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RENAL PHARMACOLOGY

By Gilbert H. Mudge
Department of Medicine, Dartmouth Medical School and Mary Hitchcock Memorial Hospital, Hanover, New Hampshire

Annu. Rev. Pharmacol. 1967.7:163-184. Downloaded from www.annualreviews.org by John Carroll University on 12/16/11. For personal use only.

This review covers the literature on some aspects of renal pharmacology published approximately during the calendar year 1965.

Salt and Water Excretion

A symposium has been held on the physiology of diuretics by the New York Academy of Sciences (1), including an extensive analysis of micropuncture data. Other reviews have analyzed problems of clinical trials (2) and general therapeutic problems (3–6). Baer & Beyer (Ann. Rev. Pharmacology, 1966) presented an extensive summary of two new potent agents, ethacrynic acid and furosemide. A wide spectrum of agents is now available for the mobilization of edema fluid. As anticipated, the most severely ill patient, particularly with diminished cardiac and renal function, has become the major problem of therapy. Iatrogenic disturbances attributable to diuretic therapy commonly include hyponatremia and hypokalemia, and more rarely the excessive or too rapid net loss of extracellular fluid. In terms of therapeutic programs, I agree with Berliner's criticism (5) that a major cause of hypokalemia may be the use of oral diuretics on a continuous regimen. Intermittent administration warrants serious clinical trials.

Physiological parameters of renal function are becoming increasingly complex, but also clearer. Multiple levels of interaction can now be recognized, including extrarenal factors such as total extracellular fluid volume, hemodynamic responses, the interplay of the renin-angiotensin-aldosterone system, the operation of the nephron, not only in its entirety but also subject to intersegmental adjustments and controls, and finally the phenomena of transport as examined at the cellular, membrane, or biochemical level.

Saline loading produces a variety of dynamic responses. Hypernatremia itself decreases tubular reabsorption of sodium independently of systemic volume changes and presumably by a direct renal action (7). Isosmotic expansion and the resultant changes in sodium excretion may be related to extrarenal factors of a hormonal nature, but not necessarily of adrenal origin (8) and possibly of hepatic (9). Alterations in distribution of intrarenal blood flow have also been implicated (10). Further studies on the escape from the sodium-retaining action of deoxycorticosterone also suggest the possibility of a nonadrenal humoral agent (11).

By micropuncture analysis in the dog, the inulin F/P (tubular fluid/plasma) ratios from the proximal segment were significantly lower during saline diuresis than in hydropenia (12). This must be a reflection of altered sodium reabsorbing activity of tubules, and is independent of changes in

filtration rate. The depression of proximal sodium reabsorption can be reversed by partial obstruction of the thoracic inferior vena cava but appears independent of adrenal steroid control (13). In the rat, comparable alterations in saline load (14, 15) or filtration rate (16) are accompanied by proportional adjustments in proximal sodium reabsorption and hence the fraction of sodium reabsorbed and the inulin F/P ratio do not change. At present, the data suggest a fundamental difference in renal dynamics between the rat and the dog. This may have implications for the assay of diuretic agents.

Analysis of diuretic action in the dog by micropuncture technique has revealed a proximal site for mannitol and acetazolamide, but no proximal action of mercurials, ethacrynic acid, furosemide, or benzthiadiazines (1, 17). Other data based largely on the magnitude of changes in the free water clearance in the intact dog have indirectly identified a proximal action for furosemide (18). By the same criteria, although less conclusively perhaps, a proximal site cannot be excluded for mercurials (19) or for ethacrynic acid (20). A critique of the micropuncture method in the evaluation of diuretic action has been presented by Rector (1).

There can be little doubt that the renin-angiotensin-aldosterone system is assuming increasing importance not only in the physiological control of net excretion, but also as a homeostatic mechanism involved in the intersegmental control of nephron function. Micropuncture methods are becoming more essential in the analysis of these problems (1). No attempt can be made here to review these interrelationships in their entirety. Recent contributions are summarized largely in relation to the elaboration and definition of certain experimental variables involving renal function.

Angiotensin has previously been observed to be natriuretic in hypertensive patients and non-natriuretic in normotensives. The phenomenon may be reproduced in rats (21) with unilateral renal lesions and renovascular hypertension, in which the abnormal kidney has a natriuretic response; the normal kidney is nonresponsive. The paradoxical effect may in part be due to endogenous angiotensin either in the systemic circulation or formed and distributed within the kidney. Supporting evidence comes from dose-response studies in the dog in which small doses of exogenous angiotensin were pressor but not diuretic, larger doses were natriuretic (22, 23). Chronic infusions of angiotensin in man yield results consistent with the above (24, 25), although changes in pressor activity, sodium balance, aldosterone secretion rates, and endogenous angiotensin release complicate analysis of either natriuresis or antinatriuresis. Renal blood flow likewise demonstrates a paradoxical response to exogenous angiotensin. In dogs, a dose of angiotensin that produced marked renal vasoconstriction in control periods was associated with an equally striking renal vasodilatation when the kidneys had been previously rendered ischemic (26). Equipressor doses of levarterenol showed no such reversal of action.

