lipid lowering agents whenever they are found to be elevated.

Hyperparathyroidism

Renal function never returns completely to normal after renal transplantation. In patients who have suffered acute or chronic rejection renal function may be even more depressed. Hyperparathyroidism, therefore, is far more common in transplant recipients than is generally realized. Among patients with a normal serum creatinine Bittar *et al.* [6] found that parathyroid hormone (PTH) levels were twofold greater in those taking anti-hypertensive medications than in those not taking any. Analysis revealed that the dominant contribution to this association was the use of loop diuretics. The difference in PTH levels was even greater in the patients with poorer graft function, but the underlying mecha-

nism is not certain. It is likely that the effects on PTH are related to the effects of loop diuretics to increase calcium excretion. Renal wasting of calcium could in turn induce secondary hyperparathyroidism. Supplementation with oral calcium and calcitriol in an effort to suppress parathyroid hyperfunction would seem prudent.

Erythrocythemia

Posttransplant erythrocythemia occurs in nearly 10% of transplant recipients. Risk factors for its development include pretransplant hypertension, retention of the native kidneys, higher pretransplant hematocrit, and diuretic use for posttransplant hypertension. In one study [33] 20 of 22 patients with erythrocythemia were receiving concurrent diuretic therapy, and hematocrits fell to normal levels following cessation or dose reduction of diuretics. Accordingly, it would be advisable to withdraw diuretics first and monitor the response before launching an expensive workup for the underlying cause of erythrocythemia, including CT scanning of the native kidneys to search for cysts or tumor.

RENAL TUBULAR ACIDOSIS

Systemic acidosis resulting from tubule dysfunction comprises a complex group of disorders of diverse underlying pathophysiology. A detailed discussion of the pathophysiologic alterations in renal tubular acidosis (RTA) is beyond the scope of this chapter. However, a brief survey of the pathophysiologic principles involved helps to understand better the role(s) that diuretics might play.

PATHOPHYSIOLOGY

The acidification functions of the kidney may be divided into two basic components: reclamation of filtered bicarbonate and excretion of net acid into the urine in order to regenerate buffer, largely bicarbonate, previously titrated by dietary and metabolic acid. The reclamation of filtered bicarbonate is effected primarily in the proximal convoluted tubule and a defect in this process results in proximal renal tubular acidosis (RTA type II). Net acid excretion occurs predominantly in the distal nephron and defects in this process result in distal RTA (type I, classical), or in Type IV RTA when it is associated with hyperkalemia.

1. *Proximal acidification* depends on normal brush border function with Na^+/H^+ antiporter and carbonic anhydrase activity. Diseases of the proximal

convoluted tubule, such as cystinosis, heavy metal poisoning, volume expansion, hyperparathyroidism, carbonic anhydrase deficiency, or inhibition by drugs often results in proximal RTA.

2. *Distal acidification* requires adequate delivery of sodium to the distal nephron, normal sodium absorption with generation of a lumen-negative potential, adequate H^+ pump activity, and the ability to maintain a steep pH gradient between tubule lumen and cell. In addition, the collecting ducts play a major role in the effective secretion of ammonium.

Use of Diuretics

Based upon the simple principles discussed above one can come to a ready appreciation of the potential for using diuretics in treating several varieties of RTA.

Proximal RTA

One of the known side-effects of diuretic therapy is the generation of contraction alkalosis, a condition caused by contraction of the intravascular volume that results in an increased threshold for bicarbonate excretion and enhanced capacity for HCO_3^- absorption. This property of diuretics can be used to advantage in Type II/proximal RTA to correct the underlying defect in proximal tubular absorption. Without thiazide diuretics these patients require large doses of HCO_3^- (10–30 mEq/kg/day) to restore the normal range of serum HCO_3^-. Thiazide diuretics have proved useful in reducing the requirement for HCO_3^- [11].

Distal RTA

Based on the above discussion of distal acidification one can envision several opportunities for the use of diuretic drugs.

Enhanced Distal Na^+ Delivery

A number of conditions lead to decreased Na^+ delivery to the distal nephron and impaired acidification by limiting the distal absorption of Na^+ and the negative lumenal potential. Under conditions such as diarrhea and cirrhosis, where impaired distal acidification has been described, furosemide and ethacrynic acid have been reported to correct the defect [9, 20] by enhancing the delivery of Na^+ to the distal nephron. However, furosemide has been shown only in a few patients with distal RTA to lower urine pH [4].

Enhanced Distal Lumen Negativity

If the negative potential generated by the absorption of Na^+ were to be shunted by the concurrent absorption of Cl^-, distal RTA would result. In addition, K^+ secretion will also be impaired and hyperkalemia will result. When serum K^+ is elevated NH_3 production becomes impaired, which would contribute further to the acidosis (type IV RTA). In a report of familial hyperkalemic acidosis, Licht *et al.* [25] observed that correcting the hyperkalemia normalized NH_4^+ excretion but the HCO_3^- threshold remained low. Since Na_2SO_4, but not NaCl, increased K^+ excretion they invoked increased reabsorptive avidity for Cl^- in the distal nephron. Hydrochlorothiazide promptly corrected the acidosis and the hyperkalemia in a dose of 50 mg daily.

Enhanced Distal H^+ Secretion

The administration of thiazide or loop acting diuretics, by shrinking intravascular volume, stimulates the secretion of renin and aldosterone. Increased mineralocorticoid activity, coupled with increased distal Na^+ delivery, not only stimulates distal Na^+ absorption but also augments H^+ secretion. In patients with RTA, three patterns of response may be observed after furosemide administration [4]: in some patients mineralocorticoids increase the excretion of both K^+ and H^+; these patients benefit from thiazide and loop-acting diuretics. In a second group of patients neither K^+ nor H^+ secretion increase dramatically; these patients must have an inability to generate a normal tubular potential and are unlikely to benefit from diuretics. A third group of patients will increase K^+ excretion but not H^+ secretion [4, 34]; these patients will not benefit from diuretics since they appear to have a defect in the H^+ pump.

Correction of Hyperkalemia

Elevated serum K^+ depresses acid excretion and ammonia production and results in type IV RTA. Furosemide and the thiazide diuretics have been used extensively to treat this disorder. In patients with moderate hypoaldosteronism furosemide alone may alleviate hyperkalemia by increasing distal Na^+ delivery and increasing K^+ excretion [40]. To augment the correction of acidosis without causing hypertension fludrocortisone can be added to the therapy in patients with more severe aldosterone deficiency. In one case report [38] enhanced NaCl absorption in the thick ascending limb was implicated in volume expansion and hypertension, the suppression of renin and aldosterone, hyperkalemia, and development of type IV RTA. Diminished PGE_2 production was thought to be involved in stimulation of NaCl reabsorption in the thick ascending limb. Treatment with oral furosemide reversed the hypertension and hyperkalemic acidosis and increased urinary PGE_2 excretion twofold.

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CHAPTER VE

Toxic Agents: Drug Overdose, Poisons, Contrast Media

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INTRODUCTION

This chapter focuses on the use of diuretics in the management of life threatening poisonings, drug overdoses, and radiocontrast agent-induced disease. These problems occur relatively frequently and continue to be major challenges for clinicians. Radiocontrast-induced acute renal failure may occur in a hospital setting, especially in an age of more aggressive interventional radiological techniques. This chapter examines the specific role of diuretics in the therapy of medical conditions caused by these toxic agents.

GENERAL PRINCIPLES

The first line of treatment of poisons and drug overdoses taken by mouth is an attempt to prevent absorption of these agents from the gastrointestinal tract. Once intestinal absorption has occurred, detoxification, blockade of toxic effects and elimination by metabolism or excretion can be considered as a second line of defense. The kidneys are perfused with plasma at the rate of about 36 liters/hour, and about 7 liters of this plasma will be filtered per hour. Thus, an absorbed toxic agent in the blood will traverse the kidney very frequently.

Diuretic Agents: Clinical Physiology and Pharmacology

Substances can be removed from plasma by two mechanisms: filtration and secretion. The filtration of a drug depends on the rate of glomerular filtration, the degree of plasma protein binding, and its size and filterability. The ability to excrete a substance by filtration decreases as GFR falls or plasma protein binding increases. The proximal tubule, particularly the S2 and S3 segments, has the capacity to actively secrete a large number of drugs [17, 20]. In general, these secreted drugs are either organic anions (such as thiazides, loop diuretics, most penicillins, and cephalosporins) or organic cations (such as amiloride, triamterene, cimetidine, and trimethoprim) [20]. The relatively nonspecific nature of the secretory pathways permits these mechanisms to play a major role in the excretion of a variety of hydrophilic drugs, poisons, and chemicals. These pathways are important because many toxic agents are highly protein-bound and therefore excretion by glomerular filtration is sharply limited. Many foreign substances, drugs, and toxins which enter the body are organic anions and cations or are metabolized to anions or cations. Some of these compounds are toxic and must be eliminated as promptly as possible, and this is the primary function of the renal organic anion and cation secretory systems [19]. Both of these transport systems are strikingly effective. For instance, a good substrate like the anion *p*-aminohippurate (PAH) or the cation tetraethylammonium (TEA) may be completely cleared from plasma in a single pass through the kidney [19]. In addition, the organic anion and organic cation transport systems are capable of eliminating a wide range of agents, requiring only an organic backbone and an appropriate charge. This also implies that certain drugs compete with each other for these secretory sites. An example of an acidic drug which competes for proximal tubular secretion is probenecid which can be used to reduce the elimination of penicillins and prolong their half-life in the body. The energy for most of the tubular secretory processes is supplied indirectly by the sodium/potassium ATPase pump in the basolateral membrane and the favorable electrochemical gradient for sodium entry into the cell [20]. Less is known regarding the competitive interplay among basic drugs.

Once a substance has entered the proximal tubule, by either filtration or secretion, it may be reabsorbed along the rest of the nephron. The degree to which this reabsorption occurs depends on at least four factors: (i) the concentration of the agent in the tubule fluid, (ii) the flow rate of the tubule fluid, (iii) the pH of the tubule fluid, and (iv) the lipid solubility of the particular agent. Let us examine how each affects the ultimate elimination of a particular substance.

As water is reabsorbed from the tubule fluid, drug concentrations can rise more than 100-fold, and the developing transepithelial concentration gradient favors passive reabsorption [20]. Decreasing the concentration of a particular substance by a forced diuresis will decrease the passive backdiffusion and result in its increased excretion. Increasing tubule fluid rate past the tubular trans-

portive sites will also decrease the reabsorption of the agent. This can be achieved by either the use of a diuretic drug or by the intravenous administration of an isotonic fluid.

Charged molecules cross biological membranes less well than uncharged molecules [10]. Thus, in the case of organic acids, changing the pH of the tubule fluid can produce a charged form of a drug which will then become lipid impermeable. Altering the tubule fluid pH to produce such a diffusion imbalance has been termed ion trapping [10]. Urine pH can play a critical role in modifying which ionic form of a particular substance will be favored, and this can greatly facilitate net secretion or net reabsorption. Increasing the pH of tubule fluid increases the degree of ionization of weak acids and reduces passive tubular reabsorption. Similarly, decreasing the pH of tubule fluid increases the degree of ionization of weak bases with a resultant decrease in tubular reabsorption. Figure 1 illustrates this point for phenobarbital, a weak acid, and quinine, a weak base. As shown in Fig. 1a, at a urine pH of less than 7.0, phenobarbital is predominantly un-ionized, highly lipid permeable, and shows a reabsorption pattern consistent with an extremely high membrane permeability [22]. On the contrary, at a urine pH of 7.8–8.0, the phenobarbital clearance is

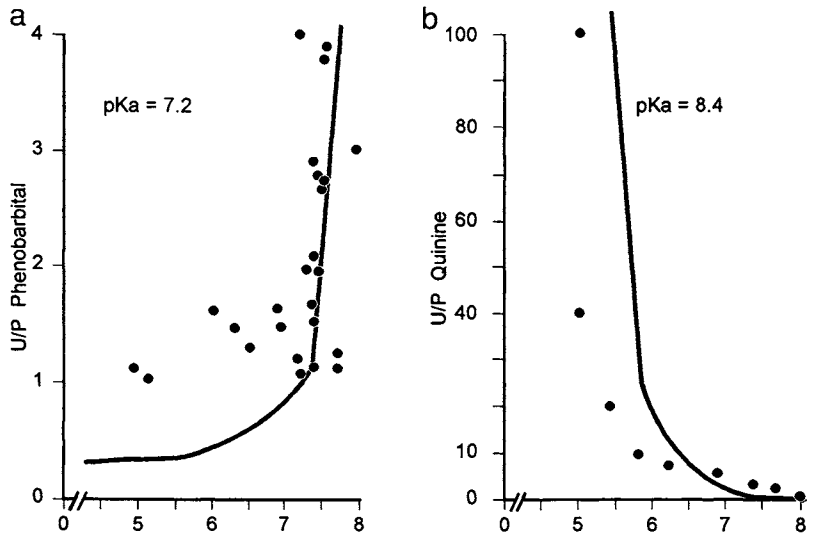

FIGURE 1 Experimentally determined urine-to-plasma concentration ratios at various urine pH values for (a) phenobarbital, a weak acid, and (b) quinine, a weak base. In each case the theoretical equilibrium U/P values are shown as solid lines. Note that the deviation from ideal behavior for each substance becomes more pronounced as the urine pH deviates progressively from the pK_a. Adapted from Reference 22, Figure 10, page 958.

markedly enhanced and shows a pattern of low membrane permeability, consistent with a lower luminal concentration of the more permeable, un-ionized species [22]. In contrast, quinine shows the opposite relationship to urine pH as shown in Fig. 1b. Furthermore, substances which are eliminated partially by virtue of being present in a polar form in the renal tubule will be rapidly excreted if two additional conditions are satisfied: (i) that the drug not be metabolized and (ii) that the volume of distribution be such so that at any given load of the drug the serum concentration be high. Since the ratio of polar to nonpolar form of a particular substance changes logarithmically with alterations in tubule pH, the final effects in net excretion or reabsorption can be of significant magnitude.

The dissociation of a weak acid or base is determined by its dissociation constant (pK_a). Elimination of some weak acids by the kidneys is increased in alkaline urine if the pK_a of the drug lies in the range of 3.0 to 7.5. In contrast, the elimination of some weak bases is increased in acid urine if their pK_a is 7.5 to 10.5 [24]. Tables 1 and 2 list a number of agents which will be discussed in greater detail below. These physiological principles explain the rationale for using diuretics to increase urine flow and adjusting urine pH to achieve ion trapping. Combining diuresis and ion trapping enhances the elimination of certain toxic substances.

There are several potential problems associated with this approach. Aggressive use of diuretics could result in the following: (i) salt depletion, which will enhance proximal tubule reabsorption and may increase tubule reabsorption of the toxic substances, (ii) some diuretics may compete with drugs or toxins for proximal tubule secretory sites and thus interfere with their secretion, (iii) systemic and acid–base abnormalities may complicate these treatments, and (iv) severe electrolyte disturbances including hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia may occur. Accordingly, during forced diuresis, close attention must be paid to the patient's fluid status, acid–base status, and electrolyte balance.

TABLE 1 Drugs Whose Excretion Is Enhanced by Acid Diuresis

Weak base	pK_a value
Amphetamine	9.9
Fenfluramine	9.9
Chloroquine	9.2
Quinine	8.4
Phencyclidine	8.5
Lidocaine	7.9

TABLE 2 Drugs and Poisons Whose Renal Excretion Is Enhanced by Alkaline Diuresis

Weak acid	pK_a value
2,4-dichlorophenoxyacetic acid (chlorophenoxy herbicides)	2.6
Salicylic acid	3.0
Acetylsalicylic acid	3.49
Diflunisal	3.3
Methotrexate	5.5
Phenobarbital	7.2
Thiopental	7.6
Amobarbital	7.7
Barbital	7.91
Pentobarbital	8.2

In the following sections, the potential role of acid, alkaline, and neutral diuresis will be discussed. The role of diuretics in the prevention of radiocontrast-induced nephrotoxicity is also discussed.

ACID DIURESIS

A number of drugs are weak bases with pK_a values between 7.5 and 10.5 and have distribution and solubility characteristics which result in enhanced renal excretion with acid diuresis. They are listed in Table 1. Before initiating a forced acid diuresis, it is essential to measure baseline electrolytes, blood gas parameters, and urine pH. Urine flow rates and pH should be monitored closely. Placement of a bladder catheter may be needed in patients with severely altered mental status or in case of lower urinary tract obstruction. Patients with compromised cardiac function may require a pulmonary arterial line (Swan–Ganz catheter) to monitor volume status and to avoid pulmonary edema.

Urinary acidification is achieved by systemic acidification. Ammonium chloride (NH_4Cl) may be administered orally at a dose of 100 mg/kg over 30 to 40 min, or a similar dose given intravenously as a 1–2% solution of NH_4Cl in normal saline can be utilized. With either technique, the urine pH should be 5.0 or less without inducing a severe systemic metabolic acidosis. In addition, normal saline should be infused at a rate of 200 to 300 cc/hr together with intermittent doses of intravenous loop diuretics to increase urine flow. In normal subjects, maximum diuresis is produced by 40 mg of furosemide or 1 mg of bumetanide [20]. At such high rates of intravenous fluid infusion, close attention must be paid to the patient's urine output to avoid congestive heart

failure. Loop diuretics may increase distal tubular urinary hydrogen ion secretion and thus contribute to urinary acidification. Administration of arginine and lysine hydrochloride intravenously has also been used to achieve urinary acidification, but these agents can generate severe hyperkalemia and are therefore no longer used.

Phencyclidine (PCP) is a weak base with a pK_a value of 8.5, which is 90% metabolized and 10% secreted into the urine unchanged. Between 52 and 77% of the drug in blood is bound to α_1-acid glycoprotein, and the volume of distribution is more than 6 liters/kg [10]. PCP was originally developed as an anesthetic agent but was found to induce hallucinations and psychosis in some patients [25]. Since the 1960s this drug has been frequently used illegally, by oral, intravenous, or inhalation routes.

Acidification of the urine to a pH of 5.0 or less together with a furosemide-induced diuresis increases overall PCP elimination twofold [10]. Although most patients with phencyclidine overdose can be managed conservatively, a forced acid diuresis should be considered in severe cases, especially if prolonged coma is present. Some of these patients develop rhabdomyolysis (0.5 to 2.2% of PCP overdoses), and then acid diuresis is contraindicated because it increases myoglobin renal toxicity.

Quinine has a pK_a value of 8.4 but only 5% of the drug is excreted into the urine unchanged. Therefore, acid diuresis only modestly enhances overall elimination. Nonetheless, diuresis should be considered in patients with serious intoxication, since hemodialysis, peritoneal dialysis, and plasmapheresis remove very little quinine [21]. *Quinidine,* an isomer of quinine, has a larger volume of distribution, but since 20% of a quinidine load is excreted unchanged in the urine, acid diuresis is indicated in severe quinidine overdose [10] and is more effective than in the case of quinine.

Acid diuresis also enhances the renal elimination of chloroquine, lidocaine, amphetamine, and fenfluramine. This method, however, may be difficult with the latter two sympathomimetic amines because of the prominent excitatory central nervous system effects seen in overdose patients, which will make efforts at urine and plasma collection hard.

ALKALINE DIURESIS

A number of drugs and poisons are weak acids with pK_a values between 3.0 and 7.5 which result in enhanced renal excretion with alkaline diuresis. These compounds are sufficiently polar to limit their lipid solubility and restrict their volume of distribution. This further enhances renal elimination. Table 2 lists some of these drugs and poisons and their pK_a values.

To achieve an alkaline diuresis one should first achieve brisk urine flow. If preexistent volume depletion exists it should be corrected with an infusion of isotonic saline. If extracellular fluid (ECF) volume is adequate, mannitol or a loop diuretic may be used. Once brisk diuresis is established, intravenous sodium bicarbonate ($NaHCO_3^-$) should be given to achieve a urine pH in the range of 7.5 to 8.5. Intravenous bicarbonate should be given as an isotonic solution to avoid severe hypernatremia. Acetazolamide at a dose of 5 mg/kg every 6 hr may also be used to alkalinize the urine and maintain diuresis. This carbonic anhydrase inhibitor decreases H^+ secretion and thus increases sodium bicarbonate concentration in the proximal tubule. During an alkaline diuresis, serum electrolytes should be monitored frequently to avoid severe hypokalemia, hyponatremia, or a systemic metabolic alkalosis.

Salicylate poisoning remains an important and common clinical entity. The use of alkaline diuresis in the treatment of salicylate intoxication has achieved wide acceptance over the past 40 years [10]. Over 22,000 cases of aspirin overdose were reported to the American Association of Poison Control Centers in 1989, with a 0.1% mortality [15]. Mild salicylate intoxication may cause nausea, vomiting, lethargy, tinnitus, and dizziness, while more severe cases will present with tachypnea, fever, sweating, restlessness, and volume depletion. The most severe acute poisonings may lead to disorientation, coma, seizures, pulmonary edema, and severe acid–base disturbances. In children, metabolic acidosis usually predominates while in adults respiratory alkalosis is much more common [15]. Salicylates stimulate respiration via a direct action on the central nervous system respiratory center. When respiratory alkalosis predominates, bicarbonate should be administered more carefully to avoid exacerbating the systemic alkalosis.

Alkaline diuresis is effective with salicylate intoxication for several reasons. The volume of distribution of salicylate is relatively small (0.35 liter/kg). Renal excretion becomes increasingly important as serum concentrations progressively rise and salicylate albumin binding reaches a plateau. Salicylate renal clearance continues to rise as urine pH increases. For instance, there is a fivefold increase in excretion when the urinary pH rises from 7 to 8 [10]. Finally, enhanced urine flow alone results in an increase in salicylate clearance [18].

Barbiturates are weak organic acids with pK_a values ranging from 7.2 for phenobarbital to 8.2 for pentobarbital and secobarbital (Table 2). Renal clearance accounts for a substantial fraction of the total elimination of phenobarbital, while hepatic metabolism accounts for the majority of the elimination of other barbiturates in clinical use [10]. In general, short-acting barbiturates are metabolized by the liver, while long-acting barbiturates are renally excreted. Barbiturates with a low lipid-to-water partition coefficient (e.g., barbital, aprobarbital and phenobarbital) are largely excreted unchanged in the urine, but

this occurs very slowly. Only 20% of an oral hypnotic dose of barbital is eliminated in the urine of normal adults in the first 24 hr [13]. Alkalinization has two beneficial effects in phenobarbital toxicity. First, in systemic metabolic alkalosis there is a decrease in intracellular barbiturate concentration and a rise in extracellular barbiturate concentration. Second, alkaline diuresis doubles the renal clearance of phenobarbital. Alkaline diuresis only slightly increases the elimination of the other barbiturates [4]. Phenobarbital is best removed by hemodialysis in patients with life-threatening phenobarbital overdose, but in less severe cases, or in patients with unstable hemodynamic parameters, a forced alkaline diuresis is an effective alternative mode of therapy.

Diflunisal is a nonsteroidal anti-inflammatory agent structurally related to salicylic acid, with a pK_a of 3.3, which is partially cleared by the kidney. Although urinary alkalinization increases renal clearance of diflunisal, the total amount eliminated is only 5 to 7% of the ingested dose in healthy volunteers, while the rest is hepatically metabolized. Therefore, alkaline diuresis is of little value in patients with this drug overdose [1].

Chlorophenoxy herbicides, used to control broad-leaved weeds, have pK_a values between 2.6 to 3.3 and are excreted in the urine largely unchanged. Alkaline diuresis should be used to treat patients with acute chlorophenoxy poisonings especially if metabolic acidosis and coma are present, or if plasma total chlorophenoxy concentrations are > 0.5 g/liter [9].

Urinary alkalinization will also enhance the renal clearance of methotrexate, fluoride, and uric acid. *Uric acid* is particularly important since it can contribute to severe renal injury. A clinically relevant example where acute urate nephropathy may develop is tumor lysis syndrome. This syndrome is usually associated with some highly malignant lymphomas or leukemias and may occur spontaneously or after chemotherapy. Serum uric acid levels may rise very rapidly and lead to acute renal failure. Chemotherapy may result in massive tumor necrosis and patients at risk for this syndrome should be premedicated with allopurinol at high doses (600 mg/day for 2 to 3 days prior to treatment). In addition, a high urine flow rate is desirable during the chemotherapy. This will both enhance uric acid excretion and lessen the likelihood of uric acid crystal formation in the tubule. Finally, urinary alkalinization will also enhance renal uric acid clearance.

NEUTRAL DIURESIS

Neutral diuresis refers to the induction of a large urine output in an attempt to enhance the excretion of a drug or poison without pH dependent ion trapping effects. This treatment can be effective in the therapy of a drug overdose if the drug has a relatively small volume of distribution and is excreted by the kidneys

TABLE 3 Drugs Whose Renal Excretion Is Enhanced by Neutral Diuresis

Ethanol
Methanol
Ethylene glycol
Lithium
Meprobamate

in substantial quantities. The diuresis can be initiated by infusing isotonic saline followed by either mannitol and/or loop diuretics to maintain a brisk urine output. The excretion of some of these drugs increases proportionately as urine volume increases. This therapy is effective in poisoning with the common *aliphatic alcohols* such as *ethanol* and *methanol,* as well as with *ethylene glycol* (see Table 3). It can also be employed for the treatment of lithium intoxification. This treatment is limited by the need to induce large urine flow rates with the potential problems of hypo- or hypernatremia, hypokalemia, hypocalcemia, or hypomagnesemia. If rapid removal of these substances is required, hemodialysis is the treatment of choice.

