The hemodynamic effects of diuretics

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Diuretics are among the most heavily utilized therapeutic agents in the world. They have both systemic and renal hemodynamic effects which are of importance to clinicians as well as to basic scientits. Because of their utility in patients with edema formation and in hypertensives, much of our knowledge about this aspect of their actions has been obtained in various patient populations. However, an extensive literature has also developed with respect to their effects in normal man, as well as in the experimental animal. It is this experimental data base that will be explored in this review, including observations obtained in the author's laboratory.

SYSTEMIC HEMODYNAMIC EFFECTS OF DIURETICS

The majority of the experimental findings indicate that, as expected, the *acute* effects of diuretic administration on systemic hemodynamics are related to volume contraction [1-3]. Thus, whether one examines the data obtained in hypertensive [4-8] or edematous man [9-14], in normotensive and normal human subjects [15, 16] or animal models [17-20], *acute* depletion of the extracellular fluid (ECF) volume related to diuretic action results in reductions in blood pressure associated with reduced total blood and/or plasma volume, reduced cardiac output and, generally, increases in total peripheral resistance (tables 1 and 2) [4-20]. These hemodynamic effects of diuretics occur irrespective of the chemical category of the drug employed and regardless of whether the agent inhibited transport in the early distal convolution (e. g., the thiazides) or in the loop of Henle (ethacrynic acid, furosemide) (tables 1 and 2). Additionally, the fact that these effects were primarily related to volume depletion and not to some direct effect upon the vasculature is verified by studies in which their hemodynamic actions were obviated either by preventing the diuresis or by carefully replacing the urine volume and its electrolyte composition [18, 21]. While hypertensive patients, in general, responded to diuretics either acutely (table 1) or subacutely (table 2) with a decrease in cardiac output, some patients with congestive heart failure (CHF) showed either no change or an increase in this parameter [9, 14, 22]. Especially in the case of the patients described by Wilson and coworkers, this may have been related to the fact that, over several days, enough diuresis had occurred to allow the patients' cardiac function to achieve a more favorable position on Starling's curve [22]. However, Diksit et al. found an improvement in cardiac function following intravenous furosemide administration even before diuresis occurred, which they attributed to an acute venodilatory effect of the drug [9].

However, when one evaluates the data obtained following long-term diuretic administration in the hypertensive population, it is clear that, although blood pressure is generally maintained at its new (lower) level, the mechanisms by which this blood pressure lowering effect of diuretics occurs is apparently no longer related primarily or entirely to ECF volume contraction [23, 25-38] (tables 2 and 3). In fact, exactly what the mechanism(s) is (are) which explain this phenomenon remain largely unknown [39]. Thus, Villareal and his colleagues [5], Wilson and coworkers [22] and Gifford et al. [40] have documented a gradual return of plasma (blood) volume towards normal (fig. 1), whereas a persistent effect of the diuretics on blood pressure was observed. Accordingly, it has been postulated that the chronic hypotensive effect of diuretics is related to the development of a fall in total peripheral resistance, mediated by some as yet unknown mechanism or mechanisms [1, 2, 39]. Additionally, it is clear that vigorous acute diuresis in the hypertensive may lead to so great a stimulation of the renina-angiotensin system that the beneficial effects of diuretics on blood pressure may be canceled or even overridden [30, 33, 41]. Thus, in patients chronically treated with diuretics, the initial response of the renin-angiotensin system to volume depletion appears to moderate as treatment continues and as plasma volume returns to or toward control levels (fig. 1). Alter-

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Table I. The acute effects of diuretics on systemic hemodynamics[a]