Surgical renal denervation eliminates the renal vasoconstriction response to angiotensin. Pharmacological agents that reduce the release of adrenergic

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neurotransmitter also block the renal vascular activity of angiotensin; alpha adrenergic blockade or ganglionic blockade appears not to affect angiotensin renal vasomotor action (27). However, tissue analysis of rabbit kidneys shows no change in norepinephrine or epinephrine levels after pressor doses of angiotensin (28). Data do not appear to be available on the role of the renal sympathetic system as a possible mediator of the natriuretic action of angiotensin.

Present theories hold that renal release of renin is the major factor determining circulating angiotensin levels (see 29). In the normal dog, renal venous renin concentration is elevated following reduction of renal arterial pressure, elevation of ureteral pressure, stimulation of renal nerves, and infusion of epinephrine or norepinephrine (30). Under these conditions, renin release may be blocked by the prior administration of osmotic diuretics, chlorothiazide, and acetazolamide (31, 32). The conditions stimulating renin release share in common the probable capacity to reduce intraluminal sodium concentration in the area of the macula densa of the distal tubule; the diuretics increase tubular fluid sodium concentration. The findings are consistent with the theory that the macula densa acts as a chemoreceptor sensitive to sodium and thus modulates renin release from the adjacent juxtaglomerular apparatus. Elegant data substantiating this theory have been obtained by micropuncture (1). Morphological evidence indicates that the specific height of the macula densa cells are inversely correlated with urinary sodium concentration (33). Although catecholamines increase renin release, this is not observed with approximately equipressor doses of angiotensin (30, 34). This may suggest an additional regulatory mechanism of the juxtaglomerular cells not necessarily mediated through the macula densa.

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Various Diuretic Agents

The mechanism of mercurial action has been further examined with the important introduction of an analytical method capable of distinguishing between the intact organic mercurial (C–Hg) and mercuric ions (Hg) in renal tissue (35). Evidence for the *in vivo* rupture of the carbon-mercury bond seems now unequivocal. In rats, the kidney level of mercuric ion following chlormerodrin administration correlated well with the time course of diuresis. However, the results with *p*-chlormercuribenzoate are paradoxical (36). Unlike the commonly employed organic mercurial diuretics, this agent is highly stable *in vitro*; it is nondiuretic in the dog. However, in the rat, over a limited dose range, a delayed diuresis may be produced which is associated with the appearance of mercuric ions in the renal tissue. This provides further evidence that diuretic-sensitive tubular mechanisms have a marked species variation between the rat and the dog. Of related interest is the fact that ethacrynic acid reduces protein-bound sulfhydryl groups and is an active diuretic in the dog, but by the same criteria has no demonstrable activity in the rat (37).

With autoradiographic techniques, no consistent pattern was found cor-

relating distribution of intrarenal mercury (presumably both C–Hg and Hg) to diuretic action of chlormerodrin (38). This confirms many previous studies that total renal mercury content cannot be correlated with diuresis. More conclusive results might be obtained with mersalyl since the far lesser renal concentration of total mercury observed with this agent might imply that a greater fraction of the mercury present was affiliated with specific receptors related to diuresis, and correspondingly a smaller fraction with nonspecific receptors.

The transport of mercurials into or through renal tissue remains obscure. Slice studies suggest a component of active transport (39). The possibility that ethacrynic acid transport and uptake has features in common with that of mercurials is complicated by the observation that a competitive type of phenomenon can be demonstrated in trichloracetic acid fixed tissues as well as in viable slices. In the rabbit, stop-flow analysis suggests that mercuric ions, given as mercuric chloride, may undergo tubular secretion (40). On the basis of known association constants and previous excretion data, one would presume that the mercury is transported as the mercury-cysteine complex, rather than as the free mercuric ion.

The mechanism of mercury toxicity has been examined by micropuncture in the rat. Oliguria can be primarily attributed to a reduction in filtration rate (41). Further studies confirm the thesis that an action of dimercaptol is to redistribute mercury within the body, rather than necessarily to increase its renal excretion (42).

Studies with the microsomal enzyme inhibitor SKF 525-A have confirmed a moderately brisk diuretic action after unilateral infusion into the renal artery in the dog (43). Inhibition of both proximal and distal sodium reabsorption has been deduced. Since the natriuretic response is additive to that of other diuretics, a different mechanism of action has been proposed.

Definitive studies have been published on triamterene in the rat (44), amplifying previous data available in abstract on its natriuretic activity associated with reduction of potassium excretion, particularly evident when used in conjunction with other diuretics. By the combination-of-drugs technique, it has been proposed that the pteridine diuretic Wy-3654 acts on the same tubular mechanism as the mercurials but a different one from chlorothiazide or ethacrynic acid (45). This reviewer recognizes certain useful operational data that can be obtained by this method, but it is doubtful whether it can be employed either to identify or characterize transport mechanisms at either the cellular or biochemical level. It would be surprising if eventually shown that mercuric ions and Wy-3654 reacted chemically in a similar manner and with the same cellular receptor.

Further studies on a series of triazine and pteridine derivatives have correlated natriuretic and antiglycogenic activities (46). Partial purification has been achieved of a factor from urine with mild diuretic activity (47), possibly related to an action on renal hemodynamics rather than tubular function per se. A new renal action of parathyroid hormone has been described, consisting

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of an inhibition of the renal tubular acidification mechanism (48), resulting in a moderate sodium and bicarbonate diuresis. The mechanism is unknown; inhibition of renal carbonic anhydrase seems unlikely.