Lithium carbonate is used extensively to treat bipolar affective disorders, and lithium intoxification is a frequent complication of chronic lithium therapy. Lithium is completely absorbed from the gastrointestinal tract, is not protein bound, and is freely filtered by the glomerulus. Most of the filtered lithium is reabsorbed in the proximal convoluted tubules, with further reabsorption occurring in the pars recta and/or the thick ascending loop of Henle [12]. Eighty percent of the filtered load of lithium is reabsorbed and 20% excreted in the urine in normal subjects [16]. Polyuria, a common side-effect of lithium use, is primarily the result of an impaired renal concentrating ability which is resistant to exogenous anti-diuretic hormone (nephrogenic diabetes insipidus).

Hemodialysis is indicated to treat lithium intoxification when the serum lithium concentration exceeds 3.5 mmol/liter or in patients who develop acute renal failure, severe central nervous system toxicity, or life-threatening bradyarrhythmias [8, 11]. When hemodialysis is not available, or toxicity less severe, forced neutral diuresis with isotonic saline infusion, mannitol, and furosemide may be indicated. Furosemide increases urinary lithium excretion, probably by inhibiting lithium reabsorption along tubule segments beyond the proximal tubule [5]. Amiloride attenuates the inhibitory effect of lithium on vasopressin mediated water reabsorption and thus substantially reduces urine volume without lowering lithium clearance [3]. The combination of amiloride and saline diuresis has also been successfully employed in the treatment of lithium toxicity [6]. Thiazide diuretics and furosemide have the disadvantage, however, of potentially inducing volume contraction, thereby potentiating lithium toxicity

due to increased proximal tubule reabsorption of lithium [12]. Furthermore, thiazide diuretics may cause hypokalemia which is not caused by amiloride. Thus, amiloride and saline diuresis remains the most successful therapy of lithium toxicity when hemodialysis is not otherwise indicated.

RADIOCONTRAST-INDUCED NEPHROTOXICITY

Radiocontrast-induced nephropathy is a leading cause of hospital-acquired acute renal failure (ARF) with an incidence ranging from 2 to 10% depending on the population's risk factors. Risk factors include preexistent volume depletion, age, underlying chronic renal insufficiency, diabetes mellitus, proteinuria, and the amount of the radiocontrast dye used. The pathogenesis of ARF in this setting is probably related to decreased renal blood flow and medullary ischemia resulting from an imbalance of vasodilative and vasoconstrictive factors [14]. Radiocontrast agents may also be directly toxic to the renal tubule epithelium. This form of ARF is somewhat unique because preexisting risk factors can be identified and the timing and dose of dye can be controlled. Measures which have been proposed to prevent or reduce the severity of contrast-induced nephrotoxicity include volume expansion and the administration of furosemide, mannitol, calcium channel blockers, dopamine, atrial natriuretic peptide, and theophylline [2].

The protective effect of *furosemide* in preventing contrast-induced ARF may be related to medullary renal vasodilation, reduction of the oxygen demand imposed by active sodium reabsorption, release of vasodilators, prostaglandins, and a reduction of the intratubular concentration of contrast media. The infusion of *hypertonic mannitol* may be protective by causing renal vasodilatation, inducing an osmotic diuresis, and increased atrial natriuretic peptide release and as a free oxygen radical scavenger. In some experimental animal models both mannitol and furosemide have attenuated contrast-induced renal dysfunction. In contrast, three randomized controlled studies in humans have shown that mannitol has either no effect or is deleterious in diabetic patients with renal insufficiency [7]. Similarly, two randomized prospective studies have shown that furosemide may increase the incidence of radiocontrast-induced ARF in uremic diabetic patients [7]. In a randomized trial of the efficacy of 0.45% saline alone compared with saline plus either furosemide or mannitol, saline alone was superior to the other two regimens in preventing contrast-induced nephrotoxicity [23]. Thus, the use of mannitol and/or furosemide remains controversial in preventing contrast media induced ARF.

In patients at risk for developing this complication, intravenous saline should be given before and after the administration of contrast agents. When the patient also has congestive heart failure or renal insufficiency, the use of

furosemide may be indicated. In nondiabetic patients with normal renal function there is no need to use mannitol or furosemide to prevent contrast-induced nephrotoxicity.

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CHAPTER VF

Diuretics and Glaucoma

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INTRODUCTION

Glaucoma is a series of eye diseases characterized by increased intraocular pressure, optic nerve degeneration, and visual field defects [3, 4, 8]. It is one of the leading causes of blindness in the United States. The incidence of the disease increases with advancing age and ranges from 1 to 5% of adults over the age of 40. The disease is insidious in its origin and most patients are asymptomatic until late in the course of the illness. By the time the diagnosis of glaucoma is made, permanent visual loss often has already occurred.

The primary basis of glaucoma is an increase in intraocular pressure (greater than 20–24 Torr) leading to progressive deterioration of the optic nerve [3, 4, 8]. The mechanism of the increased intraocular pressure is an obstruction to aqueous humor outflow: from the posterior chamber, from the anterior chamber through the trabecular meshwork on the way to the canal of Schlemm into the venous drainage system, or via drainage through uveal vessels and the sclera. While in theory an increase in aqueous humor production could lead to an increase in intraocular pressure, practically this rarely occurs. Initially the direct mechanical effect of the increased intraocular pressure on the optic nerve was thought to be the cause of the optic nerve damage. However, more recently

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the cause of the optic nerve deterioration has been felt to be pressure-mediated axonal degeneration of the optic nerve.

CLASSIFICATION OF GLAUCOMA

Glaucoma is not a single disorder, but rather multiple disorders (Table 1). There are multiple classification schemes. Glaucoma can be classified into congenital glaucoma, primary glaucoma, and secondary glaucoma. Congenital glaucoma is caused by an abnormality in the aqueous humor outflow tract in the anterior chamber. There may be other associated developmental ocular abnormalities. Primary glaucoma is divided into two categories, primary open angle glaucoma, and primary closed angle glaucoma. Primary open angle glaucoma is the most common form of glaucoma [9]. It is caused by chronic obstruction of outflow of aqueous humor from the anterior chamber through the trabecular network. The angle between the iris and the cornea is open and there is free passage of aqueous humor from the posterior chamber to the anterior chamber. The reported causes of obstruction at the level of the trabecular network are multiple and include accumulation of debris in the trabecular network, loss of the normally functioning trabecular cells, loss of permeability of the trabecular network, loss of the normal trabecular cleaning mechanism, and poor drainage through the canal of Schlemm due to a loss of adequate spaces. Primary closed angle glaucoma is caused by sudden increase in intraocular pressure due to blockade of aqueous humor flow from the posterior chamber because of pupillary block. Secondary glaucoma is an increase in intraocular pressure due to trauma, hemorrhage, infection, tumor, or surgical procedures.

MEDICAL THERAPY OF GLAUCOMA

Medical treatment for glaucoma involves multiple medications (Table 2) [3, 5, 10]. The principal goal of medical treatment is lowering of intraocular pressure. Local administration of cholinergic agents, beta-adrenergic blockers, and alpha-

TABLE 1 Classification of Glaucoma

1. Congenital glaucoma
2. Primary glaucoma
   a. Open angle glaucoma
   b. Closed angle glaucoma
3. Secondary glaucoma

TABLE 2 Medical Therapy of Glaucoma

1. Cholinergic agents (pilocarpine)
2. Beta-adrenergic antagonist agents (timolol)
3. Alpha-adrenergic agents (epinephrine)
4. Diuretics
   a. Osmotic diuretics (mannitol)
   b. Loop diuretics (ethacrynic acid)
5. Ocular (ciliary) carbonic anhydrase inhibitors
   a. Systemic (acetazolamide)
   b. Topical (dorzolamide)

adrenergic agonists have been used to treat glaucoma. Cholinergic agents, with the prototype drug pilocarpine, lower intraocular pressure by stimulation of the ciliary muscle and by constriction of the pupil, with the resultant reduction of trabecular resistance to aqueous humor outflow. Beta-adrenergic antagonists, with the prototype drug timolol, lower intraocular pressure by blockade of the ciliary process production of aqueous humor. Alpha-adrenergic agonists, with the prototype drug epinephrine lower intraocular pressure by stimulation of receptors in the trabecular network with a marked increase in aqueous humor outflow.

Diuretics have been used to treat glaucoma for many years. The major mechanism involved is not an increase in renal salt and water excretion, but rather a decrease in local eye aqueous humor production, leading to a reduction of intraocular pressure. However, other mechanisms of diuretic action have been suggested as well.

The classic diuretic used in the treatment of glaucoma is the carbonic anhydrous inhibitor acetazolamide [6]. A similar agent, methazolamide, has also been used. Carbonic anhydrase inhibitors block the hydration reaction of carbon dioxide, with the subsequent formation of bicarbonate in many tissues including the ciliary body. The enzyme carbonic anhydrase is located in the ciliary body, but its specific role in aqueous humor production is not certain. Reduction of bicarbonate production with carbonic anhydrase inhibitors is directly correlated with a fall in aqueous humor production. There does not appear to be a role for these agents in direct fluid removal from the anterior chamber. The development of systemic metabolic acidosis has little effect on intraocular pressure or aqueous humor production. Use of carbonic anhydrous inhibitors clinically has resulted in a decrease in aqueous humor flow rate by approximately 40–60%. This results in a decrease in intraocular pressure of 2–10 Torr. It has long been held that carbonic anhydrase inhibitors are effective in the treatment of glaucoma only when given systemically. When administered

by this route, they have many side-effects and are difficult to use clinically, as up to 50% of patients may need to stop these agents because of intolerable side-effects [3]. Frequent side-effects include fatigue, malaise, confusion, depression, paresthesia, and loss of appetite. All of these side-effects may be related to the systemic acidosis that develops with the use of these agents. Significant gastrointestinal side-effects include nausea, vomiting, and diarrhea. Hyperventilation in response to the metabolic acidosis may compromise patients with marginal pulmonary reserve. Hypokalemia, metabolic acidosis, and transient polyuria occur in virtually all patients who use these medications. Renal calculi can occur in part related to a decrease in urinary citrate excretion. Severe bone marrow toxicity has been described rarely with the development of aplastic anemia and agranulocytosis.

The recent development of topical carbonic anhydrase inhibitors of the sulfonamide family, such as Dorzolamide, that rapidly penetrate the cornea represents a significant advance in the treatment of glaucoma [7]. This route of administration precludes the undesirable side effects mentioned above as there is no detectable drug or metabolite in the blood. Such agents display high activity against corneal carbonic anhydrases II and IV, and their efficacy in reducing intraocular pressure is similar to that achieved by intravenous administration of potent carbonic anhydrase inhibitors [1, 7].

Intravenous administration of the osmotic diuretic mannitol by drawing fluid out of the eye into the hypertonic plasma has been used to acutely lower intraocular pressure. Mannitol, however, is rarely used in the routine treatment of glaucoma.

Conventional diuretics, including thiazides and loop diuretics have been tried in the treatment of glaucoma. There is very little effect, however, on either aqueous humor production or intraocular pressure. The traditional loop diuretic ethacrynic acid has recently been used in a nontraditional manner to treat glaucoma [1]. Ethacrynic acid when injected locally into glaucomatous eyes has resulted in a marked reduction in intraocular pressure. The effect is immediate and lasts for approximately 1 week. The absorption of the drug into the eye after oral and intravenous administration is suspect and may limit its clinical utility. The proposed mechanism of action for ethacrynic acid is a washout of debris from the trabecular network, thereby allowing an increase of aqueous fluid outflow from the anterior chamber.

The use of diuretics in the treatment of glaucoma has been sharply reduced, as it has been appreciated that glaucoma is primarily a disease of inadequate drainage of aqueous humor rather than an excess of fluid production. Therefore the major forms of therapy involve increasing aqueous humor drainage either medically or most often by surgical methods, rather than reducing aqueous humor production using systemic diuretics.

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CHAPTER VG

Diuretics and Cerebral Edema

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INTRODUCTION

Cerebral edema is defined as an increase in the volume of the brain due to an increase in brain water content [4]. The water content of the brain in health is about 80% of wet weight for the gray matter and 70% of wet weight for the white matter. For the same degree of cerebral edema only small increases in brain water occur in the gray matter, while much larger increases in brain water occur in the white matter. Therefore, most of the manifestations of cerebral edema involve symptoms related to white matter dysfunction. The adverse effects of cerebral edema are not thought to be caused by the direct effects of the swelling itself, or on impaired neuronal transmission, or by disturbances in the chemical composition of brain tissue, or by deficits in oxygen delivery. Rather, the adverse effects appear to be indirect and mediated by cerebral ischemia, increased intracranial pressure, and brain shift with displacement [13]. The manifestations of cerebral edema range from minimal to focal to generalized neurologic deficits. The dreaded complication of cerebral edema involves brain herniation. Various forms of brain herniation can occur (Table 1). They include: (i) cingulate herniation of the cingulate gyrus and the hemisphere beneath the falx to the contralateral side, (ii) uncal herniation of the medial portion of the temporal lobe through the tentorium with subsequent midbrain

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TABLE 1 Types of Brain Herniation

1. Cingulate herniation
2. Uncal herniation
3. Tonsillar herniation
4. Transcalvarial herniation

compression, (iii) tonsillar herniation of the cerebellum through the foramen magnum with brain stem compression, (iv) transcalvarial herniation of any portion of the brain through craniotomy sites [2, 4].

CLASSIFICATION OF CEREBRAL EDEMA

Cerebral edema has been classified into several categories (Table 2). The initial classification system by Klatzo involved two categories: (i) vasogenic edema and (ii) cytotoxic edema [10]. More recently, other categories have been described. They include: (iii) ischemic edema, (iv) hydrostatic edema, (v) hydrocephalic edema, (vi) osmotic edema [4, 13]. The mechanisms of edema in each of these categories are different as are the responses to therapy.

Vasogenic cerebral edema is characterized by an increased permeability of the brain capillaries arising from a disruption of the blood–brain barrier [4, 13]. This leads to an exudation of protein-rich fluid into the brain tissue. Initially this form of cerebral edema was described following cold application to the brain, direct stab wounds, and experimental brain tumors. In clinical medicine, this form of cerebral edema is seen most commonly with brain tumor, abscess, hemorrhage, infarction, and contusion. Meningitis and lead neurotoxicity can also cause this form of cerebral edema. Corticosteroids are useful in the treatment of all types of vasogenic cerebral edema, while osmotherapy has little effect.

Cytotoxic cerebral edema is characterized by intracellular swelling of all brain cells due to energy depletion [4, 13]. It occurs in the setting of an intact blood–brain barrier. The loss of energy supply to the brain leads to a malfunction of the ATP-dependent sodium pump which is responsible for maintenance of a low cellular sodium content. Sodium rapidly accumulates in the damaged cells,

TABLE 2 Classification of Cerebral Edema

1. Vasogenic	4. Hydrostatic
2. Cytotoxic	5. Hydrocephalic
3. Ischemic	6. Osmotic

with water following to maintain osmolar equilibrium. The result is intracellular swelling at the expense of extracellular fluid reduction. In clinical medicine, this form of cerebral edema is most commonly seen with hypoxia due to an inadequate circulation, or frank cardiopulmonary arrest. Corticosteroids have little effect in the treatment of cytotoxic edema, while osmotherapy may be useful in reduction in cellular water content.

Ischemic cerebral edema is characterized by a combination of initially cytotoxic cerebral edema, followed by vasogenic cerebral edema. Clinically this can be seen with inadequate cardiac output in excess of compensatory cerebral vasodilatation, or increased cerebrovascular resistance (e.g., acute hyperventilation with a rapid reduction in pCO_2), or cerebral shunts (e.g., arterial pH < 6.8). Following cerebral ischemia and subsequent reflow, cerebral edema follows a predictable sequence. There is first cellular uptake of sodium and water due to cellular cytotoxic injury. No net increase in brain water occurs, as there is inadequate blood flow to act as a fluid source. However, as reflow occurs, protein-rich fluid leaks into the brain interstitium resulting in vasogenic cerebral edema. Corticosteroids and osmotherapy have no specific beneficial effect in the treatment of ischemic cerebral edema.

Hydrostatic cerebral edema is characterized by increased brain water due to increased blood pressure leading to a transudation of protein-free fluid into brain tissue. Malignant hypertension is the usual clinical presentation of this form of cerebral edema. No specific therapy is available except for reduction of blood pressure.

Hydrocephalic cerebral edema is characterized by increased brain water due to cerebrospinal fluid blockage. The blood–brain barrier is intact. The cerebral edema is confined to the extracellular interstitial space and is of the same composition as the cerebrospinal fluid. Treatment involves relief of the intraventricular obstruction.

Osmotic cerebral edema is characterized by increased brain water due to systemic hypoosmolality. In clinical medicine this can be seen with acute hyponatremia and with glucose or urea disequilibrium states. All forms of hyponatremic states induce osmotic cerebral edema. The edema is within both the intracellular and extracellular spaces. Neurologic sequelae are related to the speed of development of the hypotonic state. Treatment involves the correction of hyponatremia.

THERAPY OF CEREBRAL EDEMA

The specific therapy of the cerebral edema depends on the cause and kind of cerebral edema (Table 3) [5]. Apart from diuretic therapy, treatment of cerebral edema involves establishment of adequate airway, delivery of adequate oxy-

TABLE 3 Treatment of Cerebral Edema

Type	Treatment
1. Vasogenic	Corticosteroids
2. Cytotoxic	Osmotherapy
3. Ischemic	No specific therapy
4. Hydrostatic	Blood pressure control
5. Hydrocephalic	Neurosurgical shunt placement
6. Osmotic	Correction of hypoosmolality

genation, correction of volume disturbances, and control of blood pressure. Hyperventilation reduces the CO_2 tension of the blood which causes an increase in cerebrovascular resistance; as a result cerebral blood flow falls, reducing cerebral blood volume, thereby lowering intracranial pressure. Hypotonic fluids should be avoided as osmotic cerebral edema could be superimposed on preexisting other forms of cerebral edema. Appropriate neurosurgical therapy is necessary to treat anatomic complications (e.g., drainage of abscess, evacuation of subdural blood, or placement of intraventricular shunt). Medical therapy of cerebral edema varies with the cause, but often involves corticosteroids, mannitol used as a osmotic diuretic, and conventional diuretics to lower intracranial hypertension.

Diuretics have a certain rational appeal in the treatment of cerebral edema. Diuretics have long been used for fluid mobilization therapy of many forms of edema including pulmonary edema, ascites, and peripheral edema, by primarily increasing the renal excretion of salt and water, with secondary removal of excessive fluid from tissues. It would seem reasonable for diuretics to be used for fluid mobilization in some forms of cerebral edema as well.

Both mannitol and conventional diuretics can have effects not only on renal salt and water excretion, but also on local fluid transport mechanisms. Most if not all of the important clinical effects of diuretics in the treatment of cerebral edema are due to nonrenal mechanisms.

Osmotherapy with hypertonic mannitol is the use of an osmotic diuretic in a nonrenal way for the treatment of cerebral edema. The mechanism of mannitol reduction in cerebral edema has traditionally been ascribed to a rise in the effective osmotic pressure of the extracellular fluid, thereby directly dehydrating cerebral cells. Fluid removal therefore occurs from the whole brain, not just from isolated damaged brain areas. More recently an alternative explanation has been offered. Mannitol leads to a reduction in blood viscosity [3, 14]. The natural response to a decrease in blood viscosity would be a transient increase in cerebral blood flow, followed by intense cerebral vasoconstriction in an attempt to maintain constant intracerebral pressures. This vasoconstriction results in limited cerebral swelling.

The effect of osmotherapy with mannitol is unpredictable. Osmotherapy is effective only in a disequilibrium state, that is, when there is an effective mannitol gradient between the blood and the brain. The duration of action of osmotherapy is short (lasting only hours) as equilibration between blood levels and brain levels of mannitol occurs quickly. Renal excretion of mannitol limits the effectiveness of therapy as well. As the drug gradient is dissipated, the effectiveness of osmotherapy disappears. Osmotherapy is effective only in the presence of an intact blood–brain barrier. This suggests that osmotherapy is very useful only in the cytotoxic cerebral edema and not in vasogenic or ischemic cerebral edema. Paradoxical rebound cerebral edema can occur if mannitol is used in cerebral edema characterized by a disrupted blood–brain barrier [9]. The drug can not be effectively eliminated from the damaged brain tissue, and as the blood level falls, fluid is pulled back into the hypertonic brain tissue. Finally the long–term use of osmotherapy with mannitol remains suspect as the brain can adapt to chronic hypertonicity by creation of its own osmoles, which would minimize the effective osmotic gradient between the brain cells and the blood, thereby limiting further osmotic fluid removal.

The clinical use of mannitol involves the intravenous administration of the drug. There is a dose dependent reduction in cerebral edema and intracranial pressure to mannitol. The optimal dose of mannitol is 1–2 g/kg loading dose given over 30 min, with responses in most patients within 30–45 min, but a prompt return of intracranial pressures back to baseline within 2 hr [12, 17]. This return of intracerebral pressures to pretreatment levels usually requires further mannitol doses, either via bolus administration or via continuous infusion. There is little outcome data for specific mannitol regimens. Careful monitoring of intracranial pressures is necessary. Optimal intracranial pressures are less than 20–25 Torr. Plasma osmolality needs to be carefully monitored. Plasma osmolality greater than 310 mOsm/kg should lead to a reduction in mannitol therapy. Complications of mannitol therapy include: (i) hypotension, (ii) hyperosmolality recognized clinically as unexpected hyponatremia [1], (iii) hypokalemia, and (iv) reversible acute renal failure [6, 19]. This acute renal failure is seen following massive mannitol infusions, in excess of 1000 g per day. It is typically oliguric acute renal failure characterized by a low fractional sodium excretion [19]. Recovery of renal function is universal, but often patients have died of their underlying neurologic catastrophe. The mechanism of the renal failure has been hypothesized as appropriate tubuloglomerular feedback in the setting of ongoing large salt and water losses associated with continued large mannitol doses [6].

Loop diuretic either alone or in combination with mannitol have been used in the treatment of cerebral edema [20]. The effect of loop diuretics is via inhibition of local brain transport mechanisms rather than via renal salt and water excretion. Furosemide given intravenously in doses of 0.3–1.0 mg/kg has resulted in significant decreases in intracranial pressure [18]. The fall in intracra-

nial pressure has been variable but ranged from 5 to 12 Torr with the peak drop seen at 30–90 min. Combination therapy with furosemide and mannitol has consistently led to a significantly greater reduction of intracranial pressure than either agent alone [15, 16]. The effect of furosemide in the treatment of cerebral edema is thought to be mediated by multiple mechanisms, direct inhibition of Na^+–Cl^- transport into the brain, removal of salt and water from both normal and edematous brain tissue, and reduction in cerebrospinal fluid production by the choroid plexus. Most of the studies with furosemide have been done in experimental animals, and there are few human clinical studies with outcome data. Ethacrynic acid likewise has resulted in a reduction in cerebral edema and intracranial pressure in experimental studies. Complications of loop diuretics include: (i) hyponatremia, (ii) hypokalemia, (iii) volume depletion with hemodynamic instability, and (iv) prerenal azotemia, arising from salt depletion.

Other diuretics have been used in the treatment of cerebral edema. Carbonic anhydrase inhibitors have long been used to treat the cerebral edema associated with hydrocephalus [8]. This class of diuretics lower cerebrospinal fluid production [11]. The mechanism of action of these drugs is local inhibition of the carbonic anhydrase activity of the choroid plexus. However, at least 99% of enzyme activity needs to be inhibited before a significant slowing of cerebrospinal fluid flow is seen. Usual doses of acetazolamide, the most commonly used drug in this class, are 500–1000 mg/day in divided doses. The effect of carbonic anhydrous inhibitors is blunted by the obligatory metabolic acidosis resulting from drug-induced sodium bicarbonate diuresis, which leads to reflex cerebral vasodilatation. Side-effects of carbonic anhydrase inhibitors include: (i) hypokalemia, (ii) metabolic acidosis, and (iii) significant drug allergy.

Finally weak diuretic agents have been tried in the treatment of cerebral edema. Thiazides, amiloride, and spironolactone all lower cerebrospinal fluid production but there are virtually no clinical studies to look at their utility in the treatment of cerebral edema.

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PART VI

Diuretic Complications

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CHAPTER VIA

Sodium: Volume Depletion and Hyponatremia

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VOLUME DEPLETION

The two most common complications of diuretic therapy are volume depletion and hypokalemia; the latter will be discussed in detail in the next chapter. The diuretics most commonly associated with volume depletion are thiazides and loop diuretics.

CLINICAL CONSEQUENCES, DEGREES OF SEVERITY, AND EPIDEMIOLOGY

The symptoms of volume depletion depend on the etiology, magnitude, and presence of accompanying electrolyte and acid–base disorders. The earliest complaints are lassitude, thirst, easy fatigability, muscle cramps, and postural dizziness. More severe hypovolemia may cause symptoms of decreased tissue perfusion. The elderly are especially prone to developing symptoms of cerebral or coronary insufficiency, mesenteric ischemia, and renal underperfusion manifested by a rise in blood urea nitrogen (BUN) and creatinine [19]. In extreme cases, hypovolemic shock is associated with a marked increase in sympathetic activity (tachycardia, cold and clammy extremities), cyanosis, a low urine out-

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put, as well as agitation and confusion due to reduced cerebral blood flow. Diuretic-induced volume depletion is especially likely to occur in the elderly and patients with severe congestive heart failure (CHF) or cirrhosis who have decreased effective circulating volume. Women are more prone to volume depletion than men.

A reduction in the effective circulating volume secondary to diuretic treatment decreases renal perfusion and, consequently, the glomerular filtration rate (GFR) such that the daily endogenous load of nitrogenous wastes cannot be excreted until a new steady state is reached at higher plasma concentrations. This causes prerenal azotemia, manifested by an increase in BUN, and a smaller increase in creatinine. The azotemia can be reversed by extracellular fluid (ECF) volume repletion.