Study No.	Experimental Subjects	Drug/Dose/Route	Results									Author (Ref.)
			PV/BV	BP	CO	CVP	RAP	TPR	PCWP	PAP	LVFP	LAP	
A) Studies in Man													
1.	Hypertensive patients (n = 2)	CTZ, 500 mg I.V.	↓	↓	↓			↑					Dustan et al.[4]
2.	Hypertensive patients (n = 12)	CTZ, 500 mg I.V.		↓	↓			↑					Villarreal et al[5]
3.	Hypertensive patients (n = 17)	F, 100-200 mg I.V.	↓	↓	↓	↓							Davidov et al.[6]
4.	Hypertensive patients (n = 9) Patients with mild heart disease (n = 5)	F, 80 mg I.V.			(↓)[b]		↓		↓	↓			Hesse et al[7]
5.	Hypertensive patients (n = 6)	ECA, 45-90 mg I.V.			↓		↓	↑					Nash et al.[8]
	Normotensive subjects (n = 3)				↔		↔	↔					
6.	Patients with CHF, acute MI (n = 20)	F, 45-90 mg I.V.		↔	↔		↓				↓		Dikshit et al.[9]
7.	Patients with CHF, acute MI (n = 35)	F, 80 mg I.V.		↓		↓				↓	↓		Tattersfield et al.[10]
8.	Patients with CHF, acute MI (n = 15)	F, 40 mg I.V.		↓	↓			↑	↓				Kiely et al.[11]
9.	Patients with increased LAP (n = 8)	F, 40 mg I.V.	↓		↓			↑		↓	↓	↓	Lal et al.[12]
	Patients without increased LAP (n = 15)	F, 40 mg I.V.			↓			↑					
10.	Patients with CHF, acute MI (n = 17)	F, 40 mg I.V.		↔	↓		↔	↑	↓	↓	↓		Mond et al.[13]
11.	Patients with CHF	ECA, 50-75 mg I.V.			↔					↓	↓		Scheinman et al.[14]
12.	Patients with cardiac disease, not in CHF (n = 24)	ECA, 100 mg via PA catheter	↓	↔	↓				↓			↓	Samet and Bernstein[15]
13.	Normotensive patients with heart disease (n = 5)	ECA, 1-2 mg/kg I.V.	↓	↓	↑	↓		↓					Ramírez and Abelmann[16]
	Normal male controls (n = 5)		↓	↑	↓	↓		↑					
B) Studies in experimental animals													
14.	Dogs	CTZ, 25 mg/kg I.V.		↔	↓	↓		↑					Lohmiller et al.[18]
15.	SHR Rats	HCTZ, 3 mg or 30 mg, s.c.		↓	↓			↑					Struyker-Boudier et al.[19]
		CTD, 10 mg/kg, i.a.		↓	↓			↑					
		F, 8 mg/kg, i.a.		↓	↓			↑					
16.	Rats	F, 1-5 mg/kg I.V.	↓	↔									Leenen et al.[20]

[a] Abbreviations: PV = Plasma Volume; BV = Blood Volume; BP = Blood Pressure; CO = Cardiac Out;,CVP = Central Venous Pressure; RAP = Right Atrial Press; TPR = Total Peripheral Resistanceñ PCWP = Pulmonary Capillary Wedge Pressure; PAP = Pulmonary Artery Pressure; LVFP = Left Ventricular Filling Pressure; LAP = Left Atrial Pressure; CTZ = Chlorothiazide; F = Furosemide; ECA = Ethacrynic Acid; HCTZ = Hydrochlorothiazide; CTD = Chlorthalidone; SHR = Spontaneously hypertensive rats.

[b] Mean values trended downward but did not reach statistical significance.

Table II. Subacute effects of diuretics on systemic hemodinamics [a]