Little new information is available on the natriuretic action of the benzothiadiazines. With a new experimental preparation in the rabbit, employing radioactive potassium, it has been found that chlorothiazide-stimulated potassium excretion may be attributed to distal secretion rather than inhibition of potassium reabsorption (49).

Some of the untoward side reactions to the benzothiadiazines have been examined. A high incidence of drug-induced vasculitis is claimed (50). Chronic medication in the rat is associated with increased thyroid size and accelerated thyroid release of I^{131} (51). Studies on carbohydrate metabolism indicate that the rate of glucose uptake by rat hemidiaphragm and fat pad may be decreased by chlorothiazide, but that this is not related to insulin action (52). With the tolbutamide challenge test, serum phosphorus falls more profoundly in subjects pretreated with chlorothiazide (53). These, as well as other studies, suggest systemic nonrenal effects of chlorothiazide within the generally accepted therapeutic dose range.

Although previous work has not shown a significant change in the papilla-cortex tissue sodium gradient after chlorothiazide, a significant reduction in papillary sodium has been observed in the rat after the administration of the related agent, benzylhydroflumethiazide (54). The significance of this apparent discrepancy is not clear. As to further studies on various aspects of mechanisms of action, it is conceivable that more attention should be given to various analogues of chlorothiazide rather than to the more or less monopolistic study of the parent compound itself.

Last year's review dealt extensively with the potent new diuretics, ethacrynic acid and furosemide. No attempt is made to review these agents in systematic fashion. The reader's attention is called to a symposium on diuretic action (1). Ethacrynic acid induces metabolic alkalosis for which the major contributing factor is the renal loss of sodium, chloride, and water (55, 56). This is a clear-cut example of "contraction alkalosis" and differs in no significant manner from the older findings with mercurial diuretics. However, a minor contribution to the distortion of extracellular fluid composition may be the drug-induced increase in hydrogen ion excretion, both as ammonium and titratable acid, particularly apparent in acute studies (57). The mechanism of this latter phenomenon is not clear. Certainly, all data indicate that distal tubule cationic exchange is not inhibited by ethacrynic acid. In control periods sodium excretion was high, being further increased by the drug. The findings are consistent with the thesis that, other factors being equal, distal sodium-hydrogen exchange is approximately proportional to tubular fluid sodium concentration. A direct drug action on the exchange mechanism is not excluded, but is improbable.

Intravenous ethacrynic acid increases urate clearance transiently, then depresses it (55, 58). The effect is probably related to the drug concentration

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itself, rather than to the time sequence, and is similar to that observed with chlorothiazide.

The intravenous route for the administration of ethacrynic acid may prove effective, particularly in the management of otherwise refractory pulmonary edema of cardiac origin (58–60). A completely controlled clinical trial is manifestly difficult. Nevertheless, experience to date suggests that under these conditions about 500 ml urine may be voided within the first hour. Further experience may be anticipated. In nephrosis and other forms of chronic renal disease, the results with ethacrynic acid are variable but, in general, more positive than with less potent diuretic agents (61–63).

As with chlorothiazide, urine volume and water intake are eventually reduced by ethacrynic acid in diabetes insipidus (59), but possibly at the expense of, and probably as a result of, marked reduction of effective extra cellular fluid volume. An extensive examination of the mechanism of chlorothiazide antidiuresis has been reported in surgically induced diabetes insipidus in the dog (64). Other diuretics, including other benzothiadiazines, were also examined. The effect was specific for benzothiadiazines but the mechanism persists as an unknown entity. It is claimed that at high rates of solute excretion, chlorothiazide had no demonstrable antidiuretic action as measured in terms of free water clearance. Unlike the rat, in these experiments the dog shows no antidiuretic response to diazoxide.

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Chlorpyrazine Carboxamides

This new class of diuretic agents promises to be of interest primarily because of their antikaliuretic action. The three amino derivative (ACP) was the first to be reported (65). Both orally and parenterally, this agent produced a slight sodium diuresis in adrenalectomized rat treated with deoxycorticosterone acetate, but the most striking effect was diminished potassium excretion. Since this action could be demonstrated in the absence of adrenal mineral corticoids, it does not represent a true competitive antagonist of aldosterone, but, like triamterene, may be considered a nonspecific inhibitor of the aldosterone effect. An interesting series of synthetic maneuvers combined with analysis of biological metabolites led to the development of the 3,5-diamino derivative as the more potent and more promptly acting compound (66). This is N-amidino-3,5-diamino-6-chloropyrazine carboxamide and has thus far been reported under the names MK-870, amipramizide and amipramidine. As to sodium excretion, it is synergistic with either acetazolamide, benzthiazidines, or ethacrynic acid in the rat and dog (67). At the same time kaliuresis is depressed. Stop-flow experiments in potassium-loaded dogs show an inhibition of distal potassium secretion. Urine anion appears variable, but with significant increments of bicarbonate. Preliminary clinical trials (68, 69) in edematous states have suggested similar actions. Variable degrees of hyperkalemia have been encountered, presumably as a consequence of decreased kaliuresis.