PATHOPHYSIOLOGY

Generation Phase

Diuretics increase sodium excretion by inhibiting transport at different sites of the nephron (see Chapter IIIA). This enhanced sodium loss is limited in duration and is greatest after the first dose (Fig. 1). If the sodium loss is large enough, it will lead to volume depletion.

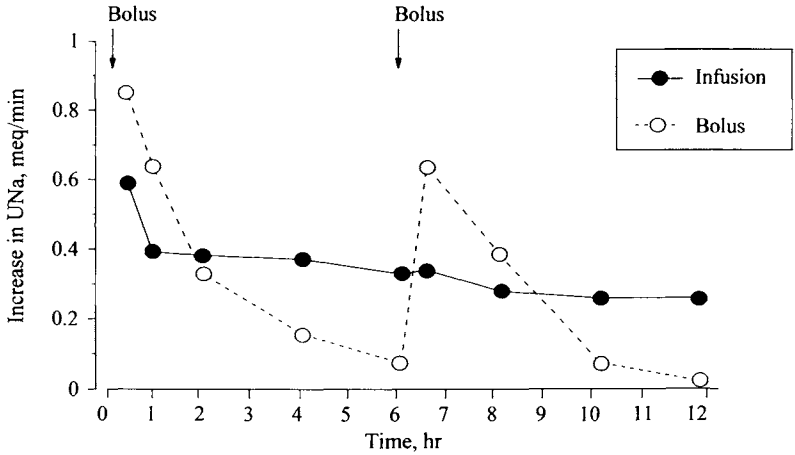

FIGURE 1. Urinary sodium excretion (U_{Na}) after intravenous bolus or infusion of bumetanide in patients with stable chronic renal failure. The peak natriuresis following iv bolus is 25% less during the second dose. In contrast, the natriuresis slowly declines during continuous iv infusion. The continuous infusion produced a greater natriuresis than bolus. (Adapted from Rudy DW, Voelker JR, Greene PK, et al *Ann Intern Med* 115:360, 1991 with permission).

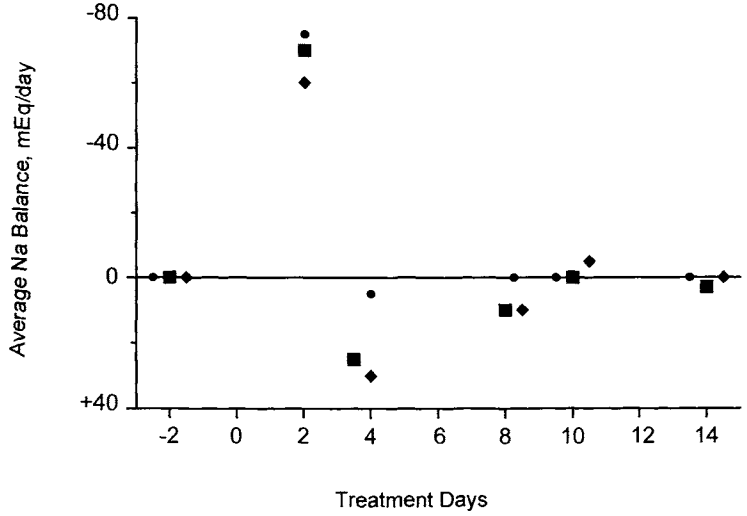

FIGURE 2. Sodium balance in three nonedematous patients treated with 100 mg of hydrochlorothiazide per day. Data for each patient reflect the average balance for each 3- or 4-day period. Net sodium loss is seen for only 3 days before a new steady state is reestablished. (Adapted from Maronde RF, Milgrom M, Vlachakis ND, Chan L, *J. Am. Med. Assoc.* 249:237, 1983, with permission.)

Maintenance Phase

Once fluid loss and volume depletion occur, the response to further doses of diuretics will be limited by the activation of sodium retaining mechanisms. If the diuretic dose and sodium intake remain constant, a new steady state is readily established usually within 4 days in normal subjects (Fig. 2). At the new steady state, sodium intake and output are equal; however, the effective circulating volume has decreased due to the initial period of negative sodium balance during the generation phase [26]. These same effects can be observed even during constant diuretic infusions (Fig. 1).

The proposed mechanisms of diuretic resistance are discussed in Chapter IVB1 and include:

1. Neurohumoral mediated increases in tubular reabsorption at sites that are not diuretic-sensitive. Examples include the proximal tube (angiotensin II and to a lesser degree norepinephrine) and the collecting tubule (aldosterone).
2. Flow-mediated increased in tubular reabsorption distal to the site of action of the diuretic. For example, loop diuretics cause increased downstream delivery of sodium to the distal tubule and collecting tubules, producing hypertrophy and increased Na/K ATPase activity with resultant enhanced sodium reabsorption.

3. Diminished entry of the diuretic into the lumen when renal perfusion becomes impaired.

Postdiuretic Sodium Retention

The therapeutic effect of the diuretic during a 24-hr period will be determined by the balance between the sodium loss that occurs while the diuretic inhibits sodium transport and the sodium gain that occurs while the drug concentration is low [26]. When the diuretic concentration falls below a critical threshold, positive sodium balance may develop. This phenomenon is called postdiuretic sodium retention. The magnitude of this postdiuretic sodium retention depends on four factors (see Table 1).

If sodium intake is high and the half-life of the diuretic is short, postdiuretic sodium retention will compensate for the sodium lost while the drug was active, and there will be no net sodium loss (see Fig. 3). This commonly occurs when short-acting loop diuretics such as furosemide are given one or twice a day. In contrast, if the patient is placed on a low salt diet, even one or two doses of furosemide a day will cause a negative sodium balance.

Extrarenal adaptations contributing to postdiuretic sodium retention include ECF volume-dependent increases in circulating renin, angiotensin, and aldosterone, stimulation of renal nerves, and decreases in GFR [17, 21, 22]. Reductions in ECF volume can also inhibit sodium excretion due to a reduction in the filtered sodium and an increase in fractional sodium reabsorption. Therefore, sodium excretion rates decline gradually until they match the sodium intake [10, 26]. This is known as the "braking phenomenon."

However, sodium retention occurs even when these compensatory responses are blocked or when decreases in ECF volume are prevented [1, 25, 26]. This suggests that the diuretic action directly triggers some intrarenal processes that may play an important role stimulating sodium retention. For example, loop diuretics increase solute delivery to the distal tubule, chronically increasing solute transport by distal tubule cells, resulting in their hypertrophy (see Fig. 4). These structural changes are associated with functional changes that

TABLE 1 Factors Contributing to Postdiuretic Sodium Retention

Diuretic pharmacokinetics
Dietary sodium content
Extrarenal adaptations
Intrarenal adaptations

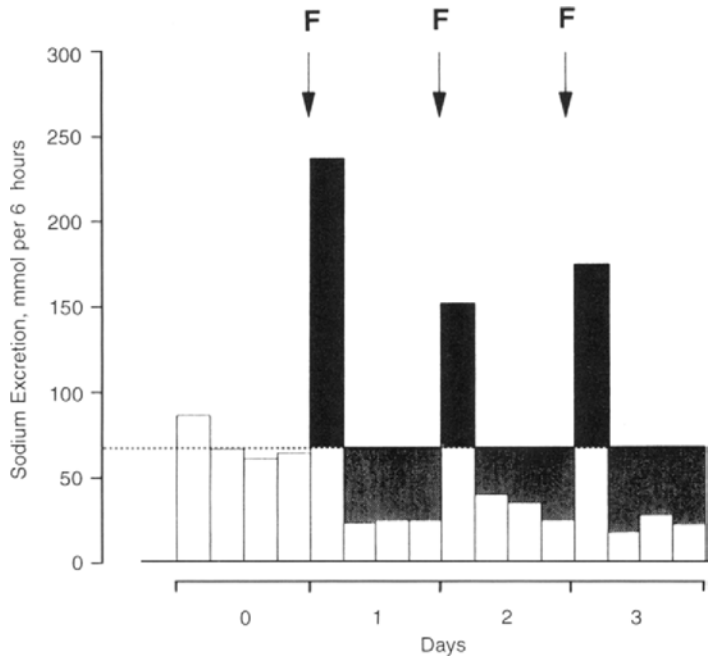

FIGURE 3. Effect of furosemide on sodium excretion in normals ingesting high sodium diet containing 270 mEq/day. Sodium excretion was measured over 6 hr intervals. The dotted line represents the mean sodium excretion, averaged over a 24-hr period. (From Wilcox et al, Kidney Int. 31:135, 1987, with permission.)

include increases in thiazide-sensitive sodium chloride cotransporters in the distal convoluted tubule and Na/K ATPase activity in the cortical collecting tubule, resulting in enhanced sodium transport [5, 7, 12, 16, 20, 23]. These changes may contribute to the return to neutral sodium balance. Once the effects of the diuretic have worn off, distal nephron segments may be primed to reabsorb more sodium [6].

Treatment

Volume depletion is treated with sodium chloride. This can be administered orally; however, in more severe cases the patient should be given 1–2 liters of normal saline. Saline should be administered until the orthostatic symptoms and signs are corrected. Accompanying potassium deficits should be replaced.

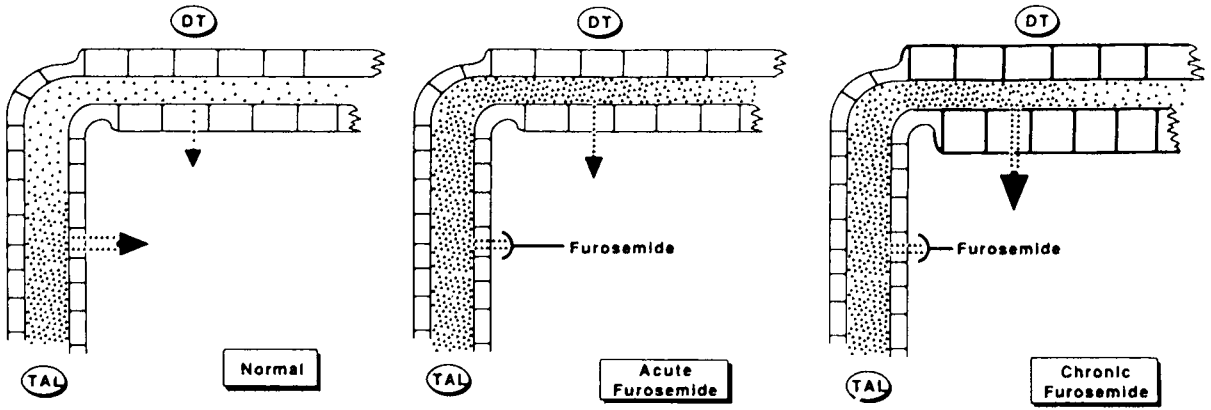

FIGURE 4. Chronic furosemide causes hypertrophy of the distal tubule. (From *American Journal of Kidney Disease* [6] with permission)

HYPONATREMIA

INCIDENCE

Recently, diuretics have been identified as the cause or at least a major contributing factor in over half the patients hospitalized for severe chronic hyponatremia [8, 24]. Every diuretic can be associated with hyponatremia, either alone or in combination with other diuretics. Although a common complication, it is usually mild. Diuretic-induced hyponatremia is usually seen with thiazide diuretics, including metolazone [2, 3, 8]. Since loop diuretics impair both the renal concentrating and diluting capacities, they are less often associated with hyponatremia. This is because inhibition of sodium reabsorption in the thick ascending limb reduces free water formation in this segment as well as free water reabsorption in the medullary collecting duct. Severe acute or chronic hyponatremia is usually seen in patients on thiazide diuretics who also drink large volumes of water [9, 14]. Severe diuretic-induced hyponatremia affects primarily the elderly [2, 4, 15]. Hyponatremia is more common in women than in men. Small, elderly women are very susceptible to diuretic-induced hyponatremia because only small gains in water and losses of salt are required to produce this effect [8, 24].

TIMING

Like volume depletion, diuretic-induced hyponatremia usually develops within the first days to 1 week of therapy if the diuretic dose and dietary salt intake are maintained constant. Plasma sodium concentration begins to fall within 6 to 24 hr in susceptible subjects [3, 9]. After this time, the patient enters a new steady state in which further sodium and water loss does not occur [18]. In contrast, acute hyponatremia can develop within 1–2 hr if a patient drinks a large amount of water.

PATHOPHYSIOLOGY

A major role of the kidneys is to excrete excessive water ingested in the diet and thereby prevent hyponatremia. Maximal free water excretion requires formation of free water in the thick ascending limb and inhibition of free water reabsorption in the medullary collecting duct. Free water formation, in turn, requires unimpaired delivery of filtrate to the thick ascending limb (normal GFR, normal proximal fractional reabsorption, normal Na transport in the ascending limb), while inhibition of free water reabsorption requires principally

suppression of anti-diuretic hormone (ADH) secretion. Should water intake suddenly increase, plasma sodium (and osmolality) will decrease, thereby suppressing the pituitary secretion of ADH. This results in decreased water reabsorption in the collecting tubules, production of dilute urine, and rapid excretion of excess water. In the absence of ADH, the urinary osmolality can fall to 40 to 100 mOsm with a maximum free water excretory capacity of 25 liters/day in patients on regular diets.

In contrast, diuretics interfere with this process by inhibiting free water excretion. The measured urine osmolality is inappropriately high (greater than 100 mOsm) for the particular degree of plasma hypoosmolality reflecting the impairment of free water excretion. As outlined above, maximal water excretion requires (i) normal GFR and delivery to the tip of the loop of Henle, (ii) normal distal sodium absorption, and (iii) suppression of arginine vasopressin (AVP), reducing water reabsorption in the collecting duct system.

Diuretics interfere with these processes (Fig. 5). Diuretic-induced volume depletion reduces delivery of filtrate to the ascending limb and increases circulating ADH levels. Elevated circulating ADH levels lead to increased free water reabsorption in the collecting ducts and therefore hyponatremia. In addition, diuretic-induced potassium losses promote a sodium shift from the extracellular space into the intracellular space, thereby amplifying volume deficiency.

Hyponatremia is particularly severe with diuretics that effectively inhibit the action of the cortical transport system (e.g., thiazides), since they do not impair medullary hypertonicity. Thus, there is less free water generation, coupled with increased free water reabsorption (Fig. 5). Moreover, in contrast to furosemide, thiazides are longer-activity and therefore prevent replenishment of volume deficits. In the case of loop diuretics, volume depletion can also lead to augmented ADH secretion, but the degree of water retention and therefore the tendency to hyponatremia is limited by the decrease in medullary hypertonicity. (Fig. 5B).

Treatment

Monitoring plasma sodium concentration for the first few days of diuretic therapy is prudent. This is especially true in elderly women, patients who ingest large volumes of water, or patients on nonsteroidal anti-inflammatory drugs. If hyponatremia develops, the treatment consists of stopping the diuretic, water restriction, and replacement of any sodium deficit by administering isosmotic saline (see Chapter VC1). This does not apply to edematous states (e.g., heart failure, cirrhosis with ascites, nephrotic syndrome, etc.) where massive edema is conjoined with a persistently shrunken effective arterial blood volume

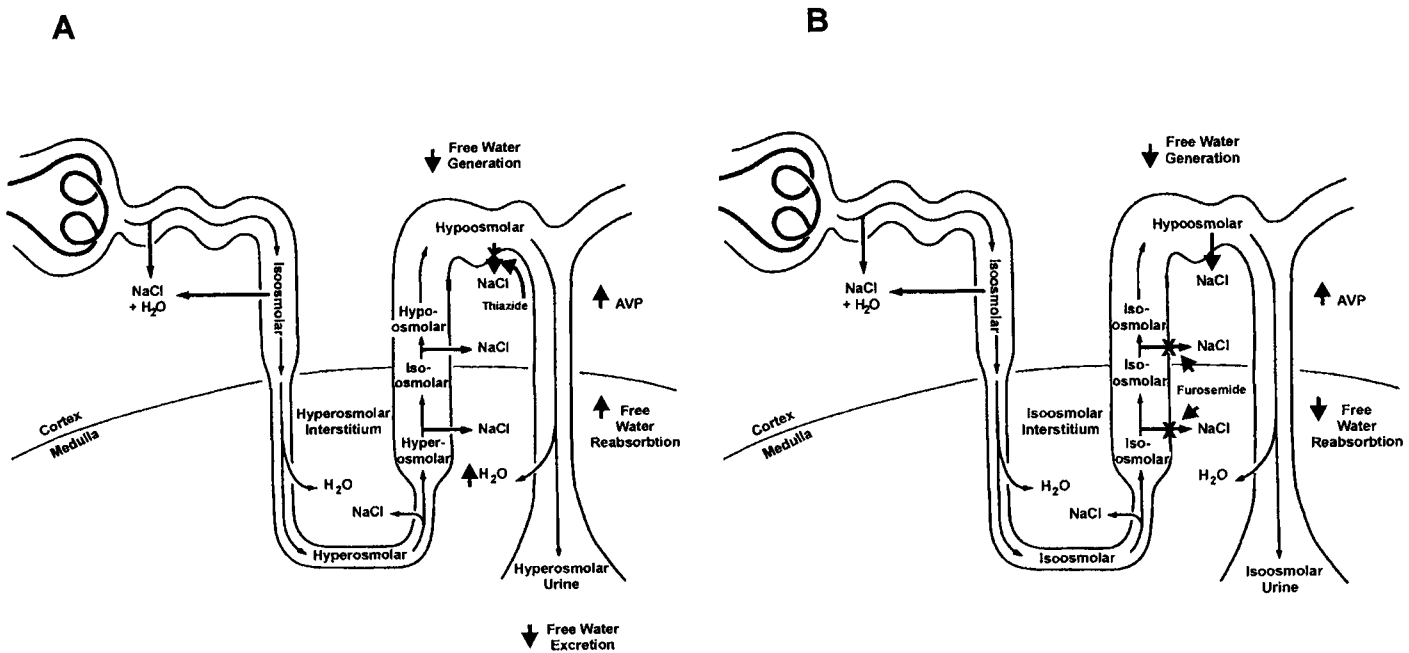

FIGURE 5. Mechanisms of diuretic induced hyponatremia. (A) Thiazide diuretics. Since thiazides act on the distal tubule, they have no effect on the increased medullary hypertonicity. The action of ADH in the collecting tubules will allow water reabsorption into the hypertonic medullary interstitium. The decreased the free water excretion will increase the tendency to hyponatremia. (B) Loop diuretics. Since loop diuretics act on the TAL, they impair the generation of a medullary hypertonic interstitium. Upon ADH action, free water reabsorption will be limited by a lack of medullary hypertonicity and the tendency to hyponatremia is limited. (Modified and adapted from The Kidney: Physiology and Pathophysiology. Second edition. Seldin DW and Giebisch G. Chapter 28, with permission).

(EABV). In consequence, salt administration increases edema, but does not significantly augment EABV. Therapy is therefore primarily directed at reducing free water intake. If the hyponatremia is severe or symptomatic, administration of hypertonic saline may be necessary; a loop diuretic is generally added to prevent volume overload. Patients with moderate to severe hyponatremia have to be monitored closely as the rapid correction of volume contraction with isotonic saline will make the patient euvolemic. Once euvolemic, the patient will have an appropriately suppressed ADH secretion and the result will be the production of a dilute urine. The resultant rapid excretion of excess water will produce rapid correction of hyponatremia and will increase the risk for osmotic demyelination.

Paradoxically, loop diuretics are sometimes used in conjunction with hypertonic saline infusion in the treatment of hyponatremia. By limiting medullary hypertonicity, they decrease urinary concentration and net electrolyte-free water excretion. The combination reduces the risk of volume overload. [11].

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CHAPTER VIB

Potassium Disturbances Associated with the Use of Diuretics

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INTRODUCTION

Disturbances in the serum potassium concentration are some of the most common metabolic side-effects associated with the use of diuretics. Those agents which act proximal to the collecting duct are associated with hypokalemia. The development of hypokalemia is primarily the result of diuretic-induced changes in extracellular fluid volume, mineralocorticoid activity, and distal sodium delivery. These alterations lead to enhanced potassium excretion at sites distal to where the drug exerts its diuretic effect. Diuretics which act at the level of the collecting duct are associated with hyperkalemia and are commonly referred to as potassium sparing diuretics. These agents predispose to the development of hyperkalemia by disturbing potassium transport mechanisms localized in the collecting duct. This chapter will review both the direct and the indirect mechanisms by which diuretics disturb normal potassium homeostasis. The clinical consequences of these disturbances will also be discussed. To understand better how diuretics lead to disturbances in the serum potassium concentration, a brief overview of renal potassium handling will be presented.

Diuretic Agents: Clinical Physiology and Pharmacology

RENAL POTASSIUM HANDING

Potassium is freely filtered by the glomerulus. The bulk of filtered K is reabsorbed in the proximal tubule and loop of Henle such that only 10% of the filtered load reaches the distal nephron. In the proximal tubule potassium absorption is passive and is in rough proportion to Na and water. In the thick ascending limb of Henle, potassium reabsorption occurs via transport on the apical membrane Na/K/2Cl cotransporter. Secretion of K occurs in the distal nephron primarily in the initial collecting duct and the cortical collecting duct. Under most physiologic and pathologic conditions, K delivery to the distal nephron remains small and is fairly constant. By contrast, the rate of K secretion by the distal nephron varies and is regulated according to physiologic needs. K secretion in the distal nephron is generally responsible for most of urinary K excretion.

In addition to secretion, the distal nephron is also capable of reabsorbing K. This reabsorption is mediated by an apical H/K ATPase pump located on intercalated cells in the cortical and outer medullary collecting duct. Activity of this pump results in H secretion and K reabsorption. Under normal circumstances, the activity of this pump is low such that net K secretion occurs in the distal nephron. Under conditions of hypokalemia, however, the activity of this pump increases such that net K reabsorption may result in this nephron segment.

CELL MODEL FOR K SECRETION

The cell which is responsible for potassium secretion in the initial collecting duct and the cortical collecting duct is the principal cell. This cell possesses a basolateral Na/K ATPase which is responsible for the active transport of K from the blood into the cell. The resultant high cell K concentration provides a favorable diffusion gradient for movement of K from the cell into the lumen. In addition to establishing a high intracellular K concentration, activity of this pump lowers intracellular Na concentration, thus maintaining a favorable diffusion gradient for movement of Na from the lumen into the cell. The movement of both Na and K across the apical membrane occurs via well defined sodium and potassium channels.

The cellular determinants of K secretion include the cell K concentration, luminal K concentration, potential (voltage) difference across the luminal membrane, and permeability of the luminal membrane for K. Any condition which increases cellular K concentration, decreases luminal K concentration, or renders the lumen more electronegative will increase the rate of K secretion. In addition, any condition which increases the permeability of the luminal membrane for K will increase the rate of K secretion. All of the physiologic deter-

minants of renal K secretion are found to affect one or more of the above cellular determinants of collecting tubule K secretion. Two of the most important physiologic determinants are mineralocorticoid activity and distal delivery of Na and water.

PHYSIOLOGIC DETERMINANTS OF K SECRETION

The major mineralocorticoid in humans is aldosterone. Aldosterone stimulates potassium secretion by effecting several of the cellular determinants discussed above. First, aldosterone stimulates Na reabsorption across the luminal membrane which increases the electronegativity of the lumen, thereby increasing the electrical gradient favoring K secretion. Second, aldosterone increases intracellular K concentration by stimulating the activity of the Na/K ATPase in the basolateral membrane. Third, aldosterone directly increases the permeability of the luminal membrane to K. Thus, aldosterone increases the rate of K secretion by increasing cell K concentration, increasing luminal membrane K permeability, and making the luminal potential more negative.

A second important factor which affects K secretion is the rate of distal delivery of Na and water. Increased distal delivery of Na stimulates distal Na absorption which will make the luminal potential more negative and thus increase K secretion. Increased flow rates also increase K secretion. When K is secreted in the collecting duct the luminal K concentration rises, which decreases the diffusion gradient and slows further K secretion. At higher luminal flow rates, the same amount of K secretion will be diluted by the larger volume such that the rise in luminal K concentration will be less. Thus, increases in the distal delivery of Na and water stimulate K secretion by lowering luminal K concentration and making the luminal potential more negative.

While increased distal delivery of Na and water and increased aldosterone activity can each stimulate renal potassium secretion, under normal physiologic conditions these two determinants are inversely related (Fig. 1). It is for this reason that K excretion is independent of volume status. For example, under conditions of a contracted extracellular fluid volume aldosterone levels increase. At the same time, proximal salt and water absorption increases, resulting in decreased distal delivery of Na and water. Renal potassium excretion remains fairly constant under these conditions since the stimulatory effect of increased aldosterone is counterbalanced by the decreased delivery of filtrate to the distal nephron. A similar situation occurs in the setting of expansion of the extracellular fluid volume. In this setting, distal delivery of filtrate is increased as a result of decreased proximal tubular fluid reabsorption. Under conditions of volume expansion circulating aldosterone levels are decreased. The effect of

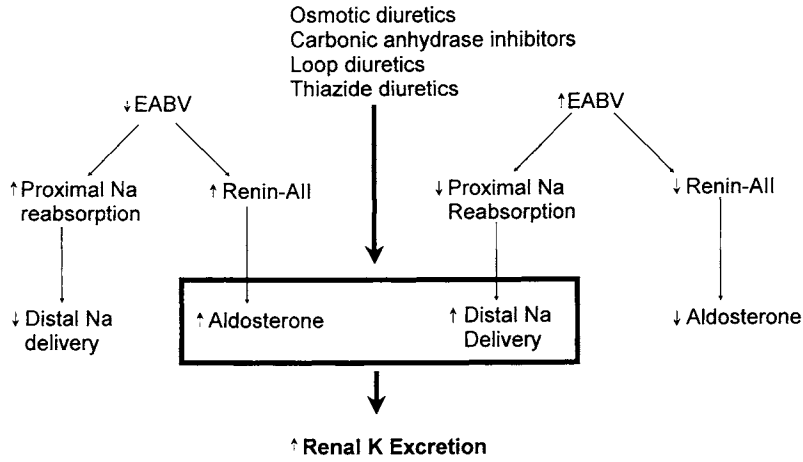

FIGURE 1. Under normal circumstances increases or decreases in the effective arterial blood volume (EABV) result in reciprocal changes in distal Na delivery and circulating aldosterone levels such that renal K excretion is independent of volume changes. Administration of diuretics causes aldosterone and distal Na delivery to both increase such that renal K excretion is enhanced and hypokalemia ensues.

the increased delivery of Na and water to stimulate potassium excretion is opposed by decreased circulating aldosterone levels such that renal potassium excretion again remains constant. Thus, there is a balanced reciprocal relationship between urinary flow rates and circulating aldosterone levels which serves to maintain potassium balance during normal volume regulation. As discussed below, diuretic-induced hypokalemia is largely the result of disturbances in this relationship.