Study No.	Experimental Subjects	Drug/Dose/Route	Results									Author (Ref.)
			PV/BV	BP	CO	CVP	RAP	TPR	PCWP	PAP	LVFP	LAP	
A) Studies in Man													
1.	Hypertensive patients (n = 9)	CTZ, 1000 mg BID p.o. × 4-6 days [b]	↓	↓	↓			↑					Dustan et al. [4]
2.	Hypertensive patients (n = 23)	CTZ, 1000 mg BID p.o. × days, then 500 mg BID × 1-2 weeks	↓	↓	↓			↑					Conway and Lauwers [23]
3.	Hypertensive patients (n = 7)	CTZ, 1.5 Gm/day p.o. × 3 days [c]	↓	↓	↓		↓						Frolich et al. [24]
4.	Hypertensive patients (n = 13)	CTZ, 500 mg BID p.o. × 2 days	↓	↓	↓			↑					Shah et al. [25]
5.	Hypertensive patients (n = 9)	CTZ, 500 mg p.o.q. 6 h × 8-13 days		↓	↑			↓					Villarreal et al. [5]
6.	Hypertensive patients	CTD, 50 mg/day p.o. × 1 week [c]		↓	↓								Dorhout Mees et al. [33]
7.	Patients with CHF (n = 13)	F alone or combined with thiazides or mwtolazone × 4-12 days [d]		↓	↑			↓	↓		↔ [e]		Wilson et al. [22]
8.	Hypertensive patients (n = 6)	ECA, 1.5 mg/kg/day × 4-7 days		↔	↓		↓	↑					Nash et al. [8]
	Normotensive subjects (n = 3)			↔	↔		↔	↔					

[a] Abbreviations as in table 1.
[b] The authors also noted a decrease in heart size.
[c] Decreased body weight of the patients was also noted.
[d] Diuretic drug dosages not given; patients were restudied when physical findings of CHF had disappeared.
[e] No change noted in echocardiographically determined left ventricular diastolic dimensions.

natively, it has been suggested that, with chronic therapy, while plasma renin activity may remain high, the aldosterone secretory response is limited [30, 42]. Furthermore, it should be mentioned that the hemodynamic response of the individual to diuretic administration is very much dependent upon the pre-existent sodium balance and ECF volume status [43, 44]. Finally, Krishna and his colleagues [45, 46] have recently reemphasized the observation originally reported by Kaplan et al. [47] that diuretic-induced hypokalemia can raise the blood pressure, thus minimizing the antihypertensive effects of this class of drugs. The mechanism of this phenomenon could be related to the retention of sodium induced by potassium depletion [48].

In summary, then, with respect to the *systemic* hemodynamic effects of diuretics, the initial response to these agents consists in a reduction in plasma and blood volume leading to a decline in cardiac output and accompanied by an increase in total peripheral resistance. In congestive heart failure patients, and in those few hypertensive patients in whom it has been measured, there is an associated fall in one or more of the following: pulmonary capillary wedge pressure, right atrial pressure, central venous pressure, pulmonary artery pressure, left atrial pressure, and/or left ventricular filling pressure (cf. tables 1 and 2). As time passes from the acute through the subacute to the chronic period of diuretic administration (tables 1-3), plasma (and blood) volume may either remain depressed or may normalize, despite which blood pressure usually remains reduced from pre-treatment levels. In addition, total peripheral resistance, originally elevated, falls as patients are treated for weeks to months.

RENAL HEMODYNAMIC EFFECTS OF DIURETICS

In addition to their actions on systemic hemodynamics, diuretic agents may substantially alter renal