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MANNITOL

Mannitol is usually characterized as metabolically inert and pharmacologically inactive. Hence, it may be recurrently presumptuous to include it in a consideration of diuretic drugs. Nevertheless, there has been a significant renewal of interest in osmotic diuretics, mannitol in particular. The therapeutic indications should be clearly understood as they are different from those for conventional diuretic agents. The latter owe their pharmacological importance to their ability to counteract edema, i.e., to produce a negative net fluid balance. In contrast, the current interest in mannitol is related to its ability to maintain urine flow under pathological conditions in which oliguria might otherwise be anticipated (70).

Little has been added to the fundamental notion that mannitol acts by being filterable at the glomerulus and nonreabsorbable by the tubule. The resultant increase in intraluminal osmoles obligates a greater fraction of water to remain in an intraluminal site and eventually to be voided as urine. Mannitol finds its greatest therapeutic usefulness in those conditions, many of surgical or traumatic origin, characterized by hypotension and decreased glomerular filtration. However, even at reduced rates of filtration, sufficient mannitol may be delivered to the tubular fluid to exert its osmotic effect. Many pharmacologically active drugs lose their diuretic potency under such conditions. Sporadic reports (71) suggest ethacrynic acid may be effective in impending acute renal failure; systematic studies with newer diuretic drugs have not been reported.

Mannitol, in conventional doses, appears to have the additional action of increasing renal blood flow (72) independently of inevitable expansion of extracellular fluid volume (73, 74). For reasons not immediately apparent, medullary blood flow increases disproportionately. Although this specific action has been cited as having therapeutic implications, particularly in impending renal failure, the underlying rationale is not entirely clear. Increase in flow of intratubular fluid to and through the distal nephron can thus far be quantitatively attributed to the osmotic effect of unreabsorbed mannitol. It is difficult to say whether hemodynamic changes have a significant added effect on solute reabsorption.

In impending oliguric renal failure, a persistently reasonable urine flow dilutes intraluminal proteins and provides a rational basis for preventing renal damage (see 75). The relative alkalinity of urine during osmotic diuresis has again been documented (76). Although the tubular mechanisms remain obscure, such alkalinity might have a mild prophylactic value in preventing protein precipitation. Although clinical trials must be conducted under conditions admittedly difficult to control, diverse experience justifies the prophylactic value of mannitol-sustained urine flow (77–81).

The transient changes in tubular morphology have been re-examined with electron microscopy. By careful functional correlation, these appear to have no discernible deleterious effect (82). Although indirect calculations suggest a

site of action limited to the distal nephron (83), the more conventional view holds that osmotically active agents act throughout the length of the entire nephron, an interpretation well supported by micropuncture data (17, 84). Isosorbide has been examined as an osmotic diuretic. It appears effective. It differs from mannitol in that it is almost quantitatively absorbed after oral administration (85). The physiological basis for intestinal, but not renal, permeability is not clear.

Antidiuretic Hormone

The neurohypophyseal octapeptides have been reviewed (86) and a hypothetical scheme proposed correlating biochemical evolution and functional activity throughout the vertebrates. Species variations are marked. For example, the lungfish responds to arginine vasopressin with augmentation of filtration rate, sodium and water excretion (87). Leaf (88) has reviewed the extensive studies on the toad bladder as a convenient test object mimicking the distal mammalian nephron. The physiological disposition of vasopressin has been re-examined in both the dog and rat (89, 90). The hormone is cleared from plasma by liver and kidney, but such clearances appear independent of circulating hormone levels. Hence it is the rate of secretion from the neurohypophysis, rather than the rate of removal, that is the basic determinant of plasma level and resultant renal biological effect.

In the rat, the micropuncture technique has been adapted to provide a quantitative analysis of water permeability changes in the intact kidney (91, 92). Following the intratubular microinjection of labeled inulin and tritiated water, their rate of excretion has been measured, and the permeability characteristics of the tubule through which they passed have been calculated. The findings are consistent with previous studies on the more accessible frog skin and toad bladder, namely that vasopressin acts on the kidney by enlarging the functional diameter of "pores" on the luminal membrane of the distal nephron.

The Symposium of the Second International Pharmacological Meeting (93) is recommended as an excellent summary of the structure-activity relationships and metabolism of vasopressin and oxytocin. The quantitative interrelationships between these hormones are further complicated by the finding that, over a relatively narrow dose range, oxytocin may inhibit the antidiuretic action of vasopressin (94). The finding may have experimental implications, particularly in renal function studies dependent on availability of endogenous antidiuretic hormone theoretically, at least, accompanied by release of either variable or unknown amounts of oxytocin. The 1-deamino analogue of 8-lysine-vasopressin has a longer duration of antidiuretic action in the rat assay than the parent compound (95). The absence of the N-terminal amino group appears to enhance activity. The longer duration of activity suggests possible clinical usefulness.

Both theophylline and arginine vasopressin have similar actions on water permeability and on the tissue levels of cyclic adenosine monophosphate (96),

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a finding consistent with the thesis that the nucleotide acts as an intracellular mediator of vasopressin action.