DIURETIC-INDUCED HYPOKALEMIA

DIRECT TUBULAR EFFECTS OF DIURETICS

Diuretics which are associated with the development of hypokalemia exert effects on K transport mechanisms which are located at the drug's tubular site of action. Overall, these effects tend to be of lesser importance in the generation of hypokalemia as compared to secondary changes which are discussed below.

Osmotic Diuretics

Osmotic diuretics are filtered by the glomerulus and then undergo little to no reabsorption by the tubules. These agents disrupt the osmotic gradient which

favors fluid reabsorption in the proximal tubule and as a result inhibit fluid reabsorption in this segment. Decreased fluid transport leads to a fall in the luminal Na concentration and creates an unfavorable diffusion gradient for Na reabsorption. As a result, there is a sharp increase in delivery of Na and water to downstream nephron segments. Since filtered K is isotonically reabsorbed in the proximal nephron in rough proportion to bulk fluid transport, inhibition of fluid transport results in a proportionately similar reduction in K reabsorption. As a result, there is increased delivery of K to the distal nephron. The osmotic agents also disrupt the countercurrent exchange and urinary concentrating mechanism. As a consequence, these agents may also interfere with the medullary recycling of potassium.

Carbonic Anhydrase Inhibitors

These diuretics act primarily within the proximal tubule where they inhibit luminal carbonic anhydrase. Given the central role that this enzyme plays in proximal $NaHCO_3$ reabsorption, these drugs inhibit Na and fluid reabsorption and markedly diminish acidification in the proximal tubule. Accompanying the decreased proximal fluid reabsorption is a proportional fall in the reabsorption of filtered K. The net effect is increased distal delivery of $NaHCO_3$, fluid, and K. There is also evidence that these agents may have a direct effect of increasing K secretion in the distal tubule. This later effect may be due to drug-induced alkalinization of the K-secreting cells.

Loop Diuretics

The loop diuretics act within the lumen of the thick ascending limb of Henle where they inhibit the electroneutral Na/K/2Cl cotransporter. As a result of this inhibition, there is increased delivery of NaCl and K to the distal nephron.

Thiazide Diuretics

The primary site of action of the thiazide diuretics is in the distal convoluted tubule. These drugs inhibit an electroneutral NaCl cotransporter located on the luminal surface. There is no direct effect of the thiazides on K transport in this segment. Rather, these agents are associated with increased renal K excretion through their effects to increase distal Na delivery in the setting of increased mineralocorticoid activity. Thiazide diuretics also possess the ability to inhibit carbonic anhydrase particularly when administered in high doses. As a result, they may inhibit proximal K reabsorption in the same manner as more potent carbonic anhydrase inhibitors such as acetazolamide. Clinically, however, this proximal effect is of little significance.

Secondary Effects of Diuretics

While direct effects of diuretics on K transport mechanisms contribute to the development of hypokalemia, it is secondary effects induced by these drugs which account for the bulk of increased renal K excretion. The ability of these drugs to transform the normally inverse relationship between distal salt and water delivery and mineralocorticoid activity to one in which these parameters move in a parallel fashion is what underlies the kaliuretic effect (Fig. 1).

Diuretics are potent stimulants of the renin–angiotensin–aldosterone cascade. The principal stimulant for renin release is diuretic-induced contraction of the extracellular fluid volume. In addition to causing decreased circulatory volume, loop diuretics have an additional stimulatory effect on renin release through their ability to inhibit the Na/K/2Cl cotransporter at the level of the macula densa. In this segment, there is an inverse relationship between Cl reabsorption and renin release. By inhibiting Cl transport, loop diuretics enhance renin release.

Once released, renin stimulates the formation of angiotensin II which, in turn, stimulates the release of aldosterone from the adrenal gland. In the absence of diuretics, increased circulating levels of aldosterone induced by a contracted effective circulatory volume are not associated with a marked increase in renal potassium excretion. The kaliuretic effect is blunted because there is a simultaneous reduction in distal Na and fluid delivery as a result of enhanced reabsorption at nephron sites proximal to where aldosterone exerts its principal physiologic effect. In the setting of osmotic agents, carbonic anhydrase inhibitors and loop and thiazide diuretics, distal delivery of salt and water to aldosterone responsive cells in the distal nephron is increased such that the kaliuretic effect of aldosterone is fully expressed. It is increased distal K secretion rather than decreased proximal K reabsorption which accounts for the development of hypokalemia following the use of these diuretics.

Characteristics of Diuretic-Induced Hypokalemia

The degree of hypokalemia associated with use of diuretics varies according to the agent used. In hypertensive patients taking thiazide diuretics, the serum potassium concentration falls on average by 0.5 mEq/liter. This decline can be as high as 0.9 mEq/liter with use of the long acting thiazide, chlorthalidone. While loop diuretics are more potent natriuretic agents, they typically result in a milder degree of hypokalemia as the average decline in the serum potassium concentration is 0.3 mEq/liter. This lesser effect may be related to the much

shorter half-life of loop diuretics as compared to the thiazide diuretics. Although not proven, this smaller decline may also be related to the ability of loop diuretics to inhibit calcium absorption in the loop of Henle. The ensuing increase in calcium delivery to the lumen of the distal nephron may inhibit Na reabsorption and therefore diminish distal potassium secretion.

The degree of diuretic-induced hypokalemia is also influenced by the amount of dietary sodium intake. The administration of a diuretic in conjunction with the ingestion of a large amount of dietary sodium (180–200 mEq/liter) renders a patient particularly vulnerable to the development of hypokalemia. This particular combination would allow for maximal sodium and fluid delivery to the distal nephron at the very time aldosterone secretion is stimulated by the initial diuretic-induced sodium depletion. On the other hand, extreme dietary Na restriction also tends to worsen the degree of hypokalemia associated with the use of diuretics. The basis for this effect is the curvilinear relationship between dietary Na intake and serum renin and aldosterone levels. This relationship is gradual at Na intakes of 80 mEq/liter and higher. With sodium intakes of 50 mEq/liter and less, however, a steep rise in renin and aldosterone levels results. At these levels, the kaliuretic effect of aldosterone is the predominate factor in promoting renal potassium excretion. Sodium intake between these extremes (70–100 mEq/liter) causes only a slight rise in aldosterone levels which when coupled to less delivery of sodium to the distal nephron results in an overall decrease in renal potassium excretion. Thus, moderate dietary sodium intake in hypertensive patients treated with diuretics will not only provide the maximal antihypertensive effect but may also limit the degree of potassium depletion.

The decline in the serum potassium concentration usually develops within the first 2 weeks of therapy and then stabilizes as a new steady state is achieved. Thereafter, the serum potassium concentration should remain stable. Further declines in the serum potassium concentration are prevented by several factors which serve to decrease renal potassium secretion. Increased reabsorption of sodium in the proximal nephron as a result of the diuretic-induced decreases in extracellular fluid volume serves to dampen sodium and fluid delivery to the distal nephron. In addition, a progressive increase in mineralocorticoid activity is prevented as the development of hypokalemia tends to inhibit release of aldosterone from the adrenal gland. Chronic hypokalemia is also associated with a direct cellular effect leading to decreased distal nephron K excretion. Finally, K reabsorption is stimulated in the collecting duct under conditions of chronic hypokalemia as a result of increased activity of the H/K ATPase pump. The development of more severe hypokalemia in the setting of chronic diuretic administration suggests some other perturbation in potassium balance such as an intercurrent illness leading to extrarenal potassium loss (diarrhea), a decrease in potassium intake (vomiting), or a change in diuretic dose.

Although diuretics act to increase renal potassium excretion, isotopic measurements suggest that the fall in the serum potassium concentration is greater than the decrease in total body K content. Long-term therapy of hypertensive patients with thiazide or loop diuretics is associated with an average fall in the serum potassium of 15%. Measurement of total body K content has been shown to decrease on average by less than 5% and in some studies not at all. These observations suggest that a major component of diuretic-induced hypokalemia is mediated by a transcellular shift from the extracellular to the intracellular compartment. Factors which are associated with the use of diuretics and which may mediate this transcellular shift include increased circulating levels of catecholamines and aldosterone as well as the development of metabolic alkalosis.

Consequences of Diuretic-Induced Hypokalemia

The most serious potential complication of diuretic-induced hypokalemia is the development of arrhythmias. This complication is particularly true for patients taking cardiac glycosides as the presence of hypokalemia can precipitate digitalis toxicity. A controversial issue has centered around whether diuretic-induced hypokalemia can give rise to fatal arrhythmias. In several large trials involving therapy of patients with mild hypertension, higher rates of cardiac mortality primarily manifesting as sudden death were noted among patients treated with high dose diuretics who had baseline abnormal electrocardiograms. Diuretic-induced potassium or magnesium depletion leading to cardiac arrhythmias has been suggested as the mechanism underlying an increased risk for sudden death. In support, ventricular ectopic activity has been shown to increase over baseline in asymptomatic hypertensives who developed hypokalemia after the administration of diuretics. Furthermore two recent case–control studies found that use of non-potassium-sparing diuretics were associated with an increased risk for sudden death. By contrast, recent studies examining the treatment of hypertension in the elderly failed to demonstrate an increased risk for sudden death in patients despite the use of thiazide diuretic based regimens. In these studies, however, lower doses of thiazides and in some cases a potassium sparing agent were used such that the tendency for development of hypokalemia was minimized. In summary, while a causal relationship has yet to be proven between diuretic-induced hypokalemia and the development of sudden death, the bulk of data strongly suggest the need for caution. Significant falls in the serum potassium concentration should be prevented and when present potassium replacement should be initiated.

Hypokalemia has two other effects that are potentially deleterious to the car-

diovascular system. First, hypokalemia can raise blood pressure by a mean value of 5–7 mm Hg. This hypertensive response is reversible when oral potassium supplements are given to correct the diuretic-induced hypokalemia in patients on a constant diuretic dose. Second, hypokalemia has been linked to an increased incidence of strokes independent of other cardiovascular risk factors. Other complication of hypokalemia include the development of insulin resistance and hypercholesterolemia.

Prevention and Treatment of Diuretic-Induced Hypokalemia

The first approach to preventing diuretic-induced hypokalemia is to use the lowest dose possible (Table 1). With regard to thiazide diuretics, the majority of the blood pressure lowering effect is seen at doses of 12.5–25 mg/day. At higher doses, further blood pressure lowering is minimal, but rather, metabolic side-effects such as hypokalemia, hyperglycemia, and hypercholesterolemia become more prevalent.

Dietary manipulations can also be utilized in the prevention and treatment of diuretic-induced hypokalemia. As discussed earlier, overly strict dietary Na restriction as well as excess Na intake will tend to exacerbate renal K wasting. As a result, dietary Na should only be moderately restricted. If hypokalemia does develop, the patient can be initially tried on a diet of potassium rich foods. While mild potassium deficits may correct with dietary manipulation, this approach is not generally effective for patients with more severe hypokalemia. In this setting, food intake in amounts that would replenish a large potassium deficit would be complicated by excess caloric intake, potentially resulting in unwanted weight gain.

A more feasible approach to the hypokalemic patient is to administer potassium chloride supplements at doses of 20 to 40 mEq/day. Therapy is particu-

TABLE 1 Treatment and Prevention of Diuretic-Induced Hypokalemia

Use low doses of the diuretic
Moderate Na restriction (70–100 mEq/24 hr)
Correct magnesium deficit if present
Oral K supplements (20–40 mEq/24 hr)
Combined therapy with an angiotensin-converting enzyme inhibitor
Combined therapy with an angiotensin II receptor antagonist
Combined therapy with a potassium-sparing diuretic

larly indicated for patients taking cardiac glycosides and patients with underlying cardiac disease. In these high risk patients even mild hypokalemia should be treated as more severe reductions in the serum K concentration can rapidly develop under conditions of increased stress. In this setting, stress-induced increases in catecholamines can result in a shift of K into the intracellular compartment, predisposing such a patient to complex ventricular arrhythmias. In patients who appear resistant to oral supplements, magnesium levels should be checked. Chronic use of both thiazide and loop diuretics can lead to magnesium deficiency which, in turn, can result in renal K wasting. In the setting of magnesium deficiency renal K wasting will continue unabated until the magnesium deficit is first corrected.

An alternative approach is to coadminister an agent which will counteract diuretic-induced renal potassium wasting. One such class of drugs are the angiotensin-converting enzyme inhibitors. These drugs limit the development of hypokalemia when given with diuretics and provide the advantage of further lowering the blood pressure. These agents block the conversion of angiotensin I to angiotensin II and thereby decrease circulating levels of aldosterone normally provoked by diuretic-induced renin release. The angiotensin II receptor antagonists will similarly decrease aldosterone levels and minimize diuretic-induced hypokalemia but do so by acting one step further down the renin–angiotensin–aldosterone cascade.

Potassium-sparing diuretics can also be utilized to counteract the effects of diuretic-induced hyperaldosteronism. Spironolactone is the most direct acting of these in that it blocks aldosterone binding to its cytoplasmic receptor. Triamterene and amiloride indirectly inhibit the kaliuretic effect of aldosterone. As discussed below these agents decrease the luminal electronegativity in the aldosterone sensitive distal nephron, thereby creating a less favorable electrochemical gradient for potassium secretion. The potassium sparing diuretics also diminish net acid excretion which has the effect of minimizing the development of metabolic alkalosis characteristically associated with use of loop and thiazide diuretics. By limiting the development of an alkaline pH renal K losses will be further minimized since metabolic alkalosis increases distal K secretion. Another advantage of these agents is that they decrease magnesium excretion, allowing for the correction of any magnesium deficit that might underlie loop or thiazide diuretic-induced hypokalemia. All of these agents can be given alone or in fixed-dose combinations with the thiazide diuretics. The most important complication associated with use of these agents is the development of fatal hyperkalemia. As a result, patients should be evaluated carefully for any factors which might predispose to the development of hyperkalemia. Furthermore the serum K concentration should be followed closely during the initiation of therapy and whenever the clinical condition of the patient changes.

DIURETIC-INDUCED HYPERKALEMIA

Diuretics which are associated with the development of hyperkalemia are commonly referred to as potassium sparing diuretics. This class consists of those drugs that directly antagonize the activity of aldosterone (spironolactone) and agents which block the Na channel in the distal nephron (amiloride and triamterene). Both classes of agents have the ability to increase Na excretion while at the same time limit the renal excretion of potassium.

Spironolactone blocks the binding of aldosterone to its cytoplasmic receptor in cells primarily located in the cortical collecting duct. As a result, the mechanisms by which aldosterone normally enhances renal K excretion are inhibited. Spironolactone has also been shown to inhibit aldosterone biosynthesis but only at concentrations far greater than those required to inhibit receptor binding in the kidney. Whether this decrease in biosynthesis importantly limits the rise in aldosterone levels that would otherwise occur in response to spironolactone-mediated increases in the serum potassium concentration is not known.

Amiloride and triamterene act to inhibit Na transport in principal cells of the initial collecting duct and the cortical collecting duct. In these segments, Na enters the luminal surface of the cell across a Na channel. The ability of amiloride to block this channel accounts for the drug's natriuretic effect. Although less well studied, triamterene is also thought to block Na reabsorption across this same Na channel. By inhibiting luminal Na entry into the cell, amiloride and triamterene limit potassium secretion by two potential mechanisms. First, blocking the apical Na channel prevents the development of a lumen negative potential which normally provides a favorable driving force for potassium secretion. Second, decreased intracellular Na concentration leads to decreased activity of the basolateral Na/K ATPase. Since the activity of this pump is responsible for maintenance of a high intracellular K concentration, decreased activity of the pump will lead to a less favorable diffusion gradient for potassium across the apical membrane.

Thus, all three of the potassium-sparing diuretics qualitatively produce similar effects on the composition of the urine. The effects of spironolactone and the sodium channel blockers are additive since they act by distinct mechanisms. It should be noted that all three of these agents are weakly natriuretic because the bulk of filtered Na is reabsorbed in more upstream nephron segments. The development of hyperkalemia is a potentially lethal complication of these drugs. This risk is dose dependent and increases in patients with renal failure or those taking potassium supplements. Special caution should be used when these drugs are coadministered with other agents that interfere with the

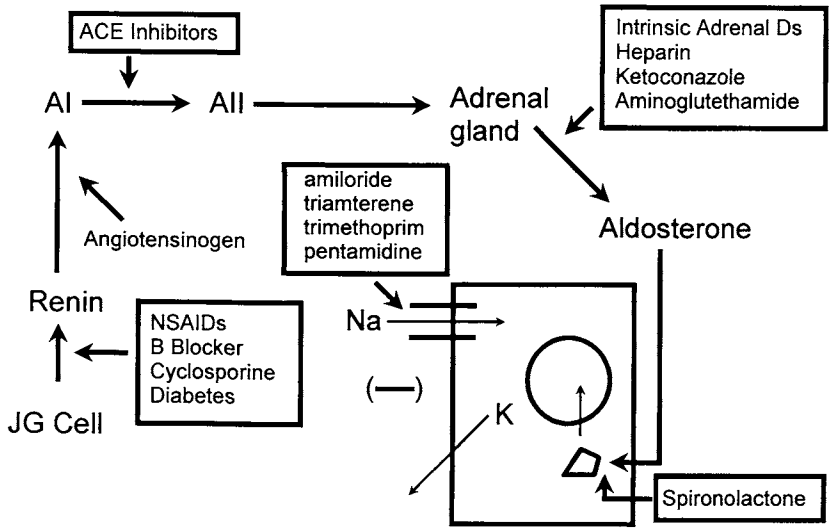

FIGURE 2. An important mechanism by which aldosterone enhances renal potassium excretion is by stimulating Na reabsorption in the cortical collecting tubule. The resultant lumen negative potential contributes to a favorable electrochemical gradient for potassium secretion into the lumen. The use of potassium-sparing diuretics in combination with other pharmacologic agents or in disease states which are associated with decreased activity of the renin–angiotensin II–aldosterone axis can potentially result in hyperkalemia.

renin–angiotensin–aldosterone cascade (Fig. 2). Such combinations can impair renal K excretion in an additive fashion.

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CHAPTER VIC

Acid–Base Disturbances Associated with the Use of Diuretics

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INTRODUCTION

One of the metabolic complications associated with the use of diuretics is disturbances in acid–base balance. Loop and thiazide diuretics are associated with the development of metabolic alkalosis. Given the widespread use of these particular agents, it is of no surprise that diuretic therapy is the most common cause of metabolic alkalosis encountered in clinical medicine. The carbonic anhydrase inhibitors and the potassium sparing diuretics are both associated with the development of metabolic acidosis. The mechanism by which acidosis develops, however, differs between these two classes of drugs. In order to appreciate the means by which acid–base disturbances occur in association with diuretic therapy a brief overview of the renal regulation of acid–base balance will be provided.

RENAL REGULATION OF ACID–BASE BALANCE

The kidneys' role in acid–base balance is to maintain the serum bicarbonate concentration within the normal range. Two basic steps are involved in accomplishing this function: (i) reclamation of filtered bicarbonate and (ii) regenera-

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tion of bicarbonate which has been consumed as a result of buffering of metabolic acids. Both of these processes are dependent upon hydrogen ion secretion.

The process of bicarbonate reclamation occurs in the proximal tubule. This segment of the nephron has a high capacity for bicarbonate reabsorption and normally reabsorbs 80–90% of the 4500 mEq/liter of bicarbonate filtered daily. The majority of bicarbonate reabsorption in this segment is mediated by proton secretion on the apical membrane sodium/hydrogen antiporter. A smaller component of hydrogen ion secretion occurs via a sodium independent hydrogen ion translocating ATPase also located on the apical membrane. Once secreted, protons combine with bicarbonate to form carbonic acid. Carbonic acid is then acted upon by the enzyme carbonic anhydrase to form H_2O and CO_2. This enzyme is located within the lumen of the tubule on the brush border membrane. CO_2 diffuses into the cell where it reacts with hydroxyl ions to form bicarbonate. This reaction is catalyzed by intracellular carbonic anhydrase. Most of the bicarbonate exits the basolateral membrane into the blood by way of a $Na(HCO_3)_3$ cotransporter.

In contrast to the high capacity of the proximal tubule, the distal nephron has a much more limited ability to secrete hydrogen ions and reabsorb bicarbonate. Under conditions in which proximal reabsorption is inhibited, increased bicarbonate delivery to the distal nephron quickly overwhelms the capacity of this segment such that significant bicarbonaturia results. Normally, however, very little bicarbonate is delivered to this segment such that a relatively large transepithelial pH gradient can be generated. The large pH gradient ensures the generation of titratable acid and the entrapment of NH_4. The excretion of titratable acid in association with H^+ secretion generates one new bicarbonate for each H^+ secreted. Similarly one new bicarbonate ion is formed when ammonium salts are excreted. The utilization of nonbicarbonate buffers (ammonia and to a lesser extent phosphate) in the distal nephron allows for proton secretion to acidify the urine and to regenerate bicarbonate which has been lost as a result of extracellular buffering.

Acidification in the distal nephron is mediated by a hydrogen ion translocating ATPase located on the luminal membrane of intercalated cells. The bicarbonate generated intracellulary exits the basolateral membrane by way of a Cl/HCO_3 exchanger. This pump does not transport Na and therefore differs from acidification in the proximal nephron where the bulk of hydrogen ion secretion is mediated by the Na/H antiporter. Distal hydrogen ion secretion is still affected by Na transport but by an indirect mechanism. In the distal tubule, Na is reabsorbed through a Na channel located in the principal cell and accounts for the development of a lumen negative potential in this segment. In turn, this electronegative potential promotes hydrogen ion secretion. Na reabsorption in this segment is stimulated by aldosterone. Increased mineralocorticoid activity will render the lumen more electronegative, thereby enhancing

hydrogen ion secretion. In addition, mineralocorticoids also have a direct stimulatory effect on the hydrogen ion secretory pump.

Luminal buffer availability also plays an important role in net acid excretion in the distal nephron. The principal nonbicarbonate buffers are monohydrogen phosphate and ammonia. Of these, ammonia is quantitatively the most important, accounting for more than half the net acid excretion per day. Almost all of the ammonium excreted in the urine is synthesized in the kidney in the proximal tubule. Ammonia synthesis is stimulated by a low pH and a low serum K concentration while synthesis is inhibited by an alkaline pH and hyperkalemia. Once synthesized, ammonia is secreted into the lumen of the proximal tubule and is reabsorbed extensively in the thick ascending limb of Henle such that only a small fraction reaches the distal tubule. Ammonium absorption in the thick limb is through the pericellular pathway driven by the lumen positive potential in this segment. A trancellular component of absorption is also present and is mediated by the ability of ammonium to substitute for potassium on the Na/K/2Cl cotransporter located on the luminal membrane. Ammonia is then secreted into the lumen of the collecting duct by a combination of active hydrogen ion secretion and passive ammonia movement down a concentration gradient to become trapped in the acidic luminal fluid as ammonium. The availability of ammonia to act as a urinary buffer serves to minimize the drop in luminal pH such that proton secretion can keep pace with daily net acid production. A decrease in buffer availability allows for the luminal pH to fall, thereby creating a steep pH gradient which has the effect of limiting hydrogen ion secretion. Under these conditions, the rate of acidification becomes inadequate to keep up with daily acid production and systemic acidosis results.

DIURETICS ASSOCIATED WITH THE DEVELOPMENT OF METABOLIC ACIDOSIS

ACETAZOLAMIDE

The diuretic which is most commonly associated with the development of metabolic acidosis is acetazolamide. This diuretic acts by inhibiting the enzyme carbonic anhydrase. Given the central role that this enzyme plays in bicarbonate reabsorption in the proximal tubule, administration of this diuretic leads to the development of metabolic acidosis by disrupting the process of bicarbonate reclamation.

The mechanism by which acetazolamide leads to inhibition of bicarbonate reabsorption is directly related to its ability to inhibit luminal carbonic anhydrase. This enzyme normally catalyzes the dehydration of carbonic acid (produced when filtered bicarbonate reacts with secreted hydrogen ions) to water

and CO_2, thereby maintaining a favorable concentration gradient for further hydrogen ion secretion. The uncatalyzed dehydration of carbonic acid occurs very slowly. By inhibiting the activity of this enzyme, acetazolamide allows for the concentration of luminal carbonic acid to increase. The resultant increase in hydrogen ion concentration creates an unfavorable concentration gradient for further hydrogen ion secretion. Due to the lipid solubility of acetazolamide, inhibition of intracellular carbonic anhydrase may also contribute to the impairment in proximal bicarbonate reabsorption. Inhibition of the intracellular enzyme will decrease the supply of hydrogen ions available for the secretory process. In either case, decreased secretion of hydrogen ions will inhibit reabsorption of filtered bicarbonate.