The effect of pH on vasopressin action has been re-examined (97). In the rat, alkalosis decreases maximal concentrating ability; in the dog, under the influence of vasopressin, free water clearance appears independent of urinary pH. Total renal vascular resistance is reported as inversely related to pCO_2, and relatively independent of pH, in the dog (98). Differential effects on medullary resistance and blood flow are not reported but would be of significance in interpretation of vasopressin effects.

The relationship of water excretion to steroid action has been further examined. Glucocorticoids, but not aldosterone, facilitate free water reabsorption in man under vasopressin influence (99). It is also proposed that cortisol raises the osmolar threshold for antidiuretic hormone release from the posterior pituitary (100).

By analysis of kidney tissue, particularly the papilla, the acute time course of vasopressin action has been examined (101). Water deprivation in the rat is a more effective stimulus to papillary and urinary hyperosmolarity than vasopressin (102); the importance of medullary blood flow is again postulated.

In the toad bladder system, vasopressin action on water permeability and sodium transport may be dissociated by altering ambient calcium concentration (103). In man, the variable effect of vasopressin on sodium excretion has been re-examined (104). With nonexcessive antidiuretic doses, no significant effect on calcium or sodium excretion was observed.

Of pathological, or perhaps toxicological, interest is a series of papers (105, 106) on the induction of acute tubular necrosis by large doses of posterior pituitary extracts. This is attributed to prolonged renal vasospasm; it is accentuated by prior treatment with estrogen or ACTH and is prevented by prior hypophysectomy.

Autonomic Agents

For years, the role of the autonomic nervous system and of autonomic drugs in regulating salt and water excretion has been controversial. Acute or chronic effects on renal hemodynamics, particularly vasoconstriction and reduction of filtration rate, are readily understandable. The major question persists whether or not such agents have a direct action on tubular function, possibly as a consequence of altered membrane permeability [see review (107)]. With fluorescent histochemical techniques, adrenergic innervation of rat and rabbit kidneys terminates in the hilar arteries and glomeruli with no evidence of nerve terminals extending to either the veins or tubules (108).

In the dog, denervation diuresis disappears when filtration rate is mechanically reduced to control levels, a finding indicative of no significant alteration of tubular function (109).

Renal intra-arterial injection of acetylcholine increases renal blood flow and filtration rate with an accompanying augmentation of sodium chloride

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and water excretion (107), as well as calcium and phosphorus (110). Direct measurements of renal blood flow confirm the hemodynamic changes (111). In the rat (112) and in the dog (113) arecoline has a saluretic effect which, like that of acetylcholine, is atropine-sensitive. A direct muscarinic action of tubular function is proposed since simultaneous filtration rates were unchanged or decreased in three instances. However, it is becoming increasingly evident that sodium and chloride excretion in acute experiments cannot be accurately predicted solely by reference to filtration rate when other renal hemodynamic parameters are undergoing simultaneous changes. In the dog, the unilateral renal arterial injection of acetylcholine augmented renal plasma flow during variable states of hydration, from hydropenia to excessive saline or mannitol loading. However, if a "threshold" degree of renal vasodilatation had been achieved by prior saline loading, acetylcholine was no longer saluretic (114). Thus, under these conditions a direct tubular action is not demonstrable. Emphasis is placed on the possibility that noncortical blood flow, presumed to be medullary, may be a determinant of sodium reabsorption particularly in the ascending limb.

Renal vasodilatation may be accomplished by a variety of agents including also isopropylarterenol, bradykinin, kallidin, and tetraethylammonium (115, 116). DOPAmine acts in a manner different from other renal vasodilators (117, 118) in that it produces vasoconstriction in muscular and cutaneous beds and that its action on the renal vasculature, as judged by adrenergic blocking agents, is not compatible with an effect on renal β-receptors. Pharmacologically, renal vasodilatation due to DOPAmine appears to constitute a unique mechanism not shared by other autonomic receptors.

Although not an autonomic agent, the renal medullary vasodepressor substance warrants mention. It has been characterized as a lipid of the prostoglandin type (119, 120a, 120b). Future work will undoubtedly be concerned with its mechanisms of release and its physiological role.

Uric Acid

The renal pharmacology of uric acid properly concerns two problems, separate yet potentially interrelated; first the action of drugs on uric acid excretion, and second the action of urate, particularly at hyperuricemic levels, on other functions of the kidney. In the therapeutic setting, both aspects may be complicated by superimposed phenomena of renal insufficiency. Unlike many other substances, the renal pharmacology of urate is further compounded by bidirectional transport, marked species differences, and paradoxical drug effects, i.e., either increasing or decreasing urate excretion.

The metabolic abnormalities of gout and related problems of urate excretion have been extensively reviewed in a symposium (121) and review articles (122–124).

Little new information is available on the pharmacology of regularly employed uricosuric agents. A clinical observation has unearthed a new uri-

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cosuric agent, the tranquilizing drug chlorprothixene (125). Its action in man is attributed to an increased urate clearance. It is uncertain whether or not uricosuric activity is due to a metabolite; however, this may be suspected since, unlike other uricosuric agents, the parent compound is not an organic acid.

The xanthine oxidase inhibitor, allopurinol, has provided a new dimension in the therapy of gout by decreasing urate formation from xanthine precursors (126). A renal action is not directly involved, but normal excretory function is essential to permit excretion of urate precursors in increased amounts. As a hypouricosemic agent, allopurinol has been a useful drug in clinical trials (127, 128).

In the broader context, allopurinol may have its most dramatic usefulness as an adjunct to the chemotherapy of lymphoma and leukemia (129–131). In this instance, acute antineoplastic action is associated with a rapid increase in urate formation leading to severe hyperuricemia (81 mg/100 ml in one reported case), increased urate excretion, and associated renal damage. This is associated with the intrarenal precipitation of urate, although not necessarily in all instances (132). The use of allopurinol, prior to the administration of oncolytic agents, deviates purine catabolism toward the lesser formation of urate and the greater excretion of its more soluble precursors, xanthine and hypoxanthine. The nephropathy of massive purine catabolism may thereby be obviated.

The pathogenesis of urate nephropathy has been examined in the dog by analysis of intrarenal urate levels (133). Medullary and papillary levels of urate are higher than cortical, this increment in turn being dependent on the amount of urate administered. It is not certain to what extent such accumulation is related to urate transport or to the medullary concentration of solute by the countercurrent mechanism. Stop-flow analyses in a number of species fail to show evidence of tubular permeability to urate in the distal portion of the nephron (134). Of greatest therapeutic interest is that high medullary concentrations of urate are markedly lowered by mannitol diuresis, or even a modest water diuresis. Probenecid, although slightly uricosuric in the dog, had no effect on intrarenal urate concentrations.

The hyperuricemia of fasting and ketosis has been attributed to decreased urate excretion by a number of authors (see 121, 135–137a). This effect may be reproduced by infusions of acetoacetate and β-hydroxybutyrate. Since lactate may be variably elevated in ketosis, it cannot be excluded as a contributing factor.

The well-documented antiuricosuric action of lactate in man illustrates the complexities of attempting a definitive analysis of urate transport and drug action. In the dog, lactate has no effect on urate excretion; in the rabbit, it stimulates proximal urate secretion (137b). Of more recent interest are the measurements of lactate concentration within the rat renal parenchyma (138). The medullary concentration is greater than in the cortex and may be 10 to 20 times higher than in simultaneous plasma or urine. Anaerobic medul-

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lary metabolism is a reasonable basis on which to anticipate high medullary lactate levels, but the roles of medullary blood flow and the countercurrent mechanism remain unknown as determinants of the tissue level. Surprisingly, osmotic diuresis, but not water diuresis, elevates medullary lactate despite a fall in total osmolality as measured by sodium. Under many circumstances, lactate can be considered as an endogenous pharmacological agent; further understanding of its mechanism of action will require imaginative new approaches.

Basic to the quantitative assessment of renal urate transport have been the previous demonstrations that urate is freely filterable at the glomerulus. Absence of protein binding has been shown by ultrafiltration and equilibrium dialysis. Alvsaker (139) has reinvestigated the problem by gel filtration and has demonstrated reversible interactions with albumin, and possibly other plasma macromolecules, that are specific for urate and do not involve xanthine or hypoxanthine. It is not known to what extent these findings are applicable to the evaluation of urate filtration at the glomerulus.

An abnormally low glycine clearance has been observed with hyperuricemia (140). The solubility of sodium urate has been re-examined (141). Urate calculi may be dissolved by prolonged oral alkali therapy (142). Further studies on the behavior of urate in the renal cortical slice system have been reported (143). It has been postulated that unidentified metabolites associated with anaplastic bronchogenic carcinoma may markedly increase urate clearance, leading to hypouricemia, presumably by an action on renal tubular mechanisms (144). These tumors also produce antidiuretic substances (161).

Cystinuria and *d*-Penicillamine

Recent advances warrant review because of therapeutic implications as well as basic problems of renal pharmacology. In some respects this may represent the first instance in which a specific renal tubular disorder has been successfully approached by a relatively specific pharmacological agent. Therapy has raised more problems of mechanism than thus far answered.

Cystinuria is a familial disease characterized by the formation of cystine urinary calculi and an excessively high renal clearance of cystine (CysS-SCys). In normal subjects cystine is largely reabsorbed. Urolithiasis produces a significant morbidity and mortality (145). The underlying renal defect has been characterized as failure of tubular reabsorption involving ornithine, arginine, lysine, as well as cystine (146). Subsequently, a comparable defect in intestinal amino acid transport has been described (147). Recent advances have been well summarized in a symposium (148). Unequivocal renal abnormalities include: (*a*) elevated urinary excretion of cystine and dibasic amino acids, (*b*) in the kidney tissue system, a normal competitive transport between lysine and arginine, and probably ornithine, but no competition between these and cystine (148); in renal tissue from cystinuric subjects, a reduced uptake of lysine and arginine, but normal rates of accumulation for

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cystine; (*c*) in an occasional cystinuric subject, evidence of renal tubular secretion of cystine (149), (*d*) the abnormal urinary excretion of mixed disulfide of cysteine and homocysteine (150), and (*e*) an abnormally low plasma level of cystine. An abnormally high rate of renal extraction of cysteine has not been confirmed (151). No single hypothesis as yet explains these abnormalities either in terms of tubular dysfunction or abnormal intrarenal metabolic pathways. The immediate precursor of urinary cystine has not been identified. Despite these ambiguities, there is no doubt that there is an excessively high urinary concentration of cystine which is undesirable by virtue of its insolubility.