Decreased bicarbonate reabsorption in the early proximal nephron limits the development of a favorable chloride diffusion gradient which, in turn, normally creates a passive diffusion gradient for Na reabsorption in the S2 portion of proximal tubule. As a result, there is increased delivery of bicarbonate as well as NaCl to the distal nephron. Most of the chloride and part of the Na is reabsorbed in the loop of Henle. Since the capacity of the distal nephron to reabsorb bicarbonate is limited, significant bicarbonaturia results. Bicarbonate acts as a nonreabsorbable anion allowing for increased amounts of Na to be delivered to the distal nephron and as a result, potassium secretion is enhanced.

Clinical features associated with the use of acetazolamide are similar to those found in proximal renal tubular acidosis. Patients develop a hyperchloremic metabolic acidosis in association with a bicarbonate diuresis (Fig. 1). Increased renal potassium excretion leads to hypokalemia. The magnitude of the bicarbonaturia is directly related to the serum bicarbonate concentration. As the serum bicarbonate concentration falls, the clinical effectiveness of the drug declines in a parallel fashion. This relationship explains why the acidosis tends to be mild in severity and not progressive despite continued use of the drug.

The development of metabolic acidosis makes acetazolamide particularly useful in the treatment of patients with metabolic alkalosis who require diuretic therapy. In edematous states such as congestive heart failure, cirrhosis, and nephrotic syndrome use of loop diuretics is often complicated by the development of metabolic alkalosis. Normally, the initial approach to correcting alkalosis induced by diuretic therapy is the administration of isotonic saline. In these patient groups, however, saline may be ineffective in correcting the alkalotic state as a result of an inability to correct the hemodynamic factors maintaining the alkalosis. In addition, further volume expansion will increase the severity of edema and possibly precipitate pulmonary edema in those patients with borderline cardiac function. The diuretic and bicarbonaturic effects of acetazolamide make this diuretic particularly attractive in this setting.

Acetazolamide has also been used in the treatment of certain pulmonary disorders. In patients with central sleep apnea, induction of systemic acidosis

with acetazolamide may prove effective in stimulating the respiratory center and reducing the number of apneic episodes. High altitude pulmonary edema can be prevented in susceptible individuals by prophylactic administration of acetazolamide. While the mechanism of this protective effect is multifactorial, the development of metabolic acidosis stimulates the respiratory center and has favorable effects on the oxygen disassociation curve.

The induction of an alkaline urine also has potential beneficial clinical effects. Acetazolamide has been used in the treatment of aspirin toxicity as urinary alkalization increases the urinary excretion of salicylates. Use of this drug for this purpose, however, is not generally recommended because the systemic acidosis that develops tends to enhance the movement of aspirin into cells, potentially increasing toxicity. Although of limited clinical benefit, alkalinization of the urine with acetazolamide will also increase the solubility of uric acid and cystine. Finally, acetazolamide has potent phosphaturic effects and is a useful agent in increasing phosphate excretion in the setting of normal renal function. On the other hand, urinary alkalinization will decrease the solubility of calcium phosphate, increasing the risk for stone formation. In addition, an alkaline urine will tend to decrease urinary ammonium excretion and in patients with advanced liver disease could contribute to the development of hepatic encephalopathy.

Potassium-Sparing Diuretics

The potassium-sparing diuretics can be associated with the development of metabolic acidosis. Unlike the carbonic anhydrase inhibitors which affect the process of bicarbonate reclamation in the proximal nephron, these agents interfere with the ability of the distal nephron to regenerate bicarbonate. The mechanism by which these drugs impair distal hydrogen ion secretion is related to their ability to decrease the luminal electronegativity of the collecting duct and to decrease the availability of buffer (Fig. 1).

The potassium-sparing diuretics decrease the luminal electronegativity of the collecting duct by inhibiting the reabsorption of Na in this segment. The manner in which this is accomplished, however, differs between the various agents. Amiloride and triamterene directly inhibit Na reabsorption by blocking the Na channel located on the luminal membrane. Spironolactone inhibits sodium reabsorption indirectly by blocking the binding of aldosterone to its cytoplasmic receptor, thereby inhibiting aldosterone-induced sodium reabsorption. The decrease in luminal electronegativity impairs distal acidification as a result of the decrease in driving force for hydrogen ion secretion into the tubular lumen. Spironolactone can further limit distal hydrogen ion secretion because this drug not only inhibits aldosterone-stimulated Na reabsorption but

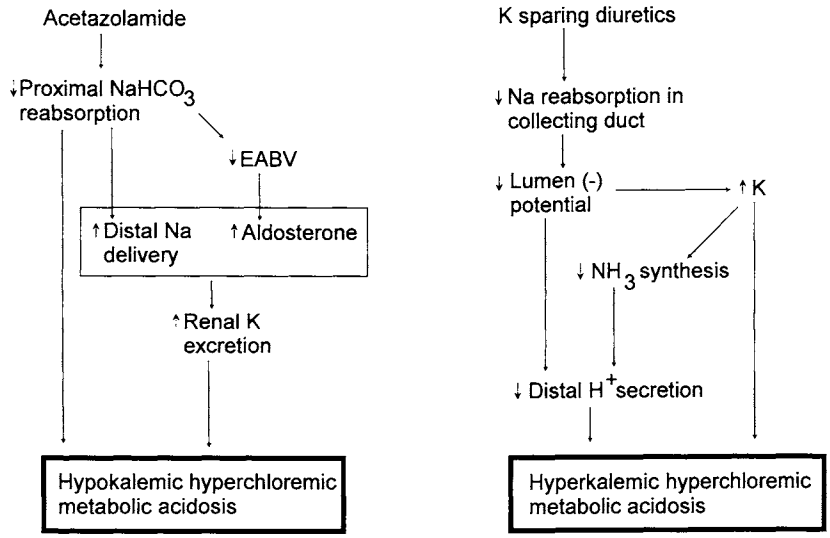

FIGURE 1. The mechanism by which acetazolamide and potassium sparing diuretics give rise to metabolic acidosis.

also blocks the direct stimulatory effect of aldosterone on the hydrogen ion secretory pump.

In addition to impairing hydrogen ion secretion, the decrease in luminal electronegativity also impairs potassium excretion. The development of hyperkalemia, in turn, will further limit distal acidification by decreasing ammonia availability to act as a urinary buffer. Hyperkalemia limits the availability of ammonia in two ways. First, hyperkalemia decreases ammonia production in the proximal tubule. Second, ammonium transport in the thick ascending limb is inhibited because the large increase in medullary K concentration effectively competes with ammonium for both pericellular transport as well as transport on the Na/K/2Cl cotransporter. Net acid excretion decreases as a result of limited buffer availability for titration of secreted hydrogen ions.

The nature of the acidosis which develops in patients taking potassium-sparing diuretics is a hyperchloremic normal gap acidosis. Hyperkalemia is usually present and in this regard serum chemistries mimic a type 4 renal tubular acidosis (RTA). Patients at risk for this complication include those with diseases which are commonly associated with deficiencies in aldosterone. For example, diabetic patients with the syndrome of hyporeninemic hypoaldosteronism are particularly prone to develop a type 4 RTA in which life threatening hyperkalemia can be present. Similarly, patients with chronic renal insufficiency are at high risk for this complication. Discontinuation of the drug should suffice in returning serum chemistry values back to baseline.

DIURETICS ASSOCIATED WITH THE DEVELOPMENT OF METABOLIC ALKALOSIS

Loop Diuretics

The use of loop diuretics is commonly associated with the development of metabolic alkalosis (Fig. 2). Loop diuretics inhibit salt transport in the thick ascending limb of Henle, resulting in a reduction in the extracellular fluid volume. The contraction of extracellular fluid around a fixed concentration of bicarbonate will cause the bicarbonate concentration to rise. This effect has been called a contraction alkalosis. The magnitude by which this mechanism contributes to the alkalosis is small, however, as a result of intracellular buffering. Both release of hydrogen ions by cell buffers and increased uptake of bicarbonate into bone tend to minimize the rise in bicarbonate concentration induced by volume contraction. A much more important mechanism by which loop diuretics induce metabolic alkalosis is related to the ability of these drugs to increase net acid excretion in the distal nephron, thereby increasing the renal input of new bicarbonate. At the same time, these agents lead to alterations in the renal handling of bicarbonate in the proximal nephron such that the rise in serum bicarbonate is sustained. Stated differently, loop diuretics lead to the gen-

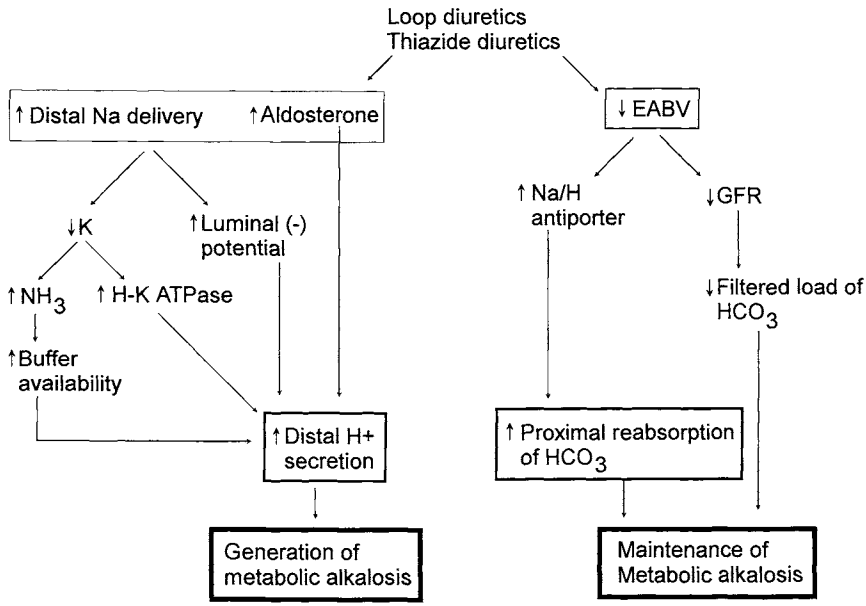

FIGURE 2. The generation and maintenance of metabolic alkalosis induced by loop and thiazide diuretics.

eration of a metabolic alkalosis by increasing acidification in the distal nephron. At the same time, these drugs maintain the alkalosis by enhancing bicarbonate reclamation in the proximal nephron.

The generation of metabolic alkalosis through increased net acid excretion in the distal nephron is the result of indirect effects induced by the loop diuretics. Diuretic-induced volume contraction leads to secondary hyperaldosteronism. At the same time distal delivery of sodium is increased due to the direct effects of the diuretic in the thick limb of Henle. Aldosterone-mediated sodium reabsorption increases the luminal electronegativity of the collecting duct and results in increased hydrogen ion secretion. Hydrogen ion secretion is also directly stimulated by aldosterone. Diuretic-induced hypokalemia also contributes to increased distal hydrogen ion secretion as the activity of the H/K ATPase is increased in the setting of hypokalemia. As net acid excretion increases, newly generated bicarbonate is added to the venous blood.

In addition to increasing hydrogen ion secretion in the collecting duct, loop diuretics have also been shown to increase hydrogen ion secretion in the thick ascending limb of Henle. In this segment, bicarbonate reabsorption is mediated by a Na/H antiporter located on the apical membrane. Loop diuretics secondarily stimulate the activity of the antiporter by inhibiting NaCl entry across the luminal membrane, lowering cell Na, and increasing the transmembrane Na gradient. The quantitative importance of increased HCO_3 reabsorption in this segment to the overall increase in distal hydrogen ion secretion is unknown but may be greater than previously thought.

Secondary effects of the loop diuretics also account for the increased capacity of the proximal tubule to reclaim bicarbonate and thereby maintain the alkalosis. Diuretic-induced reductions in effective arterial blood volume decrease the glomerular filtration rate and lower the filtered load of bicarbonate. A decrease in effective circulatory volume is also associated with increased activity of the Na/H antiporter. Diuretic-induced potassium depletion can also affect the kidney's ability to maintain metabolic alkalosis. Potassium depletion can lead to further decreases in glomerular filtration rate and filtered load of bicarbonate. In addition, potassium depletion has been demonstrated to stimulate rates of proximal and distal tubular hydrogen secretion. Furthermore, hypokalemia stimulates ammonia production, thereby providing for increased buffer capacity for ongoing hydrogen ion secretion distally. While these effects of potassium depletion on acid–base balance would be predicted to both generate and maintain metabolic alkalosis, potassium depletion only mildly increases the plasma bicarbonate concentration in humans. The blunted rise in serum bicarbonate concentration is accounted for by an inhibitory effect of hypokalemia on aldosterone secretion. This effect will inhibit renal acidification. A final factor which serves to maintain diuretic-induced alkalosis is an increase in the pCO_2 concentration. In the setting of metabolic alkalosis, the increase in pH is attenuated by a rise in the pCO_2 which results from compensatory hypoventi-

lation. This hypoventilatory response to metabolic alkalosis is limited by the development of hypoxemia such that the pCO_2 concentration rarely exceeds 50–55 mm Hg.

Metabolic alkalosis is not a typical baseline feature of the clinical conditions in which loop diuretics are most commonly used. Nevertheless, these conditions are commonly associated with the development of metabolic alkalosis once diuretic therapy is initiated. In addition, the alkalosis tends to develop rapidly and can be large in magnitude. For example, cirrhosis, congestive heart failure, and nephrotic syndrome are all characterized by a contracted effective arterial blood volume. In the basal state, circulating aldosterone levels are already increased but distal sodium delivery is low. Initiation of diuretic therapy allows for the increased circulating levels of aldosterone to be coupled to increased distal sodium delivery, resulting in stimulated distal acidification. Newly generated bicarbonate is readily reclaimed in the proximal nephron as these patients already have a contracted effective arterial blood volume.

The rapid development of metabolic alkalosis in the edematous states after initiation of loop diuretic therapy should be contrasted to what happens in an otherwise normal individual given loop diuretics. In a euvolemic salt replete individual the development of metabolic alkalosis tends to be much more gradual in onset and less severe. In this circumstance, baseline aldosterone levels are normal and begin to increase only once the diuretic achieves some degree of volume depletion. It is only at this point that increased distal sodium delivery becomes coupled to increased circulating levels of aldosterone and generation of a metabolic alkalosis is initiated. The ability to maintain the alkalosis is directly related to the degree of volume depletion which is determined by dietary intake of salt, dose of diuretic, and frequency of administration. The ingestion of a large sodium diet serves to minimize any decrease in volume induced by the diuretic, thereby impairing the ability to maintain the alkalosis. By contrast, a diet overly restricted in sodium would exacerbate the contraction in extracellular fluid volume and allow for the alkalosis to be maintained. By similar mechanisms, large doses of loop diuretics given at more frequent intervals would tend to increase those factors involved in both the generation and the maintenance of metabolic alkalosis.

Thiazide Diuretics

The thiazide diuretics can also be complicated by the development of metabolic alkalosis. The mechanisms by which the thiazide diuretics lead to alkalosis are identical to those involved with loop diuretics (Fig. 2). The degree of alkalosis tends to be less severe since the physiologic changes induced by these agents are much less in magnitude than those induced by loop diuretics.

TABLE 1 Therapy of Diuretic-Induced Metabolic Alkalosis

Discontinue diuretic
Correct hypokalemia
Restore extracellular fluid volume with intravenous 0.9% NaCl
In setting of heart failure or volume overload
—Acetazolamide
—NH_4Cl orally or intravenously
—0.1% HCl via central line

TREATMENT

The initial step in treating a patient with diuretic-induced metabolic alkalosis is to discontinue the drug and replenish the potassium deficit if present (Table 1). In those patients in whom the alkalosis is more severe, administration of isotonic saline in order to expand the extracellular fluid volume can be given. Restoration of the extracellular fluid volume is effective therapy in this situation as volume depletion is a major factor in the maintenance of alkalosis induced by diuretics. In patients with decompensated congestive heart failure in whom saline administration may be hazardous, alternative measures may be necessary. Acetazolamide is often useful in this situation as a way to inhibit proximal bicarbonate reabsorption. Rarely, intravenous administration of ammonium chloride may be indicated in volume overloaded patients with renal disease.

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CHAPTER VID

The Effects of Diuretics on Calcium Metabolism: Physiologic and Clinical Effects

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HISTORICAL BACKGROUND

Diuretics are generally used successfully in treatment of most edematous patients. Lamberg and Kuhbäck first observed that the administration of chlorothiazide and hydrochlorothiazide caused a marked fall in urinary excretion of calcium [8]. Subsequent studies have confirmed that other drugs of the benzothiazide (thiazide) group significantly reduce urinary calcium excretion in normal subjects, in patients with idiopathic hypercalciuria, and in patients with hypercalciuria due to primary hyperparathyroidism, multiple myeloma, Paget's disease of bone, and postmenopausal osteoporosis [7].

In the following years, the development of hypercalcemia after short-term and chronic administration of thiazides was observed in normal subjects, in patients with end-stage renal disease, and in patients with parathyroid adenomas. This finding suggested the possibility of the extrarenal effect(s) of thiazides on calcium metabolism. Pickleman *et al.* initially detected the enlargement of parathyroid glands and hypercalcemia in dogs after the long-term administration of hydrochlorothiazides [12].

Several other possible mechanisms of action of thiazide diuretics were proposed: First, the direct effect of thiazides on intestinal absorption of calcium; second, the potentiation of action of parathyroid hormone (PTH) on the skele-

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ton; and third, the direct action of thiazide on bone to enhance skeletal bone resorption and the release of calcium into extracellular fluid [7].

REGULATION OF CALCIUM BALANCE AND RENAL CALCIUM HANDLING

Regulation of Calcium Balance

The total calcium concentration in extracellular fluid (ECF) is maintained within a narrow range of 8.5–10.5 mg/dl in adult humans, mean of 9.5 mg/dl (approximately 2.5 mM, 5 mEq/liter). In plasma, 35–40% of calcium is bound to macromolecular protein, especially albumin. Approximately 60–65% of plasma calcium is filtered at the glomerulus as ultrafilterable calcium [6]. Of the calcium that is ultrafiltered, about 10% is complexed as the calcium salts of bicarbonate, sulfate, and citrate.

Extracellular calcium homeostasis involves coordinated calcium absorption by the intestine, calcium resorption from bone, and calcium reabsorption by the kidney. The PTH-vitamin D axis plays a key role in calcium homeostasis, acting to normalize ECF calcium concentration. In a state of normal calcium balance, net intestinal calcium absorption and renal calcium excretion are approximately equal. The average adult human ingests 800 mg calcium daily. Approximately 600 mg of calcium is excreted in feces, and 200 mg enters the ECF. This extracellular pool equilibrates with bone calcium pools, and, to a lesser extent, with intracellular calcium pools. The final urine contains approximately 200 mg calcium daily (Fig. 1).

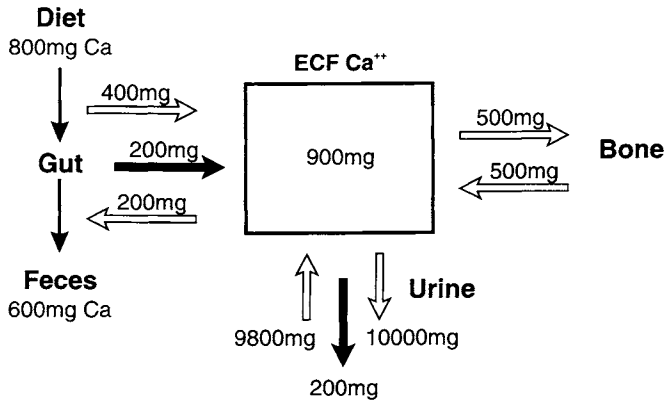

FIGURE 1. Total body calcium balance. Net calcium movement as shown by dark solid arrow.

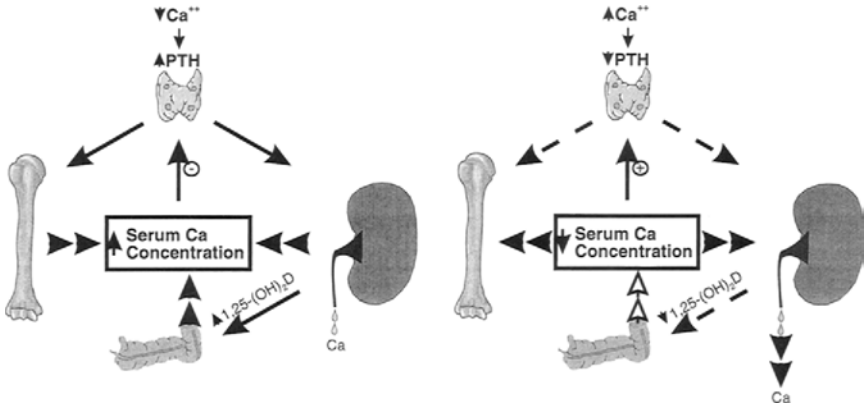

FIGURE 2. Interactions of kidney, intestine, and bone in the regulation of calcium homeostasis.

With a fall in plasma calcium concentration, PTH secretion is stimulated. Parathyroid hormone stimulates renal tubular calcium reabsorption, increases skeletal calcium mobilization, and enhances renal production of 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D]. The increase in serum 1,25-$(OH)_2$D concentrations enhances intestinal calcium absorption and decreases renal calcium excretion. 1,25-$(OH)_2$D also acts directly on bone cells to stimulate skeletal calcium mobilization (Fig. 2). With occurrence of hypercalcemia, PTH secretion is suppressed, and calcitonin release is stimulated. Consequently, renal calcium excretion increases and skeletal calcium mobilization decreases. A decrease in plasma 1,25-$(OH)_2$D concentration, due to the fall in PTH concentration, leads to a decreased absorption of calcium in the intestine and decreased skeletal calcium mobilization (Fig. 2).

Renal Calcium Handling (Fig. 3)

The normal human adult kidneys filter approximately 170 liters of water and 10 g of calcium per day. The final urine contains nearly 1.5 liters of water and 200 mg calcium daily. Thus, 99% of filtered water and 98% of filtered calcium are normally reabsorbed by the renal tubules [16].

Proximal Tubule

Most of the filtered calcium is reabsorbed from the lumen of the proximal tubules and returned to the circulation. Micropuncture studies have shown that approximately 60% of the filtered calcium is absorbed by the end of the acces-

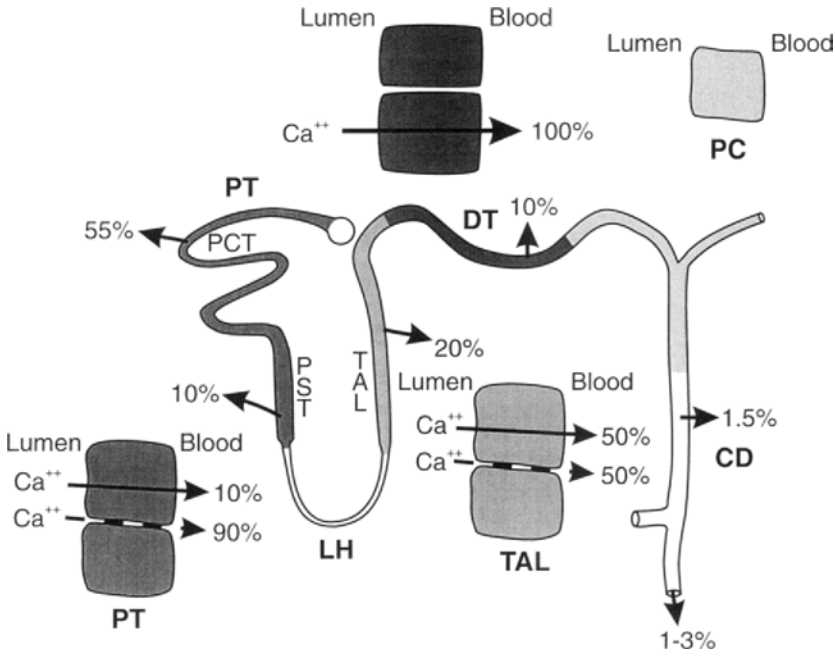

FIGURE 3. Sites and mechanisms of renal tubular calcium reabsorption. The axial location of each cell type is indicated by shading patterns. PT, proximal tubule (PCT, proximal convoluted tubule; PST, proximal straight tubule); LH, loop of Henle (TAL, thick ascending limb); DT, distal tubule (DCT, distal convoluted tubule; PC, principle cell). Active calcium reabsorption is shown by thick solid lines and passive calcium reabsorption by interrupted lines. The relative tubular reabsorption rate of calcium in various nephron segments is indicated by percentage (%).

sible portion of the superficial proximal convoluted tubule (PCT), and an additional 10% is absorbed in proximal straight tubules (PST) [3].

Calcium reabsorption in proximal convoluted tubules is passive and proceeds through a paracellular pathway. The ratio of calcium in tubular fluid to ultrafilterable calcium in plasma rises to a mean value of 1.1 within the first third of the proximal convoluted tubule and is maintained at this level [14]. The proportionality of sodium and water in proximal tubule has suggested that calcium absorption in this segment may be passive and secondary to the absorption of sodium and water. The high permeability of this segment is compatible with passive transport. A small fraction of proximal tubular calcium reabsorption is thought to be transcellular. The straight portion of the proximal tubule appears to transport calcium actively, but little is known about the mechanism and regulation of calcium absorption in this segment.

Thick Ascending Limb of Henle

Approximately 20% of the calcium filtered at the glomerulus is absorbed in Henle's loop [3]. Calcium permeability of both thin descending and ascending limbs is particularly low. Thus, all calcium absorption in Henle's loop is thought to occur in ascending medullary and cortical limbs. In contrast to proximal tubules where calcium absorption is predominantly passive, both passive and active transport mechanisms contribute to renal calcium reabsorption. The rate and the extent of the passive renal calcium reabsorption in thick ascending limbs are determined by the magnitude of electrochemical gradient favoring transport. Passive calcium absorption in thick limbs is abolished by furosemide with an attendant increase of calcium in the urine [16]. In this circumstance, salt reabsorption is virtually abolished with a concomitant reduction in transepithelial voltage.

Distal Convoluted Tubule (DCT)

Calcium transport in distal convoluted tubules and connecting tubules comprise an additional 10% of the filtered calcium. Passive calcium reabsorption is minimal, as a result of the greater transepithelial resistance or the greater selective permeability of tight junctions to calcium [2]. Since luminal calcium concentration is less than plasma ultrafilterable calcium concentration, calcium transport occurs only by an active transcellular flux. PTH stimulates renal calcium reabsorption by the kidney by enhancing the distal renal tubular calcium absorption. PTH stimulates apical calcium entry in distal convoluted tubules. This effect is mediated through the dihydropyridine-sensitive calcium channel. It has been shown that PTH, chlorothiazide, and amiloride hyperpolarize distal tubular membrane voltage by different mechanisms [3]. However, they all activate common calcium entry mechanisms that are inhibited by dihydropyridine-type calcium channel blockers. Chlorothiazide, PTH, and amiloride have been shown to enhance the transport of calcium in this segment.

Collecting Duct (CD)

Collecting ducts are involved in the absorption of the final 1 to 3% of calcium filtered at the glomerulus [3]. Calcium transport in the cortical collecting ducts has been shown to be small and passive. The transport of calcium in this segment is not affected by PTH, thiazide diuretics, or amiloride. Inner medullary collecting ducts participate in the absorption of calcium in the terminal nephron segments.

MECHANISMS OF ACTIONS OF THIAZIDE DIURETICS (FIG. 4)

Effect on Renal Calcium Transport

Under most physiological conditions, renal sodium and calcium reabsorption proceed in parallel [18]. However, under certain physiological, pathophysiological, or pharmacological conditions, the renal absorption of calcium and sodium may be dissociated. It has been shown that this relationship can be dissociated by administration of certain drugs such as thiazide diuretics or amiloride [9]. Thiazide diuretics, either alone or in combination with amiloride, reduced renal calcium excretion, secondary to the enhanced renal tubular calcium reabsorption. This action is attributed to the dual effect of thiazide to inhibit renal tubular sodium reabsorption, while increasing renal tubular calcium reabsorption [4]. The dissociation of calcium and sodium renal transport occurs in distal convoluted tubules.

Thiazide administration can reduce ECF volume by inducing natriuresis. Consequently, glomerular filtration rate and filtered load of calcium fall, fractional proximal-tubular calcium reabsorption increases, and urinary calcium falls. Extracellular fluid volume contraction may contribute to hypocalciuria, as thiazide lowers calcium excretion more promptly if ECF volume is reduced prior to its administration. The chronic effect of thiazide diuretics on urinary calcium excretion involves an enhanced proximal renal tubular reabsorption of calcium. This property is used clinically to lower urinary calcium excretion in patients with hypercalciuric nephrolithiasis.

The cellular mechanisms of action of thiazide diuretics on sodium reabsorption have been attributed to inhibition of luminal NaCl cotransporter [4] or to a parallel Na^+/H^+ and Cl^-/HCO_3^- exchange. In contrast, the mechanisms by which thiazide diuretics stimulate distal tubular calcium reabsorption and the nature of relation between renal tubular NaCl reabsorption and renal tubular calcium reabsorption have yet to be resolved.

Three hypotheses have been proposed to account for thiazide-induced dissociation of sodium and calcium transport in the distal nephron [5]. One view advanced by Walser was that thiazide diuretics reduce the transepithelial voltage (decrease in luminal voltage negativity) and, as a result, decrease the rate of passive calcium backflux into the tubular lumen. However, it has been shown that thiazide diuretics have little, if any, effect on transepithelial potential difference in distal convoluted tubules and also, the passive calcium permeability of this nephron segment is significantly low. An alternative scheme was proposed by Costanzo and Windhager. They suggested that thiazide diuretics, by inhibiting apical membrane sodium entry, would be expected to

reduce intracellular sodium concentration. This decrease of intracellular sodium concentration would in turn increase basolateral sodium entry, thereby augmenting calcium efflux through the basolateral Na^+/Ca^{2+} exchange. The third mechanism has been proposed very recently and involves four different steps: (a) thiazide diuretics block luminal membrane chloride entry by NaCl cotransporter; (b) continued basolateral chloride efflux through chloride channels results in a decrease of intracellular chloride activity; (c) the reduction of intracellular chloride hyperpolarizes the luminal and basolateral membranes; and (d) membrane hyperpolarization increases calcium entry via luminal membranes through dihydropyridine-sensitive calcium channels.

Effect on Intestinal Calcium Absorption

The effect of thiazide diuretics on intestinal calcium absorption is not clear. Thiazide has been associated with no change, a fall, or a rise in intestinal calcium absorption in patients with idiopathic hypercalciuria. However, it has been shown that the effect of thiazide on intestinal calcium absorption was selective in hypercalciuric patients with calcium nephrolithiasis [20]. In renal leak hypercalciuria (RH), thiazide typically reduces the fractional calcium reabsorption, commensurate with the "correction" of renal calcium leak and secondary hyperparathyroidism. It is recognized that PTH may play an important role in the regulation of synthesis of $1,25\text{-}(OH)_2D$, a metabolite with potent action on intestinal calcium transport. Therefore, the reduction in intestinal calcium absorption during thiazide therapy in renal leak hypercalciuric patients may then be explained by the reduced synthesis of $1,25\text{-}(OH)_2D$ metabolite consequent to restoration of normal parathyroid function.

In contrast, thiazide diuretics have been shown not to alter the intestinal hyperabsorption of calcium in absorptive hypercalciuric (AH) patients with calcium nephrolithiasis, even though it causes a fall in total renal calcium excretion. This result supports the primacy of intestinal hyperabsorption (vitamin D-independent) of calcium in AH patients. Therefore, varying effects of thiazide on intestinal calcium absorption in patients with idiopathic hypercalciuria may be due to lack of segregation of subjects into the specific subgroups.

The direct effect of thiazide on intestinal calcium absorption has been demonstrated only by some animal studies with chlorthalidone.

Effect on Bone

The direct effect of thiazide on bone metabolism has not been studied extensively. However, in two studies, one conducted in uremic patients undergoing

hemodialysis, and the other in the normal thyroparathyroidectomized dogs, thiazide administration has resulted in hypercalcemia and increased osteocystic bone resorption, respectively [7]. In the former condition, potentiation of the skeletal effect of PTH has been suggested. However, in the latter situation due to the absence of parathyroid glands, the role of PTH on skeletal bone resorption was totally excluded. Therefore, in the latter condition, the thiazide effect was attributed to a direct role in increasing bone resorption, as documented by the presence of increased numbers of osteocystic lacunae in the bone biopsy specimens.

It has been suggested that the thiazide effect on bone is exerted via acid–base changes. It has been shown that calcium balance is inversely proportional to acid balance. In a metabolic balance study, oral hydrochlorothiazide (25 mg) twice daily in healthy normal subjects caused the usual rise in blood pH and bicarbonate levels. Consequently, metabolic alkalosis induced by thiazide lowered both urinary calcium excretion and fecal calcium loss. Positive calcium balance created by the aforementioned changes then caused a significant fall in urinary hydroxyproline excretion, indicative of decreased bone resorption.

Clinical Implications of Thiazide Diuretics

Renal Stones

Thiazide diuretics have been widely used for the medical management of hypercalciuric calcium nephrolithiasis [19]. The main rationale for this treatment is the ability of thiazide to reduce calcium excretion and thereby lower the urinary saturation of stone-forming calcium salts (calcium oxalate and calcium phosphate). Thiazides also increase excretion of inhibitors of the crystallization of calcium salts (such as pyrophosphate, magnesium, and zinc). In several clinical trials, thiazides have been shown to be effective in preventing new stone formation.

Even in these favorable reports, some patients continue to form stones. This poor clinical response may be ascribed to the failure of thiazide to induce the aforementioned appropriate biochemical changes in urine under certain circumstances. Chronic thiazide use lowers urinary citrate excretion. Dietary factors, including high dietary salt and protein intake, by increasing urinary calcium and lowering urinary citrate excretion, respectively, may influence the response to thiazide.

One of the potential causes for the inadequate clinical response is thiazide-induced hypocitraturia (10). Thiazides have been shown to reduce citrate excretion, probably by causing hypokalemia and intracellular acidosis. The reduced citrate excretion produced by thiazides may therefore present a risk for

calcium stone formation, and may attenuate the beneficial effects of the decline in urinary calcium excretion.

Recently it was shown that potassium supplementation in patients taking thiazide with potassium citrate not only prevents the development of hypokalemia, but also increases urinary citrate levels. Clinically, the addition of potassium citrate to ongoing thiazide therapy caused a remission of stone disease in 77% and reduced stone formation in 100% of the patients. The favorable response to combined thiazide and potassium citrate therapy, compared with that of thiazide alone or thiazide with potassium chloride, suggests that potassium citrate was largely responsible for the clinical improvement. In patients who continued to form kidney stones during long-term thiazide treatment with sufficient potassium chloride supplementation to prevent hypokalemia, only a slight rise in urinary citrate excretion was seen. Even so, the citrate value remained low relative to normal levels. The recognition that potassium citrate could stimulate renal citrate excretion led to the substitution of this drug for potassium chloride or an addition of potassium citrate to thiazide therapy in patients with calcium nephrolithiasis.

Thiazide treatment may have a limited long-term effectiveness in patients with absorptive hypercalciuria. Despite an initial reduction in calcium excretion, with continued treatment the hypocalciuric effect becomes attenuated. It has been shown that the retained calcium may initially be accreted in bone at least during the first few years of therapy. Consequently, the radial bone density in the distal third of radius bone increases significantly in the early years of treatment. However, the rise in bone density stabilizes when the hypocalciuric thiazide effect is attenuated. The results suggested that thiazide treatment has caused a low turnover state of bone, which interferes with continued calcium accretion in the skeleton. The "rejected" calcium would then be excreted in the urine.

Thiazides may also be useful in controlling hypercalciuria in other circumstances, such as during the treatment of vitamin D-resistant rickets and in steroid-induced osteoporosis.

Osteoporosis

There is some evidence that thiazide may be clinically useful in prevention of bone loss [13]. Thus, increased appendicular bone mass and reduced hip fracture rate have been reported in patients treated with thiazide compared with untreated counterparts.

These effects have been ascribed to its hypocalciuric action [13], which causes calcium retention and reduces the turnover of bone. However, in many postmenopausal women and elderly subjects, urinary calcium excretion may be low due to impaired intestinal calcium absorption [13]. They may therefore

show an attenuated response to thiazide since the absolute decrement in urinary calcium is expected to be low. In addition, administration of thiazide, by lowering urinary calcium excretion and consequently a fall in PTH secretion, has been shown to lower serum 1,25-$(OH)_2D$ and net intestinal calcium absorption. However, the latter response has been shown to be attenuated if exogenous calcitriol is coadministered with thiazide to these patients [13].

Hypoparathyroidism

Thiazide may be a useful adjunct in treatment of hypocalcemia due to hypoparathyroidism [16]. Chlorthalidone administered to hypoparathyroid patients not receiving vitamin D was found to raise the total and ionized serum calcium into the normal range and sustain it for many months, while only supplemented with oral calcium. The rise in serum total calcium concentration during thiazide treatment was shown in patients with hypoparathyroidism, in normal subjects, and in hyperparathyroid patients. Extracellular volume contraction and consequent rise in serum protein concentration may partly account for some of the rise in the total serum calcium concentration. In normal subjects, the rise of serum calcium is offset by the patient's reduced PTH secretion. However, in subjects with autonomous parathyroid function or with hypoparathyroidism whose serum calcium is maintained with vitamin D, this compensatory mechanism is not available and hypercalcemia may occur.

Thiazide diuretics are administered to hypoparathyroid patients with vitamin D and calcium supplement to lower urinary calcium excretion and to avert complication of renal stone formation. Moreover, calcium retention created by thiazide diuretics will allow use of a smaller dose of vitamin D and calcium to maintain normal serum calcium concentrations in hypoparathyroid patients.

MECHANISM OF ACTION OF AMILORIDE

Effect on Renal Calcium Transport (Fig. 4)

Amiloride inhibits sodium transport in the late distal tubules, likely connecting tubules, and other epithelial cells by blocking sodium channels [4]. Recently, it has been shown that amiloride inhibits sodium entry into the cells and hyperpolarizes the luminal and basolateral membranes. The latter effect, in turn, stimulates calcium influx into the cells and produces a sustained rise of intracellular calcium concentration. Calcium influx and rise of intracellular calcium concentration is inhibited with calcium channel blockers (dihydropyridine type).

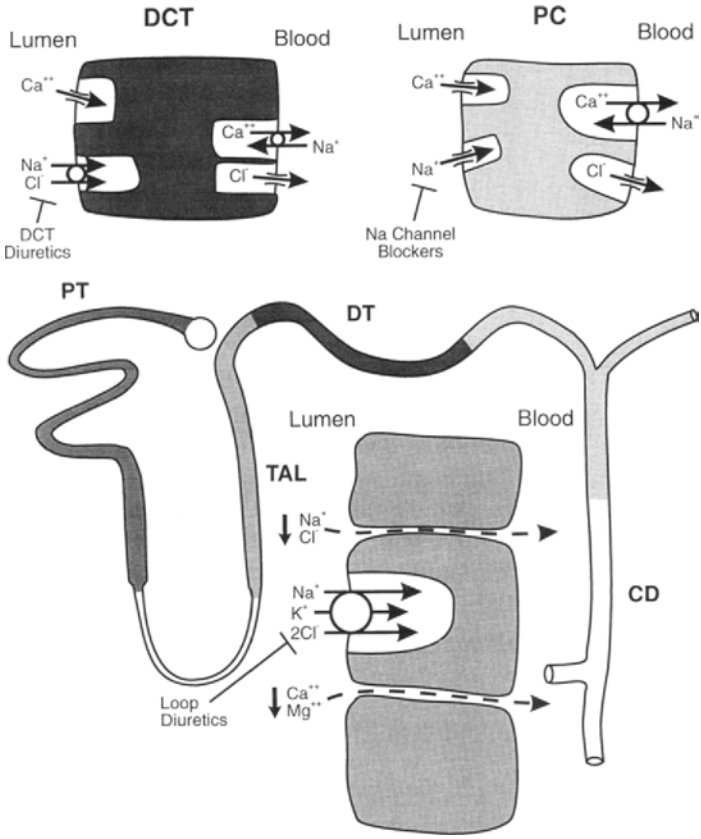

FIGURE 4. Sites and mechanisms of actions of diuretics on renal tubular calcium reabsorption. Symporters and antiporters are depicted as open circles. Channels are indicated by two lines interrupting a membrane. Shown are DCT diuretics (thiazides and indapamide), loop diuretics (furosemide), Na channel blockers (amiloride).

Clinical Application

Renal Stones

It has been shown that the addition of amiloride to thiazide is advantageous in the treatment of patients with hypercalciuric nephrolithiasis [9]. The observation that amiloride and hydrochlorothiazide produce additive hypocalciuric effects is consistent with their acting through the two different mechanisms [4]. Because of its potassium sparing action, amiloride prevents the development of

hypokalemia, as anticipated with thiazide treatment. Consequently, it may prevent the development of hypocitraturia as was detected with long-term thiazide treatment. Moreover, amiloride, owing to its high aqueous solubility, is not attendant with the potential complication of another potassium sparing diuretic (triamterene). The use of triamterene has been associated with triamterene calcium oxalate stone formation.

MECHANISM OF ACTION OF LOOP DIURETICS

EFFECT ON RENAL CALCIUM TRANSPORT (FIG. 4)

It has been shown that furosemide inhibits renal calcium reabsorption in the thick ascending limb of Henle. It has been suggested that this inhibitory effect may be due to the abolition by furosemide of normal lumen positive voltage [16], thereby retarding renal tubular calcium reabsorption.

The inhibitory action of furosemide on renal tubular calcium reabsorption in the loop may also be offset by enhanced reabsorption at other sites: in proximal tubule in response to volume depletion and in the distal tubule due to the stimulatory effect of PTH.

CLINICAL APPLICATIONS

Hypercalcemia

Furosemide is known to be a potent natriuretic agent. It also increases calcium excretion in direct proportion to sodium excretion [15]. The use of repeated doses of furosemide in conjunction with intravenous replacement of saline has been used as the first approach in treatment of the hypercalcemia of malignancy [15]. In subjects with hypoparathyroidism, furosemide causes a significant increase in urinary calcium excretion and consequently a significant fall in serum ionized calcium. However, in normal subjects, administration of furosemide does not result in a fall in serum calcium concentration. This effect is presumably as a result of an increase in PTH secretion that has been shown to occur following acute furosemide administration. The rise in urinary calcium excretion following administration of furosemide with attendant secondary PTH stimulation is responsible for the rise in serum calcium concentration in normal subjects.

Familial Hypercalcemic Hypocalciuria (FHH)

Recently, both furosemide and ethacrynic acid have been shown to increase urinary calcium excretion in FHH. In this inherited condition (autosomal-dominant), renal tubular and parathyroid gland insensitivity to calcium results in an increased renal tubular calcium reabsorption and an increased PTH secretion. Thus, they provide an appropriate probe for investigating the site of abnormal renal tubular calcium handling in this disorder [16]. This finding suggests that the site of abnormal tubular calcium reabsorption in this disorder may be the same as the site of action of furosemide, at the thick ascending limb of Henle.

MECHANISMS OF OTHER DIURETICS ON URINARY CALCIUM EXCRETION

ACETAZOLAMIDE

When administered acutely, acetazolamide has a small effect on urinary calcium excretion, though it has been shown to inhibit proximal tubular sodium reabsorption [16]. The acute hypocalciuric effect of acetazolamide is due to inhibition of proximal renal tubular bicarbonate reabsorption and, consequently, the presence of an increased luminal bicarbonate. The presence of bicarbonate in proximal tubular luminal fluid has been shown to enhance directly proximal tubular calcium reabsorption [11]. In dogs, when proximal tubular bicarbonate reabsorption was inhibited by infusion of lysine monohydrochloride (proximal-RTA induced model), urinary calcium fell in the animals with bicarbonaturia and was unchanged in animals with normal urinary bicarbonate excretion [11], despite the development of metabolic acidosis. The effect on distal tubular reabsorption is indirect, due to increased bicarbonate delivery and urinary sodium, which reduces the lumen-negative potential difference in this segment [17].

Calcium-containing renal stones are a recognized complication of chronic acetazolamide therapy for glaucoma. Several studies have shown that patients with idiopathic hypercalciuria are at a particular risk for development of this complication. Chronic acetazolamide has been shown to lower urinary citrate and enhance urinary calcium excretion due to the development of metabolic acidosis. Hypocitraturia, by increasing urinary saturation of calcium oxalate and calcium phosphate, increases the risk of calcium nephrolithiasis.

INDAPAMIDE

Indapamide is a relatively recent antihypertensive drug, the chemical structure of which differs from the classical benzothiadiazines, including chlorothiazide, hydrochlorothiazides, and bendroflumethiazide [1]. It has been shown that indapamide has a potent hypocalciuric effect in normal subjects and also in patients with hypercalciuria and calcium nephrolithiasis. Thus, indapamide could represent an alternative drug to thiazide diuretics in the treatment of calcium stones.

The renal site of action of indapamide has been shown to be similar to the thiazide diuretics and involve the distal portion of the nephron. Its hypocalciuric effect like thiazides has been shown to be independent of its natriuretic action.

Indapamide does not affect lipoprotein metabolism, but possesses the hypokalemic and hyperuricemic effects of thiazides.

SPIRONOLACTONE

The effect of spironolactone on the renal tubular calcium reabsorption and consequently urinary calcium excretion has not been recently examined. However, it was shown previously that spironolactone in a dose of 200 mg daily increases urinary calcium excretion. It was postulated that spironolactone directly affects renal calcium transport independent of the effect on sodium reabsorption.

In one study the effect of spironolactone was compared with that of placebo in normal subjects. It was shown that spironolactone administered at 400 mg per day significantly increased urinary calcium excretion. However, this rise was ascribed to the high calcium content of the tablet, averaging 45.5 mg calcium per tablet.

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CHAPTER VIE

The Effects of Diuretics on Magnesium Metabolism: Physiologic and Clinical Effects

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Magnesium is the fourth most abundant cation in the body. The adult human body contains a total of 1000 mmol of magnesium, of which 60% is in bone and 20% in skeletal muscle. Only 1% is extracellular and 39% is intracellular. Approximately 60% of serum magnesium is present as free magnesium ions, 30–35% is protein-bound, and 5–10% is complexed to bicarbonate, phosphate, and citrate.

MAGNESIUM HOMEOSTASIS

No single homeostatic control mechanism has been demonstrated for magnesium. The concentration of circulating magnesium is regulated by the intestinal tract, the kidney, and bone.

ROLE OF THE INTESTINE

The average dietary intake of magnesium is 12.5–15.0 mmol (300–365 mg) per day. Approximately 20–60% of ingested magnesium is normally absorbed. There is a small component of endogenous intestinal secretion of 0.5–1.0 mmol

Diuretic Agents: Clinical Physiology and Pharmacology

(12 to 24 mg) per day. Intestinal absorption of magnesium in the human occurs in the small intestine.

The effects of vitamin D metabolites have been examined by a segmental perfusion study in human subjects. 1,25-Dihydroxyvitamin D has been shown to enhance intestinal magnesium absorption.

Role of the Kidney

Renal handling of magnesium involves filtration and renal tubular reabsorption. Tubular secretion of magnesium is negligible and contributes in only a minor way to overall magnesium balance. In man, 3500 mg of magnesium is filtered daily, and only 3% of this amount is excreted in urine (100–150 mg/day), an amount equal to the daily net intestinal magnesium absorption [12].

Renal magnesium reabsorption has specific features when compared with that of sodium and calcium (Fig. 1) [6]. The concentration of magnesium in the proximal tubules rises to a level of 1.5 times that in glomerular filtrate. This high concentration of magnesium in proximal tubular fluid reflects the very low permeability of the proximal tubule to magnesium. Magnesium reabsorption in the proximal tubule is largely a unidirectional process, and the rate of

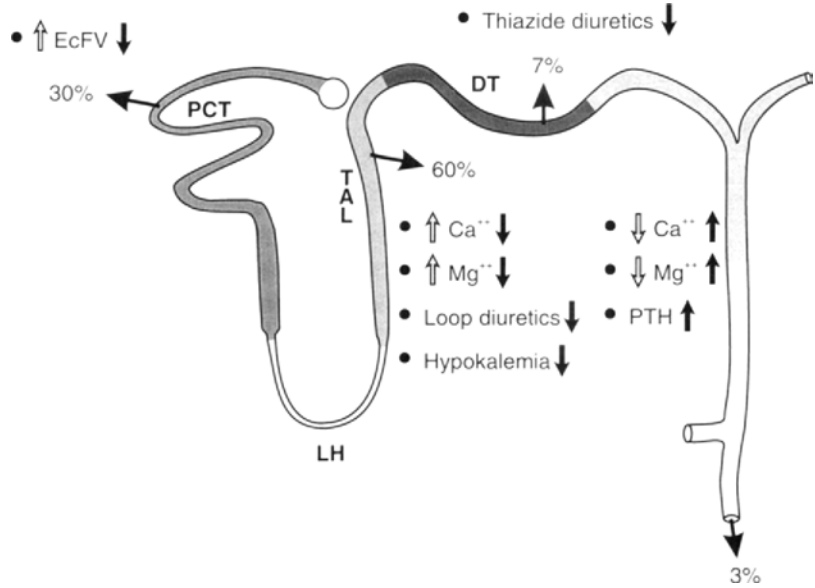

FIGURE 1. Sites of renal tubular magnesium reabsorption. The relative tubular reabsorption rate of magnesium in various nephron segments is indicated by percentage (%). Factors influencing renal tubular magnesium reabsorption is shown by ↑ for increase and ↓ for decrease.

reabsorption is directly related to the concentration of magnesium in luminal fluid. Some 20–30% of filtered magnesium is reabsorbed in the proximal tubule, compared with fractional reabsorption of sodium and calcium of 50–60%. Although the fractional reabsorption of magnesium is only half that of sodium, it changes in parallel with that of sodium in response to changes in extracellular fluid volume. The major portion (65%) of filtered magnesium is reabsorbed in the loop of Henle, mainly in the thick ascending limb. The magnesium reabsorption in the ascending limb may be voltage dependent and secondary to active sodium and chloride reabsorption. The loop of Henle is a major site where renal magnesium reabsorption is regulated. Extracellular magnesium and calcium concentration influence magnesium transport at the basolateral surface of the ascending limb of Henle [7].

The principal factors that alter magnesium reabsorption in the loop of Henle include parathyroid hormone, changes in plasma calcium and magnesium concentration, and the loop diuretics [7]. About 10% of filtered magnesium is normally delivered into distal nephron, where only a small fraction of the filtered magnesium is reabsorbed, and reabsorptive capacity is readily saturated by increased magnesium delivery.

In conclusion, the principal sites of normal tubular magnesium reabsorption are the proximal tubule and the loop of Henle, the major control site being the thick ascending limb of Henle. Factors influencing tubular magnesium will be discussed below.

Factors Influencing Renal Magnesium Handling (Table 1)

Hypomagnesemia and Hypermagnesemia

With a decline in serum magnesium concentration, the filtered load of magnesium progressively falls. Because of diminished tubular fluid magnesium con-

TABLE 1 Factors Influencing Renal Magnesium Reabsorption

Decreasing	Increasing
Hypermagnesemia (+++)	Hypomagnesemia (+++)
Hypercalcemia (+++)	Hypocalcemia (+++)
Extracellular volume expansion (++++)	Extracellular volume depletion (++++)
Diuretics (++++)	Acute and chronic metabolic alkalosis (+)
Phosphate depletion (++)	
Increased GRF and filtered load (+)	
Acute metabolic acidosis (+)	

Note. The relative potency is shown by symbol (+) in parenthesis, with (+) for weakest and (++++) for strongest relative potency.

centration, the absolute renal tubular reabsorption of magnesium declines, but fractional reabsorption remains unchanged in proximal tubule. However, the fractional magnesium reabsorption in the loop of Henle is greater than normal. Thus the loop of Henle is the major site for magnesium conservation in hypomagnesemic states [7]. When the plasma magnesium is raised, reabsorption in the loop of Henle is inhibited and the increased load of magnesium delivered to the more distal nephron exceeds its transport capacity so that most of the unabsorbed magnesium emerging from the loop of Henle is excreted in the urine. These effects of plasma magnesium concentration are exerted on the basolateral side of the cell.