Prevention of cystine urolithiasis has been attempted by alkalinization and water diuresis. Neither procedure modifies the rate of cystine excretion. The meager success of such regimens prompted a new approach (152), based on the 50-fold greater solubility of the *d*-penicillamine-cysteine disulfide (CysS-SPen) compared to cystine itself (CysS-SCys). This new rationale has tentatively justified itself in terms of clinical success (see 148). Surprisingly, the subsequent observations cannot be explained simply on the basis of the increased urinary solubility of *d*-penicillamine-cysteine disulfide.

In normal subjects, the excretion of total cystine (CysS-SCys plus CysS-SPen), is enormously increased by *d*-penicillamine (PenS-SPen), the increment being almost totally attributable to CysS-SPen, to which the renal tubule is presumably impermeable. In cystinuric subjects, after the administration of *d*-penicillamine (PenS-SPen), the total cystine of the urine is about equally partitioned between CysS-SCys and CysS-SPen, however, total cystine excretion may be reduced to as low as 20–40 per cent of pretreatment values. The clearance of CysS-SPen is comparable to the glomerular filtration rate (153). Thus, the urinary problems related to cystine insolubility are altered not only by an increased excretion of the relatively soluble CysS-SPen but also by an additional decrease in the excretion of insoluble cystine. The plasma cystine level is reduced by *d*-penicillamine; the CysS-SPen disulfide is detectable in plasma (153). In a preliminary report, Potts (148) has shown that the abnormal cysteine-homocysteine disulfide is also strikingly reduced by *d*-penicillamine. Taken in their entirety, the results strongly suggest, as postulated by the original investigators, that a major effect of *d*-penicillamine is to minimize the importance of renal excretion, either by the less likely decreased cystine production, or the more probable substitution of an extrarenal excretory route. Qualitatively, the present findings would be consistent with the passage of CysS-SPen from plasma into the gastrointestinal tract, or its formation there from ingested cysteine, cystine, or *d*-penicillamine, and its subsequent elimination in the feces due to intestinal impermeability to *d*-penicillamine-cystine disulfide. This would provide a new type of drain on the body cystine pool.

Only 30–40 per cent of administered *d*-penicillamine can be recovered in the urine (153). Analytical tests have been simplified to monitor urinary excretion and adjust dosage (154). Since *d*-penicillamine may deplete iron

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stores and act weakly as an antipyridoxine, appropriate adjuvant therapy has been recommended. The action of phlorizin on amino acid reabsorption in the dog has also been re-examined (155).

Nephrotoxicity

The kidney is uniquely susceptible to the adverse action of many agents. Underlying factors probably include the massive blood flow per unit mass of tissue, the transport across the epithelium of each nephron of large volumes of fluid and variable, and in many instances, unknown amounts of many solutes (including drugs), and, finally, the peculiar consequences of the countercurrent mechanism which establishes across the profile of the kidney not only a wide spectrum for total osmolality, but also a related range of concentration for any agent dissolved in tubular urine, interstitial fluid, or intracellular water. In addition, the metabolic attributes of the cortex and medulla are respectively aerobic and anaerobic, a juxtaposition with almost endless implications for pathophysiological mechanisms. Drug toxicity has two ultimate facets of importance. The first relates to drug safety, and is not belabored further. The second relates to pharmacological mechanisms, many of which become evident only on intensive study of the unexpected or unanticipated drug reaction. Recent examples, even though rare, are cited to justify the thesis that nephrotoxicity should be a fertile source of renal physiology.

Schreiner & Maher (156) have provided an excellent summary and have amplified on the basis of their own clinical experience. Problems peculiar to antibiotics (157) and to the therapeutic problems superimposed by renal insufficiency (158) have also been reviewed.

Excretion of large volumes of inappropriately dilute urine, with either an implied or demonstrated refractoriness to the action of antidiuretic hormone, has been reported for several agents. Dextropropoxylene polyuria (159) has been analyzed in the isolated toad bladder system (160) and analogues have been explored for potential therapeutic applications. General anesthesia with methoxyflurane has been associated with polyuria with or without nitrogen retention (162), and refractoriness to antidiuretic hormone has been demonstrated (163). Reversible nephrogenic diabetes insipidus has also been attributed to demethylchlortetracycline (164). Systematic experiments have been undertaken on the functional attributes of the concentrating defect due to radiation (165).

The multiple defects of renal tubular transport, generally entitled Fanconi's syndrome, have been reported for at least ten cases (166, 167) in which the cause is clearly related to the ingestion of deteriorated tetracycline. The relationship has been documented in laboratory animals (168, 169) and should provide a basis for the further experimental analysis of this spectrum of tubular dysfunctions. Renal amino-aciduria has been produced by ascorbic acid deficiency (170) and a concentrating defect has been attributed to pyridoxine deficiency (171). Salicylate in large doses has been implicated as a

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cause of polyuria (172) and amino-aciduria (173, 174), although the data are inconclusive, particularly in terms of clearly establishing a renal site of action.