Hypercalcemia and Hypocalcemia

Microperfusion studies have shown interaction between calcium and magnesium at renal transport sites. Hypercalcemia causes not only hypercalciuria, but also hypermagnesiuria [6]. It has been postulated that there is an active transport process at contraluminal tubule cell membrane that is sensitive to the absolute concentrations of calcium and magnesium in the interstitial fluid and more responsive to magnesium than to calcium concentrations. The effect of hypocalcemia and hypomagnesemia on the renal tubular reabsorption of these cations has not been extensively studied. However, hypocalcemia may augment calcium and magnesium reabsorption.

Extracellular Volume Expansion

The proximal tubular reabsorption of sodium and water decreases with volume expansion. Magnesium reabsorption is similarly affected because of fall in luminal magnesium concentration secondary to diminished net sodium and water flux [6]. An increased flow rate to the loop of Henle also has been shown to decrease fractional reabsorption at this site. This fall is secondary to a decrease in transtubular sodium gradient and electrical potential difference. The net effect of volume expansion therefore is an increase in the fractional urinary excretion of magnesium.

Parathyroid Hormone (PTH)

The effect of PTH on the renal tubule transport of magnesium has been disputed. The controversy results in part from the fact that insufficient attention has been given to the independent effects of PTH and calcium on the renal handling of magnesium [7]. Recently, it has been shown that PTH enhances renal tubular reabsorption of magnesium, and the effect is exerted mainly in the loop of Henle. In the parathyroidectomized animal, fractional magnesium excretion rises, a change rapidly reversed by administration of PTH, will be offset by simultaneous effects of hypercalcemia and hypermagnesemia. The role

of PTH in the normal daily regulation of renal magnesium reabsorption is unclear. Several other hormonal factors, including calcitonin, AVP, and catecholamines, have shown experimentally to influence renal tubular magnesium reabsorption.

Other Factors

Disturbances in potassium balance and renal potassium wasting are usually accompaniments of hypomagnesemia and magnesium depletion. This association may be due to development of secondary hyperaldosteronism or to a direct influence on cellular potassium metabolism by inhibitory effect on the Na/K ATPase pump with consequent cellular potassium loss.

Many other factors, including phosphate depletion, acute acidosis, alcohol, and various drugs including diuretics, cisplatinum, gentamycin, and amphotericin B also impair renal magnesium reabsorption.

Role of Bone

Approximately 60% of body stores of magnesium are in bone, of which about 50% are on bone crystal surfaces and readily available for mobilization in the event of magnesium depletion. It has been suggested that in hypomagnesemic states there is altered bone solubility leading to enhanced release of magnesium ion from crystal surfaces to correct hypomagnesemia. The hypocalcemia that occurs in magnesium depletion has been attributed in part to exchange of calcium for magnesium on the surface of bone. This alteration might render the bone resistant to parathyroid hormone, perpetuating hypocalcemia. The bone also tends to be resistant to the effects of other solubilizing factors.

Despite the roles of aforementioned factors, the normal mechanisms of magnesium homeostatic control are not well understood. In renal magnesium wasting, the serum magnesium level falls until a new steady state is achieved in which the capacity for magnesium reabsorption is sufficient to reduce urinary magnesium losses to a level equal to the net intestinal absorption of magnesium.

MECHANISMS OF ACTIONS AND CLINICAL APPLICATION OF DIURETICS ON MAGNESIUM METABOLISM

Thiazide Diuretics

Mechanisms of Action

The main site of action of thiazides is at the proximal portion of the distal convoluted tubule. Distal tubular reabsorption of magnesium affects only 5–

10% of filtered magnesium [10]. Thus, the inhibition of this process cannot account for the increase in the renal magnesium excretion induced by the thiazide diuretics. It has been shown that urinary magnesium excretion after treatment with thiazides is significantly delayed with respect to the volume of sodium and chloride excreted in the urine. Nonetheless, thiazide diuretics are well known to cause clinically significant hypomagnesemia [1].

The exact mechanisms of the magnesiuric effect of thiazides are still under debate [10]. Indirect mechanisms are thought to be prominent [3]. These indirect effects may be secondary to the alteration in the renin–angiotensin–aldosterone system, changes in calcium and PTH relation and contribution to the concurrent drug treatment, duration of drug effect, and underlying disease conditions.

It has been shown that a beta blocker and angiotensin converting enzyme inhibitor (captopril) blunt the magnesiuric effect induced by hydrochlorothiazide [8]. This finding supports a role for the renin–angiotensin–aldosterone system in thiazide induced magnesiuria [8]. On the other hand, the well known effect of thiazides on reducing calcium excretion and presumably secondary fall in PTH secretion could explain the decrease in renal tubular magnesium reabsorption [4]. The suppression of PTH secretion affects renal reabsorption of magnesium in thick ascending limb of Henle.

Clinical Application

For many years, the standard approach to the treatment of mild to moderate hypertension has been the use of thiazide diuretics, which are considered to be safe, effective, and well tolerated. Thiazide diuretics are also the cornerstone of many complex multidrug regimens used in the treatment of more severe hypertension and a mainstay in the treatment of hypercalciuric calcium nephrolithiasis.

Hypokalemia has long been recognized as a consequence of diuretic therapy and has been implicated as a cause of ventricular ectopy [11]. Recent studies, however, suggest that hypokalemia and hypomagnesemia both increase the occurrence of ventricular ectopic beats in thiazide-treated patients and that hypomagnesemia contributes to refractory potassium depletion [11]. It has been shown that repletion with magnesium and potassium administered simultaneously reduces the occurrence of ventricular ectopy more effectively than potassium administered alone. Patients with congestive heart failure are frequently treated with digitalis and diuretics. Digitalis toxicity is a common clinical problem. In this condition, potassium deficiency, concomitant with magnesium depletion may aggravate the condition, because magnesium deficiency is known to inhibit Na/K ATPase activity. This results in an accumulation of a toxic level of sodium and calcium and loss of intracellular potassium. Cardiovascular manifestations include increased sensitivity to digitalis and various arrhythmias.

Hypomagnesemia and hypokalemia clearly occur during thiazide treatment and this problem may be particularly striking in elderly patients. Probably, there are two factors involved in the development of hypomagnesemia in the elderly. They are decreased dietary intake of magnesium due to decreased appetite and a diet deficient in magnesium content. Therefore, it seems reasonable to use a diuretic product that effectively controls hypertension and repletes potassium and magnesium. Currently available preparations of magnesium cause diarrhea and are poorly absorbed. Thus, compliance can become a significant problem for any patient.

Chronic thiazide diuretics in the treatment of hypercalciuric patients with kidney stones may render them prone to the development of hypocitraturia (due to hypokalemia), hypomagnesemia, and hypomagnesiuria. Urinary citrate and magnesium are both important urinary inhibitors of crystallization of calcium oxalate and calcium phosphate salts.

A magnesium deficit may coexist with hypokalemia in the absence of hypomagnesemia. Electrolyte repletion in hypokalemic patients, therefore, must also take into account magnesium repletion in the absence of hypomagnesemia.

Loop Diuretics

Loop diuretics are potent inhibitors of magnesium reabsorption [11], having a proportionately greater effect on magnesium than on sodium and calcium reabsorption and, therefore, may contribute to hypomagnesemia secondary to renal magnesium wasting in a variety of clinical settings. The severity of the magnesium depletion that occurs with furosemide administration probably depends on the patient's magnesium intake (from food, intravenous fluid, etc), as well as on the frequency of furosemide administration. Because loop diuretics have short duration of action with daily or even twice daily use, there may be the opportunity for magnesium reabsorption to recover so that magnesium retention can occur during the interdose interval. However, with more frequent or continuous administration, there would be no opportunity for escape from the effects of loop diuretics.

Diuretics Acting in the Proximal Tubule

The effects of diuretics which act in the proximal tubule on the renal handling of magnesium have not been extensively studied. Acetazolamide is a weak inhibitor of renal tubular magnesium reabsorption. It has been shown to exert a small magnesiuric effect when administered in man.

Diuretics Acting in Late Distal Tubule and Collecting Duct

These diuretics, usually referred to as potassium-sparing diuretics, are divided into two main classes: agents whose action does not depend on the inhibition of aldosterone and agents which are classical pharmacological competitive antagonists of aldosterone. Amiloride and triamterene are the main diuretics with action independent of the antagonism of aldosterone.

Potassium sparing diuretics are usually administered concomitantly with more potent diuretics to counteract diuretic-induced potassium depletion. These agents act in the late distal tubule and collecting duct. Evidence has accumulated, indicating that these drugs may also exert some magnesium-sparing properties. In animal studies, a dose–response relationship has been established for the action of amiloride in reducing fractional excretion of magnesium and potassium during furosemide-induced diuresis. The effects of amiloride on magnesium excretion are less than those on potassium excretion. The effects of spironolactone on magnesium excretion are less well established than those of amiloride and triamterene [2, 9].

The long-term effects of potassium-sparing diuretics on magnesium metabolism have not been extensively studied. In one study, the effects of 6 months of treatment with amiloride on muscle magnesium was examined in patients with hypertension and congestive heart failure being treated with hydrochlorothiazide (50 mg daily). Treatment with amiloride resulted in a significant increase in skeletal muscle magnesium [9]. The same effect was also demonstrated with triamterene (37.5 mg) and spironolactone (100 mg) given daily over a 6-month period.

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CHAPTER VIF

Metabolic Derangements Associated with Diuretic Use: Insulin Resistance, Dyslipidemia, Hyperuricemia, and Anti-androgenic Effects

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INSULIN RESISTANCE

INTRODUCTION

Thiazide diuretics remain the cornerstone of antihypertensive therapy and have been shown to reduce morbidity and mortality in hypertensive populations throughout the world. However, their use has been associated with a high incidence of endocrine disturbances including glucose intolerance. Glucose intolerance induced by thiazide diuretics was first reported in the late 1950s. Since then a variety of thiazides as well as loop diuretics have been reported to cause mild glucose intolerance, overt hyperglycemia, and rarely nonketotic hyperosmolar states. More recently, the clinical importance of insulin resistance in relation to cardiovascular morbidity has been identified. It is now known that insulin resistance is a risk factor for cardiovascular disease, including myocardial infarction. The fact that many untreated lean and obese hypertensives exhibit underlying tissue resistance to insulin indicates that this may be a predisposing factor to glucose intolerance and development of overt hypoglycemia during treatment with thiazides and furosemide. Therefore, a better understanding of the mechanism of this effect may ultimately result in an improvement in patient outcome during treatment.

Diuretic Agents: Clinical Physiology and Pharmacology

TABLE 1 Possible Mechanisms of Diuretic-Induced Hyperglycemia

Volume depletion
Decreased filtered load of glucose
Reduced muscle blood flow
Increased catecholamines
Direct effect on tissue Insulin response
Hypokalemia
Suppression of glucose-mediated insulin secretion
Impaired muscle glucose uptake

PATHOPHYSIOLOGY

Untreated essential hypertension is itself associated with insulin resistance in at least 12% of patients and is most certainly a predisposing factor in the development of thiazide and furosemide-induced glucose intolerance. Therefore, on this background, thiazide and loop diuretics may aggravate the tendency to hyperglycemia in this population. Several mechanisms have been proposed to explain thiazide-induced insulin resistance and hyperglycemia, including volume depletion, increased catecholamine levels, direct effects on tissue uptake of glucose (glucose utilization), and hypokalemia (Table 1).

VOLUME DEPLETION AND INCREASED CATECHOLAMINES

Volume depletion may reduce both renal blood flow and glomerular filtration rate, thereby reducing the filtered load of glucose and promoting hyperglycemia. In addition, it has been postulated that reduction in blood pressure and flow to muscle, the primary site of insulin-mediated glucose uptake, may be attributed to volume depletion. Thus volume depletion could reduce tissue sensitivity to insulin indirectly by limiting delivery to muscle bed. Increased plasma catecholamine levels accompanying volume depletion may increase glycogenolysis, thereby increasing glucose input. However, most patients with diuretic-induced glucose intolerance have mild hyperglycemia and are not markedly volume depleted. Moreover, if dietary sodium intake is increased during diuretic therapy, volume depletion and increased catecholamine levels can be prevented. Thus, these catecholamines probably play a minor role in producing hyperglycemia except in patients with severe volume depletion. Therefore, other mechanisms must predominate. In this regard substantial evidence indicates that hypokalemia is the dominant factor in the pathogenesis of glucose intolerance.

Hypokalemia

Clinical trials in hypertensives treated with thiazide and furosemide have shown a close association between the development of glucose intolerance and hypokalemia. In fact the development of glucose intolerance during diuretic therapy was shown to be both time- and dose-related and was reversible after discontinuation of diuretic despite prolonged use (up to 14 years), indicating a metabolic and not a tissue toxic effect of the drug. In addition, in some studies, glucose intolerance has been prevented by coadministration of potassium supplements or potassium-sparing diuretics. Furthermore, these effects are reversible with correction of diuretic induced hypokalemia. Moreover, the role of hypokalemia is further supported by the fact that both hypokalemia and glucose intolerance are mitigated or completely abrogated by administration of low doses of thiazides (e.g., 6.25–12 mg/day hydrochlorothiazide).

Finally, increased intake of dietary sodium during diuretic therapy accelerates renal potassium losses, engendering hypokalemia. Thus there is substantial clinical evidence that hypokalemia is an important pathogenic factor in the development of glucose intolerance (insulin resistance).

Mechanism of Hypokalemia-Induced Glucose Intolerance

The precise molecular mechanism of hypokalemia-induced glucose intolerance is not completely understood; however, the bulk of clinical and experimental evidence indicates that glucose-mediated beta cell insulin release plays a major role. Studies in normal volunteers have shown that thiazide-induced potassium deficiency sufficient to produce sustained hypokalemia is associated with decreased glucose utilization and subnormal plasma insulin response to hyperglycemia of 125 mg/dl (hyperglycemic glucose clamp). However, glucose uptake is normal under these circumstances, indicating that tissue resistance is not the major cause of impaired glucose uptake. Furthermore, the plasma insulin response to hyperglycemia (an estimate of beta cell sensitivity) is directly related to the degree of body potassium deficit. Moreover, the impairment in plasma insulin response to hyperglycemia can be completely prevented by coadministration of potassium with thiazides in an amount sufficient to prevent depletion of body potassium stores (Fig. 1).

In summary, thiazides and furosemide cause glucose intolerance and hyperglycemia in hypertensives. Both clinical and experimental observations indicate that this adverse response is related to the duration and dose of diuretic therapy. Potassium depletion causing impaired beta cell insulin-release is the primary driving force. In addition, under conditions of marked volume depletion with

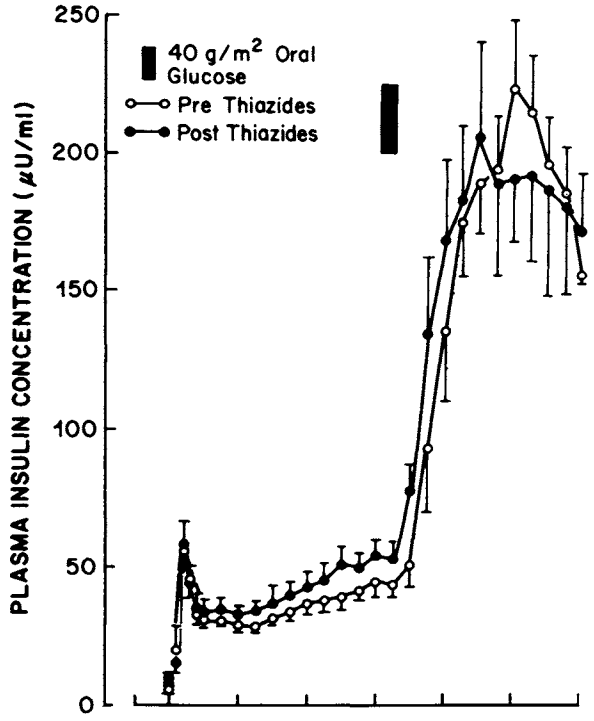

FIGURE 1. Mean insulin concentration response to steady-state hyperglycemia and an oral glucose load during glucose clamp and pre- and post-thiazide administration. Prevention of potassium depletion during thiazide treatment by concomitant oral potassium administration resulted in normal plasma insulin response to glucose loading. Data are presented as means ± SEM. Adapted from Helderman et al.

increased catecholamines and tissue insulin resistance (perhaps due to reduced muscle blood flow) may also participate.

Clinical Significance

The incidence of insulin resistance without overt hyperglycemia is unknown, but overt hyperglycemia occurs in about 15% of patients treated with thiazide diuretics. The incidence of hyperglycemia caused by loop diuretics is lower because these agents tend to cause less potassium wastage than thiazides. Glucose concentrations are mildly elevated (120–150 mg/dl) in most cases; however, severe hyperglycemia with glycosuria can be precipitated even by mild to moderate (25–50 mg/day) doses of thiazides.

As noted above insulin resistance is an acknowledged cardiovascular risk

factor. Thus, several large longitudinal studies of cardiovascular risk factors indicate that patients with insulin resistance are at increased risk for myocardial infarction. In fact, some authors have attributed the lower than predicted benefit of blood pressure lowering on myocardial infarction risk to the adverse metabolic effects of thiazides, including insulin resistance. Since most patients treated with thiazides are hypertensive, the potential added risk of insulin resistance (and hyperlipidemia, see below) should be taken into account when prescribing antihypertensive agents. If thiazides are used to treat hypertension, the relative risks and benefits must be carefully considered and very low doses (e.g., hydrochlorothiazide 6.25–12.5 mg/day) should be tried first in an effort to reduce the risk of the developing insulin resistance. Also careful attention to maintaining a normal serum potassium concentration by increasing potassium intake or by adding a potassium-sparing diuretic may be effective in reducing this risk. For individuals with a very high risk profile (a combination of hypertension, diabetes, obesity, smoking, hyperlipidemia, etc.), alternative antihypertensive agents such as angiotensin-converting enzyme inhibitors, calcium channel blockers, or angiotensin II receptor antagonists should be considered. Although cost/benefit analyses based on current data suggest that the beneficial effect of lowering blood pressure may be offset by the adverse metabolic consequences, this has not been proven in any long-term clinical trial. Trials in progress comparing various antihypertensive agents including diuretics may provide the answer to this question.

HYPERLIPIDEMIA

INTRODUCTION

Thiazide diuretics alter plasma lipids in hypertensives, leading to an atherogenic plasma lipid profile and therefore increased cardiovascular risk (Table 2). This effect is reversible after discontinuation of therapy. Several studies have clearly shown that long-term use of thiazides is associated with unrelenting

TABLE 2 Pattern of Dyslipidemia following Long-Term Administration of Thiazide Diuretics

Plasma lipid/lipoprotein	Direction of change	Magnitude of change (%)
Total cholesterol	↑	10–15
Total triglyceride	↑	5–10
LDL-cholesterol	↑	10–15
HDL-cholesterol	↓	5–10
LDL/HDL ratio	↑	15–20

increases in both total cholesterol and low-density lipoprotein (LDL) cholesterol. Moreover, plasma high-density lipoprotein (HDL)-cholesterol level may decrease, especially in diabetics. These findings indicate that treatment of hypertensives with thiazides in particular is associated with a highly atherogenic plasma lipid profile, that is, a concomitant increase in plasma LDL-cholesterol and decrease in plasma HDL-cholesterol. Although hypertriglyceridemia has also been reported with thiazides, unlike the effect on total and LDL cholesterol it appears to dissipate with time. In a recent metaanalysis of over 450 clinical trials of antihypertensive therapy it was shown that adverse effects of thiazides on plasma lipids are more prominent in males in general and blacks in particular. Since this patient population is at very high risk for stroke and end-stage renal disease, this adverse effect of thiazides must be taken into consideration when contemplating antihypertensive therapy.

Pathophysiology

There have been no careful studies performed to identify the precise mechanism(s) of thiazide-induced hyperlipidemia. Volume depletion and increased catecholamines, insulin resistance, dietary fat intake, and changes in body weight have been cited as possible pathogenic factors in diuretic-induced dyslipidemia.

Volume Depletion and Increased Catecholamines

Volume depletion and increases in catecholamines accompany thiazide treatment initially and could be responsible for increasing plasma lipid levels. Although there have been no studies which have directly examined the precise mechanisms of volume depletion and increased catecholemines in the pathogenesis of diuretic-induced dyslipidemia, several possibilities exist. For instance, reductions in peripheral blood flow may reduce tissue uptake of lipoproteins, leading to hyperlipidemia. Increased plasma catecholamine levels could increase plasma lipids by directly increasing hepatic very low-density lipoprotein (VLDL) production. This is supported by the observation that α_1-blockers may reduce plasma cholesterol in some individuals, which suggests that α-adrenergic activity could play a role in the pathogenesis. In contrast, β-blockers in antihypertensive doses have been shown to increase plasma lipids, suggesting that increased β-adrenergic activity does not increase plasma lipids and indeed may lower plasma lipid levels. Moreover, hyperlipidemia per-

sists after repair of thiazide-induced volume depletion, indicating that other mechanisms are important.

Insulin Resistance

As already mentioned the insulin-resistant state associated with hypertension may be aggravated by therapy with potassium wasting diuretics. In this regard, several authors have suggested that the responses are in part explained by insulin resistance. Increased plasma insulin levels can increase hepatic VLDL production, thereby giving rise to both hypertriglyceridemia as well as increased LDL via intravascular catabolism of VLDL by lipoprotein lipase which is stimulated by insulin. Further, hyperglycemia in untreated type II diabetics is associated with increases in dietary cholesterol, cholesterol synthesis, and plasma triglyceride and cholesterol levels. Treatment with insulin has been shown to reverse these abnormalities.

A role for hypokalemia-induced insulin resistance in the development of hyperlipidemia has also been suggested. Experimental animal studies of furosemide-induced potassium depletion suggest that insulin resistance is an important factor in the pathogenesis of hypercholesterolemia. In addition, in hypertensives, chlorthalidone-induced hyperlipidemia can be reversed by substituting spironolactone treatment. This effect is probably due to correction of hypokalemia which ameliorates insulin resistance (see above). Finally, discontinuation of diuretic therapy after long-term use has been shown to lower simultaneously plasma glucose, glycohemoglobin levels, and plasma total and LDL cholesterol concentrations, again suggesting a prominent role for insulin resistance. Nevertheless, for unexplained reasons in some individuals hyperlipidemia develops during diuretic therapy despite maintenance of normokalemia.

Taken together, these data strongly support the role of insulin resistance in the pathogenesis of elevated plasma triglyceride and cholesterol levels. Still, they cannot explain the reduction in HDL cholesterol often observed with diuretics, particularly in the diabetic population (see above).

Dietary Fat and Weight Gain

Dietary restriction of cholesterol and saturated fatty acid can mitigate and in some cases prevent increases in LDL-cholesterol, VLDL-cholesterol, and hypertriglyceridemia during thiazide therapy. In addition, increases in body weight during long-term treatment with diuretics tends to increase plasma cholesterol, whereas weight loss is associated with improvement in plasma lipids. Whether

the changes in weight reflect attendant alterations in insulin resistance or dietary effects on lipid synthesis is not known. However, the observations suggest that dietary fat and caloric intake are important in the pathogenesis of hyperlipidemia during thiazide treatment.

Clinical Significance

Use of thiazide diuretics in the treatment of hypertension and chronic edematous states is a double-edged sword. Thus, at moderate to high doses, thiazides increase LDL cholesterol about 8–10%. Although several studies indicate that blood pressure does indeed reduce cardiovascular risk despite hyperlipidemia, an increase in LDL cholesterol of 10% may offset the net reduction in cardiovascular mortality derived from blood pressure lowering alone.

Like the adverse effects of thiazides on glucose metabolism, their effect on plasma lipids is reversible. Therefore, discontinuation of thiazides and use of alternative agents which either lower (e.g., ACE inhibitors, calcium channel blockers) or do not change plasma cholesterol should probably be used for treatment of hypertension in patients with preexisting hypercholesterolemia or combinations of other risk factors such as diabetes, left ventricular hypertrophy, and cigarette smoking.

HYPERURICEMIA

Introduction

An increase in plasma uric acid level occurs in the majority of patients treated with thiazide and loop diuretics. The magnitude of the increase is variable, dose dependent, and is amplified by coexisting volume depletion. Most patients are asymptomatic and the risk of developing overt gout is relatively low in most hypertensives.

Pathophysiology

Hyperuricemia is a common complication of diuretic therapy in general (Table 1). In most mammals, uric acid undergoes bidirectional transport in the proximal nephron, i.e., both tubular reabsorption and secretion as reviewed previously (see Chapters II and IIIA). In man, net urate reabsorption occurs and is highly dependent on the filtered load, luminal concentration of urate, and luminal flow rate. Most commonly used diuretic agents can alter uric acid

transport along the nephron, leading to increased plasma uric acid. In most instances use of these agents leads to decreased renal clearance of urate and hyperuricemia (indacrinone which is uricosuric and decreases plasma uric acid and spironolactone are notable exceptions). Although acute administration of thiazides, carbonic anhydrase inhibitors, and loop diuretics inhibit proximal tubular reabsorption and cause uricosuria, chronic administration of these agents causes a decrease in urate clearance and hyperuricemia. Hyperuricemia results primarily from extracellular fluid (ECF) volume depletion which causes net renal retention of uric acid by: (i) reducing glomerular filtration rate (GFR) and thereby filtered load of urate and (ii) stimulating proximal sodium and water reabsorption, leading to increased luminal concentration of urate and decreased luminal flow rate and hence increased reabsorption.

Clinical Consequences

Mild elevation in uric acid levels are common during treatment with both thiazide and loop diuretic agents. Approximately 50% of patients will achieve and maintain plasma urate levels $\geq$8.0 mg/dl. However, most patients with diuretic-induced hyperuricemia are asymptomatic and there is no evidence that hyperuricemia in this setting causes renal damage or aggravates preexisting renal disease. Moreover, the risk of developing overt gout is very low; therefore, treatment of hyperuricemia is unwarranted and unnecessary in most patients. About 1% of patients treated with diuretics for hypertension will complain of acute gouty arthritis. However, in patients with hypertensive nephrosclerosis and chronic renal insufficiency, particularly men, the incidence is considerably higher. About 20% of patients develop gout at some time during their disease process. This may be due in part to the fact that GFR is decreased and progressively deteriorates and most of these patients require chronic diuretic therapy to control blood pressure. Therefore, for these patients and for patients with preexisting gout, administration of allopurinol is recommended to prevent gouty attacks when diuretic therapy cannot be discontinued.

ANTIANDROGENIC EFFECTS

Introduction

Mineralocorticoid antagonists are weak diuretics that act by inhibiting the effect of aldosterone on sodium transport in the cortical collecting duct of the kidney. In the kidney, mineralocorticoid specificity is a result of the action of 11β-hydroxysteroid dehydrogenase which converts glucocorticoids to meta-

bolites for which the mineralocorticoid has low affinity. However, mineralocorticoids are not metabolized by this enzyme and therefore bind to the mineralocorticoid receptor in the renal tubular cells. Spironolactone and other mineralocorticoid antagonists are competitive inhibitors of mineralocorticoid receptors in target tissues. Binding of antagonists to the receptor causes dimerization of the antagonist–hormone complex which is in turn transported into the nucleus where it binds to the mineralocorticoid promoter. However, gene transcription is inhibited which reduces the tissue response to mineralocorticoids and leads to an increase in plasma aldosterone concentration. Importantly, experimental and clinical studies have shown that spironolactone also antagonizes androgen receptors.

Pathophysiology

Antiandrogens are substances that prevent the effects of androgens at their target sites. Spironolactone, in addition to its antimineralocorticoid effects, is a potent antiandrogenic agent. The antiandrogenic effects are dose related and result from three different mechanisms. First, at low doses (50–150 mg/day) they competitively inhibit androgen receptors, resulting in a reduction in nuclear accumulation of active hormone–receptor complexes. Second, at high doses (>150 mg/day) they also inhibit testosterone biosynthesis by inhibiting 17,20-desmolase. Third, spironolactone enhances testosterone metabolism by increasing peripheral conversion of testosterone to estradiol. These latter two effects combine to reduce plasma testosterone concentration. Among these mechanisms, competitive inhibition of dihydrotestosterone binding to the androgen receptor is the most important clinical effect (Fig. 2). In normal individuals administered high doses (400 mg/day) of spironolactone gynecomastia and semen abnormalities including decreased sperm density and motility are caused. Although canrenone, the principle circulating metabolite of spironolactone, binds to and blocks the receptor *in vitro, in vivo* substitution of canrenone for spironolactone has been shown to reverse spironolactone-induced gynecomastia. These data suggest that canrenone is a less potent inhibitor of the receptor; thus, the major effects are due to the parent molecule.

Pathophysiology of Spironolactone-Induced Gynecomastia

The pathophysiology of gynecomastia after spironolactone administration has been carefully studied in man. As noted above, spironolactone induces gynecomastia (and other antiandrogenic effects) principally by binding to cytosolic

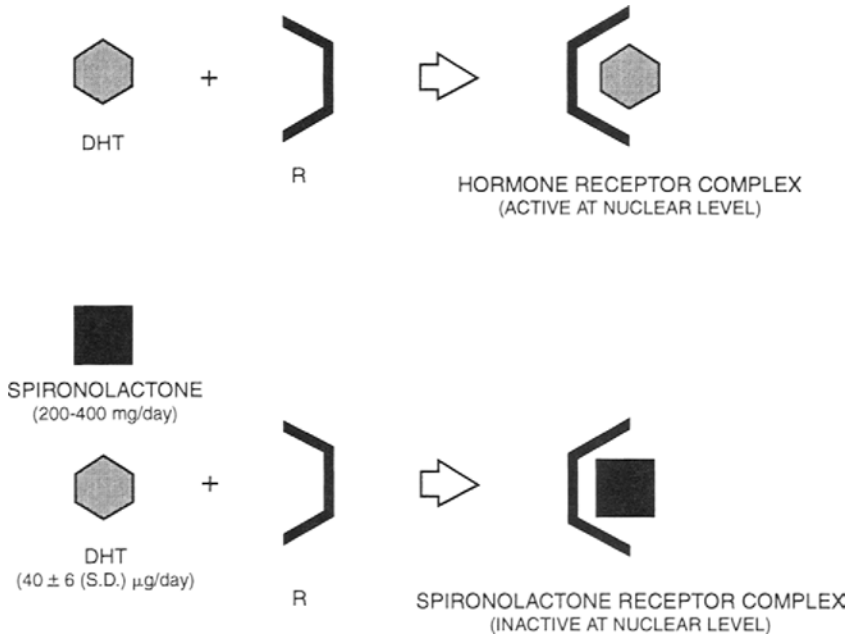

FIGURE 2. Active androgens and more specifically 5α-dihydrotestosterone (DHT) interact with the androgen receptor (R) in target tissues to form hormone receptor complexes which activate protein synthesis. Low (50–75 mg) or high (200–400) doses of spironolactone interfere with DHT binding with its receptor to form inactive complexes at the nuclear level. From Tremblay.

androgen receptors. Subsequently, in patients who develop gynecomastia, blood testosterone levels decrease and blood estradiol levels increase. These changes come about by increases in metabolic clearance rate of testosterone as well as an increase in peripheral conversion to estradiol. Consequently, excessive stimulation of breast tissue as a result of an imbalance between estrogen and testosterone in the body leads to increased ductal proliferation and tender breast enlargement in males. Discontinuation of the drug results in slow reversal of this process sometimes requiring several months for complete normalization of breast size.

Clinical Consequences

The incidence of spironolactone-induced gynecomastia in men is dose related (Fig. 3). It is estimated that 50% of men treated with ≥150 mg/day of spironolactone will develop gynecomastia. The degree of gynecomastia varies con-

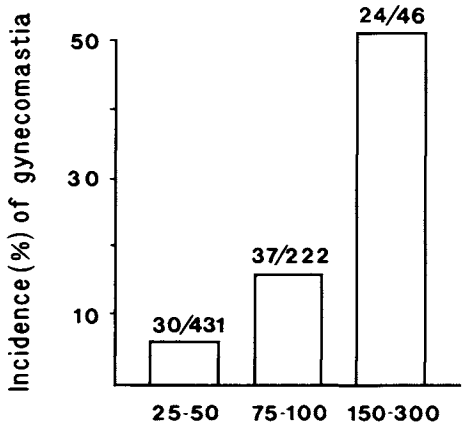

FIGURE 3. Incidence of gynecomastia according to dose of spironolactone. From Juenematire, et al.

siderably from patient to patient but in most instances causes mild symptoms. Associated breast tenderness is common but an inconsistent feature. Regression of gynecomastia usually occurs within a few weeks after discontinuation of spironolactone. More troubling symptoms and signs in some males include reduced libido and impotence; however, the incidence of these complaints is not known. These effects are also dose-dependent and disappear after discontinuation of the drug.

Spironolactone is reported to cause hirsutism, deepening voice, and menstrual irregularity in women. The menstrual irregularities are believed to be caused by concomitant inhibition of 17-hydroxylase by spironolactone. These effects are generally mild but disturbing to the patient and may result in reduced medication compliance. Interestingly, the antiandrogenic effects of spironolactone have been exploited clinically in the treatment of familial male precocious puberty and in women for both acne and hirsutism.

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CHAPTER VIG

Ototoxicity

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INTRODUCTION

Many loop diuretics, especially ethacrynic acid and furosemide, cause both temporary and permanent hearing loss (Fig. 1). The loss of hearing occurs very rapidly after intravenous administration. Ototoxicity typically occurs in the setting of high doses, acute or chronic renal failure, cirrhosis, and in premature infants. Cases of permanent hearing loss have occurred with ethacrynic acid mostly in patients with renal failure. In contrast, furosemide is more likely to cause reversible sensorineural hearing loss, although six cases of permanent hearing loss have been reported. [1, 3, 5, 11].

PATHOPHYSIOLOGY

Loop diuretics cause morphological changes, alterations in endolymph potassium concentrations, and functional decreases in cochlear electrical potentials. The morphological alterations described in humans have included extensive outer hair cell losses in the basal turn of the cochlea, cystic changes in the stria vascularis, rupture of endothelial layers, and edema of the marginal cells of the stria vascularis (Fig. 2) [9]. Death of the hair cells in the organ of Corti causes

Diuretic Agents: Clinical Physiology and Pharmacology

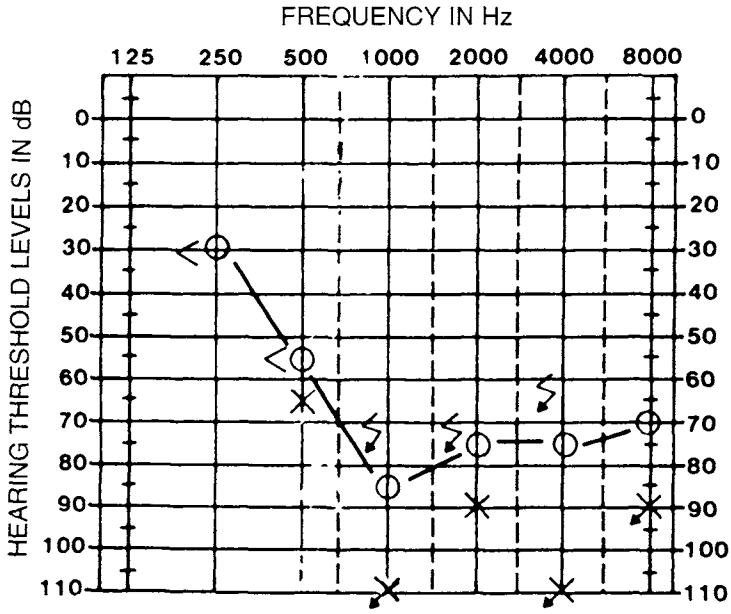

FIGURE 1. Audiogram of patient with profound bilateral middle and high frequency hearing loss after receiving ethacrynic acid. From Rybak Ototoxicity of Loop Diuretics, Otolaryngologic Clin. N.A., 1993. Reproduced (by permission).

permanent hearing loss [3]. Organ culture studies have found selective hair cell damage to the organ of Corti. In animal studies, loop diuretics alone produce reversible changes in the stria vascularis, which are temporarily correlated with transient hearing loss. However, when loop diuretics are given with aminoglycosides, morphologic changes occur within 1 hr.

The stria vascularis contains a Na/K/2Cl transporter, similar to that found in the medullary thick ascending limb of the kidney. This transporter presumably binds both ethacrynic acid and furosemide. Whether inhibition of this transporter is responsible for the observed ototoxicity is uncertain, since pretreatment with organic acids reduces the ototoxic effects of furosemide, but not ethacrynic acid. Ethacrynic acid ototoxicity may involve the production of an ototoxic metabolite.

INCIDENCE

The incidence of deafness associated with ethacrynic acid has been reported to be 0.7% [3]. The incidence of audiometric changes (defined as a 15-dB eleva-

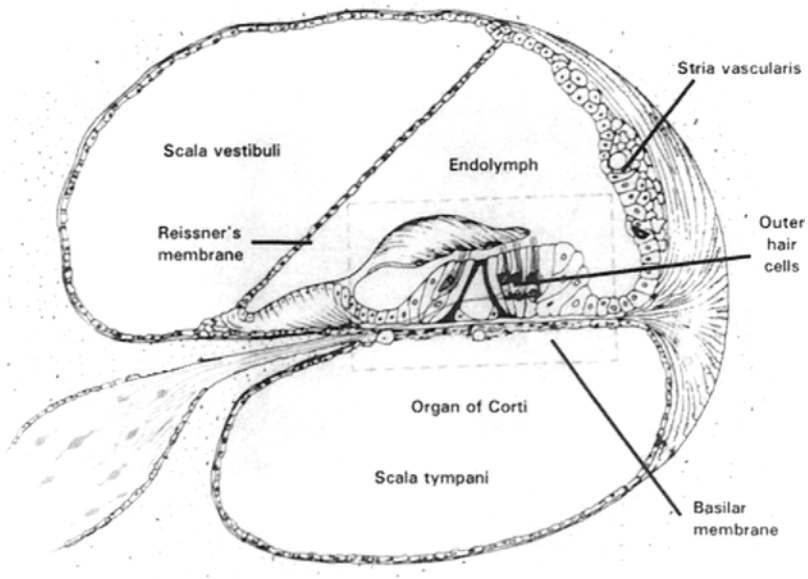

FIGURE 2. Schematic diagram of the cochlear duct. Organ of corti outlined by dashed rectangle. The endolymph is formed by stria vascularis. Scala vestibuli and scala tympani contain perilymph. Reprinted by permission from Essential Otolaryngology, K. J. Lee editor, Appleton & Lange Publishers.

tion of pure tone auditory thresholds) is estimated to be 1.1% for bumetanide and 6.4% for furosemide [4]. Animal studies also suggest that bumetanide is less ototoxic than furosemide [2].

RISK FACTORS

Risk factors can be grouped into three groups (see Table 1): reduced renal excretion, rapid infusion, and synergistic interactions with other ototoxins. Since loop diuretics are excreted via the kidneys, the first two risk factors suggest that ototoxicity is dependent on the concentration of the agent.

Reduced Excretion

The most common cause of reduced excretion is renal failure, where large amounts of loop diuretics are given to treat volume overload. Similar reductions in excretion are found in patients with cirrhosis. Neonatal kidneys have

TABLE 1 Risk Factors for Ototoxicity

Reduced renal excretion
Renal failure
Cirrhosis
Neonates
Rapid administration
Intravenous infusion >25 mg/min
Synergistic interactions
Aminoglycosides
Cis-platinum
Developmental sensitivity
Neonates

not fully developed the ability to excrete organic acids such as PAH, furosemide, and penicillin [7]. Decreased conjunction with glucuronic acid in the liver also leads to a longer circulating half-life in neonatal animals and premature infants than adults. The recommended dosing intervals of 12 hr can lead to potentially ototoxic plasma concentrations of furosemide in premature infants [4, 8].

Rapid Infusion

Infusion rates of >25 mg/min for furosemide causes noticeable hearing loss in 66% of patients, while only minor hearing loss was seen at 15 mg/min. Rapid infusion at 25 mg/min produced acute reversible hearing loss in 50% of patients, primarily in the middle frequencies [4, 6].

Synergistic Interactions

Brummett has pointed out the synergistic interaction between loop diuretics and aminoglycosides. This combination often produces permanent deafness, especially in patients with renal failure. The acute loss of hearing may occur within 30 min to 2 hr after intravenous administration of diuretics, in a patient on aminoglycosides. This interaction may be specific of loop diuretics and does not hold for other diuretics such as mannitol, hydrochlorothiazide, or mercurials. There is also a synergistic toxicity when loop diuretics are given with *cis*-platinum. This is especially important because loop diuretics are recommended to produce a diuresis to prevent *cis*-platinum nephrotoxicity.

Developmental Sensitivity

Besides the drug metabolism alterations described above, the neonatal cochlea displays a hypersensitivity to loop diuretics, as occurs for other ototoxins including loud noise and aminoglycoside. This occurs during the rapid developmental changes in anatomy and physiology of the cochlea. In rats, this sensitive period extends from postnatal Days 9–28 for furosemide, which corresponds to a period from 4.5 months' gestation to term.

DIAGNOSIS

The initial symptom is usually tinnitus. Tinnitus is a high-pitched and continuous sensation, reflecting cochlear hair cell damage in the basal turn. Objective hearing loss is manifested as a bilateral high-frequency sensorineural threshold shift. As the damage progresses, the middle frequencies are also lost. Loop diuretics do not usually cause vestibular symptoms, although transient vestibular symptoms have been seen with ethacrynic acid.

PREVENTION

The major considerations for preventing loop diuretic ototoxicity have been reviewed by Rybak (Table 2). Ototoxicity can be minimized by decreasing the amount of loop diuretic given, as well as the rate of infusion. This is particularly true in patients with advanced renal failure and congestive heart failure. In patients with renal failure, furosemide should not be given faster than 4 mg/min [6]. In neonates, furosemide should be administered at intervals longer than 12 hr to avoid toxic blood levels caused by delayed renal and hepatic clearance of furosemide [7].

TABLE 2 Prevention of Ototoxicity

Judicious use of diuretics
Decrease amount of diuretics
Increase interval in neonates
?? Organic acids (diatrizoate)
?? Albumen

TREATMENT

There is no known effective treatment for loop diuretic ototoxicity other than discontinuing the offending drug. However, radiographic contrast media such as diatrizoate, probenecid, sodium salicylate, and penicillin G have been effective in preventing morphological and functional changes in animal models of ototoxicity. Indeed, diatrizoate has been recommended to treat idiopathic sudden sensorineural hearing loss [9]. These agents are all organic acids and may interfere with an organic acid uptake system in the cochlea. These agents, in general, were given before the furosemide, which may diminish enthusiasm for their effectiveness in established ototoxicity. In summary, these agents must be classified as experimental, and are not FDA approved for this indication.

Albumin has also shown promise in protecting against ototoxicity. Analbuminemic rats which lack serum albumin are extremely sensitive to furosemide ototoxicity. Albumin protects against furosemide-induced ototoxicity in analbuminemic rats and in normal rats. Furosemide is known to bind albumin. Access of furosemide to its ototoxic site in the cochlea evidently depends on the concentration of unbound albumin in the serum [10].

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CHAPTER VIH

Allergic Interstitial Nephritis Due to Diuretic Agents

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INTRODUCTION

Allergic tubulointestinal nephritis (ATIN) is a rare complication of diuretic use. Loop, thiazide, and potassium-sparing diuretics or combinations have been reported to cause interstitial nephritis in patients with or without known underlying renal disease. The onset after treatment varies from days to months (Table 1). The renal lesion is characterized by two main features: (i) interstitial mononuclear infiltrate (often with eosinophils) accompanied by interstitial edema and (ii) varying degrees of tubular injury. In nearly all cases, the lesion is reversible after discontinuation of the offending agent.

PATHOPHYSIOLOGY

There is considerable evidence that diuretic-induced tubulointestinal nephritis is an allergic or hypersensitivity reaction to the drug. First, systemic symptoms and signs associated with hypersensitivity, including eosinophilia, skin rash, and other allergic manifestations, frequently accompany renal failure. Second, the interstitial inflammatory infiltrate is composed primarily of lymphocytes, plasma cells, and monocytes resembling acute renal allograft rejection. Third,

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TABLE 1 Clinical Features of Diuretic-Induced Interstitial Nephritis

Author	No. of Cases	Drug	Onset after drug (months)	Prior renal disease	Urinary findings			Tubular defects†	Eosinophilia	Renal recovery
					RBC	WBC	Proteinuria			
Lyons *et al.* [1]	4	F	0.25	Y	+	+	+	NR	+	Died
		F, C	3	Y	+	+	+	NR	−	N
		C	8	Y	+	+	+	+	−	N
		F	12	Y	+	+	+	NR	+	Y
Fuller [2]	1	F, H	9	Y	+	+	+	+	−	Y
Magil [3]	3	H, T	1.25	N	+	+	+	NR	+	Y
		H, T	0.3	N	+	+	+	NR	−	Y
		H, T	2.5	N	+	+	+	NR	+	Y
Magil [4]	5	H, T	1	N	NR	NR	NR	NR	−	y
		H, T	2	N	NR	NR	NR	NR	+	y
		H, T	2	N	NR	NR	NR	NR	−	Y
		H, T	2	N	NR	NR	NR	NR	+	Y
		F, T	1	N	NR	NR	NR	NR	+	Y
Ebert [5]	1	H, T	1	N	+	+	+	+	+	Y
Ten *et al.* [6]	1	H	1	N	NR	NR	+	+	−	Y
Enriquez [7]	1	H	14	N	NR	NR	+	+	−	Unknown

Note. F, furosemide; H, hydrochlorothiazide; C, chlorothiazide; T, triamterene; NR, not reported; +, present; −, absent; †, tubular function defect includes hyperkalemia, hyperchloremia and hypobicarbonaturia, and renal glycosuria.

rechallenge with structurally similar diuretic agents results in prompt recurrence of the renal failure. Moreover, the lack of significant acute tubular necrosis despite intense inflammation is against a direct toxic effect of a drug.

The precise pathophysiologic mechanisms responsible for tubulointerstitial nephritis due to diuretics are not completely understood. However, two features related to the chemical structure of these agents are very important. First, both loop and thiazide diuretics are sulfa drugs which are among the most common agents causing hypersensitivity reactions. The sulfanilamide moiety present in thiazides and furosemide is believed to be important in the inflammatory lesion in the kidney. Second, thiazides, furosemide, and triamterene have similar metabolic fates in the kidney. For instance, they are all organic acids that gain access to the tubular lumen by secretion into the proximal tubule. Therefore, they may become concentrated in the renal cortex where they may form a drug–hapten complex which in turn enters the interstitial space, is recognized by T-cells as foreign and incites an inflammatory response.

Both cellular and humoral mechanisms are believed to play a role in the pathological findings in the kidney ATIN. Antibodies to drug–hapten complexes and anti-tubular basement antibodies have occasionally been identified in the kidney of patients with this lesion. However, cellular mechanisms of injury are probably more important in the pathogenesis of diuretic-induced ATIN. The major findings in the kidney include focal or diffuse cortical infiltrates composed of mononuclear cells including plasma cells, lymphocytes, monocytes, and macrophages. In addition, eosinophils are usually present. The cellular infiltrate is accompanied by prominent interstitial edema which is evident by wide separation of the renal tubules. The second feature is tubular cell damage ranging from mild swelling to overt, but patchy tubular necrosis. Typically the cells are swollen with vaculolization and loss of brush border (proximal tubules). Finally, the tubules are often directly invaded by inflammatory cells.

CLINICAL PRESENTATIONS

The clinical features of diuretic-induced ATIN are summarized in Table 1. Furosemide, chlorothiazide, hydrochlorothiazide, and triamterene are the main agents reported to cause the syndrome. The onset of renal failure after initiating diuretic therapy is variable, ranging from 1 week to 14 months. Early reports of ATIN caused by diuretics included only patients with underlying renal disease; however, it is clear that this disorder occurs in patients with normal renal function as well. Eosinophilia is reported in about 50% of cases and is accompanied by microhematuria, pyuria, and proteinuria in the majority of cases. Renal function may deteriorate abruptly or more insidiously and the clinical

course is variable; however, in nearly all cases recovery of renal function is observed (Table 1).

At least two clinical presentations of ATIN due to diuretics occur. An insidious form in which renal failure appears to develop over a several-month period of time and an acute form which develops over days to a few weeks. In the first form the onset of renal failure from the time of initiation of diuretic therapy varies from 3 to 12 months. Gradual onset of renal failure often is associated with skin rash and peripheral eosinophilia occur in this form of ATIN. In addition, many of these patients have underlying glomerulonephropathy with nephrotic syndrome. A clue to the diagnosis of ATIN in such cases is an accelerated rate of deterioration in renal function. The second form occurs shortly after initiation of therapy ranging from a few days up to 1 month. In many of these cases thiazides and triamterene were administered concomitantly. Both forms may present with systemic manifestations including fever, myalgia skin rash, and eosinophilia. Importantly, discontinuation of the diuretic with or without concomitant administration of high dose prednisone (60 mg/day) is accompanied by recovery of renal function. Thus, both presentations of renal failure are reversible, although return to baseline renal function may take several months. Patients with both forms presents with constitutional symptoms including fever, headache, and malaise. Signs of hypersensitivity such as skin rash and eosinophilia are not constant features of the syndrome; therefore, absence of these signs does not exclude the diagnosis. Rising serum creatinine associated with mild (nonnephrotic) proteinuria, microhematuria, and sterile pyuria with or without urinary casts are constant features. Patients may also exhibit evidence of tubular dysfunction, including hyperkalemic, hyperchloremic metabolic acidosis, and nephrogenic diabetes insipidus. The combination of urinary sediment abnormalities and signs of tubular dysfunction strongly suggest the diagnosis of interstitial nephritis.

TREATMENT

Treatment of ATIN consists of discontinuation of the offending agent(s). In addition, high doses of corticosteroids (e.g., prednisone 60 mg/day) have been used in attempt to accelerate recovery of renal function in many cases. There are no established guidelines for dosage or duration of therapy in this condition. We recommend prednisone 60 mg/day for 4 (and a maximum of 8) weeks with a rapid taper (over 2–4 weeks). This therapy should be considered in patients with advanced oliguric renal failure whether or not dialysis is needed. However, since there are no controlled trials of corticosteroid therapy in diuretic-induced acute interstitial nephritis their use should be considered empiric. Careful follow-up with attention to possible adverse side-effects of high

dose corticosteroids including serious infections and development of overt diabetes should be performed. The rate of recovery of renal function is variable. Complete recovery appears to take several months according to published reports. Therefore, the patient should be seen on a biweekly basis during the first month and monthly thereafter.

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