The question of analgesic nephritis remains perplexing. Quantitative studies on the excretion in the voided urine of renal tubular epithelial cells have provided a new approach. There is an acute increase in cell excretion following salicylate and variably after phenacetin (175), but normal values are reported after chronic administration (176).

Child & Dodds (177) have extensively studied the renal mechanisms underlying the excretion of the antibiotic cephaloridine and have provided a novel approach to the problem of nephrotoxicity. Although this agent undergoes net tubular reabsorption in a variety of mammals, in the chicken it is secreted by a probenecid-sensitive mechanism. Mammalian tubular secretion has not been excluded. Of particular current interest is the preliminary demonstration in monkeys and mice that cephaloridine nephrotoxicity can be abolished by prior administration of probenecid. Assuming that the latter agent acts at the level of tubular transport, its protective action suggests that the antibiotic's toxicity is associated with its presence at an intracellular site, presumably in the proximal nephron. The general thesis obviously warrants extensive exploration.

Amphotericin B is significantly nephrotoxic. Its effect on serum potassium level suggests a specific action on the cation pump of cellular membranes (178), a finding readily demonstrable at high concentrations in an *in vitro* erythrocyte system (179). The possibility of a specific action on tubular electrolyte transport is suggested by a patient who developed hypokalemia and excessive potassium excretion. In the isolated toad bladder, amphotericin B increases permeability to sodium and urea but not to water (180).

Drug Excretion

Weiner reviews renal mechanisms in Chapter 3. Nevertheless, it may be re-emphasized that the mechanism of nonionic diffusion in the renal tubule has a profound effect on the excretory rate of any drug that is reasonably lipid-soluble and that has an appropriate pK_a. Indeed, if the excretion of such drugs is studied over the full range of urinary pH, it is evident that simply changing urinary pH has a greater effect on the rate of drug excretion than do most other pharmacological maneuvers, such, for example, as competition for active tubular transport. Additional compounds whose excretion is pH-sensitive include amphetamine (181, 182), methylamphetamine (183), methylephedrine, and ephedrine (184). In addition, the excretion of urobilinogen and probably porphyrins is pH-sensitive, a finding with obvious diagnostic and potentially therapeutic significance (185). Indeed, the pH sensitivity of amphetamine is of sufficient magnitude that relatively small doses of acidifying salts might conceivably be important adjuncts in the management of poisoning. Admittedly, however, since urine is normally acid, augmentation of basic drug excretion by further acidification may be less

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dramatic and less practical than augmentation of acidic drug excretion by alkalinization.

The clinical problems, including the role of urine flow and pH in determining drug excretion, have been reviewed in relation to poisoning by salicylate (186, 187) and barbiturate (186, 188–191). Acetazolamide appears an effective agent for increasing phenobarbital excretion (192). In all instances examined thus far, clinical measurements have confirmed both the theoretical and experimental background concerning efficacy of urine flow and pH in altering excretion and consequently toxicity. Alkalinization should not be attempted for barbiturates whose pK_a makes excretion pH insensitive or whose rate of metabolic degradation makes renal excretion unimportant. It is emphasized, in the case of organic acids, that urinary pH of 7.5 or greater is required for significant or maximal effect on excretion. Reports describing alkalinization "up to" pH 6 or 6.5 are to be deplored. Since changes in acid-base balance may also redistribute the drug between extracellular fluid and cell water (probably including cerebrospinal fluid), further systematic studies are desirable.

As a separate and unrelated problem, the role of urinary pH has been analyzed with respect to antibiotic action on strains of various bacteria obtained from patients with urinary sepsis (193). In some instances the pH effect is quite remarkable; it warrants further study. Alkalinization has controlled urinary tract infection due to yeast (194). Further experience has been reported with ascorbic acid as a urinary acidifying agent (195).

Cardiac Glycosides

These agents are becoming of increasing importance in the analysis of transport phenomena. Of continuing interest is the possibility that the glycoside-sensitive adenosine triphosphatase may play a critical role in membrane transport and be a potential target of drug action. The inhibition of the renal transport of a wide variety of electrolytes and nonelectrolytes has previously been reported. Recent contributions are summarized. A biphasic action of ouabain has been reported for the toad bladder, first stimulating, then at higher doses, depressing sodium transport (196). In dogs whose cardiac function is sustained by mechanical means, sufficiently high doses of glycoside may be given to suppress the renal tubular transport of glucose (197). The simultaneous inhibition of sodium reabsorption raises the question of a linkage between sodium and glucose transport. In isolated frog kidney, sodium reabsorption may be markedly depressed by glycosides, an action that is almost completely reversed by perfusion with potassium-free solutions (198). The tubular secretion of the organic base N-methylnicotinamide is suppressed by ouabain in the chicken (199). Uric acid reabsorption in the rabbit is inhibited (200). By unilateral renal arterial infusion, the glycosides produced a disproportionate augmentation in the clearance of calcium and magnesium relative to sodium (201). An extensive analysis has also been reported

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(202) on the action of ouabain on the tubular reabsorption of other trace electrolytes, together with an analysis of their association with subcellular particles and their selective accumulation, particularly by the microsomal fraction. On the basis of electron microscopic localization, a ouabain-sensitive carrier having a high affinity for sodium has been postulated (203).

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