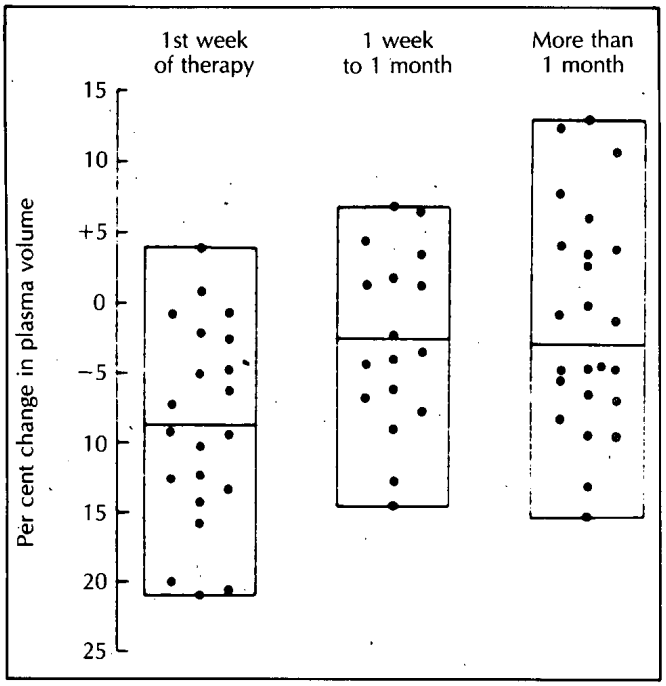

Fig. 1.—Individual (closed circles) and mean data (middle line of each bar) for the percentage changes in plasma volume in 25 hypertensive patients treated with thiazide diuretics as a function of time. Reproduced (with permission) from Gifford et al. (reference 40).

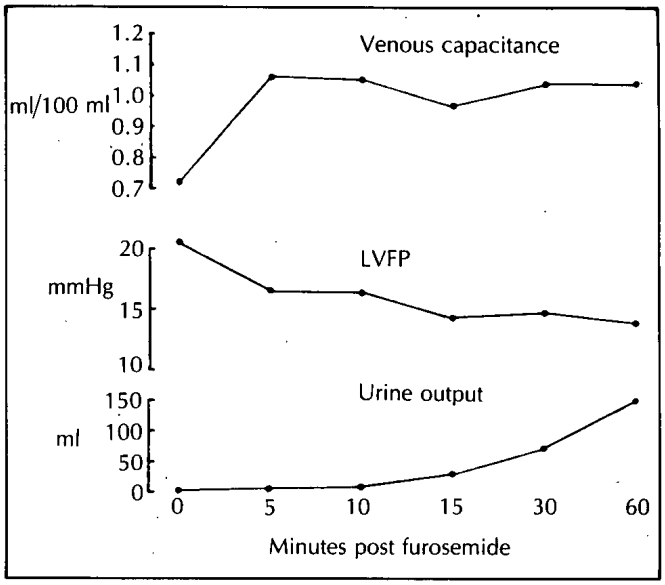

Fig. 2.—Temporal sequence of the alterations in mean left ventricular filling pressure, calf venous capacitance and urine output following the intravenous administration of furosemide to patients in congestive heart failure. Reproduced (with permission) from Dikshit et al. (reference 9).

hemodynamics[49]. The impact of such alterations could be quite significant for the following reasons: 1) Since filtered load of sodium is a function of glomerular filtration rate (GFR), variations in GFR will cause changes in the quantity of sodium delivered to the tubular system, and can thereby affect excretory rate. 2) Changes in renal blood flow, GFR and filtration fraction can modulate reabsorptive rate of the tubular system, thereby altering excretion. Thus, alterations in intrarenal hemodynamics can and do influence the efficacy of diuretic agents, affecting their utility in those disease states in which they are most widely employed: the hypertensive and the edematous patient.

The observations provided in table 4 summarize the data that are available with regard to the effects of the various classes of diuretics on renal hemodynamics. The agents are classified according to their site of action in the nephron, and then subdivided according to chemical type. It is important to recognize that the vast majority of the studies based upon which this table was constructed were acute investigations, there being rather few examinations of renal hemodynamic effects conducted in chronic models. Secondly, a significant proportion of the studies which form the basis of the information provided in table 4 were obtained in the experimental animal, in contrast to the heavy preponderance of human studies of the *systemic* effects of diuretics presented in tables 1-3.

Drugs that Primarily Inhibit Transport in the Proximal Nephron

The carbonic anhydrase inhibitors have their major site of action in the proximal nephron, which localization results from two factors: 1) They inhibit sodium reabsorption by interfering with the reclamation of bicarbonate from the tubular lumen[50] and 2) the majority (80-90 %) of bicarbonate "reabsorption" occurs in the proximal nephron[51]. Two of these drugs have received substantial investigative attention: acetazolamide, the prototypical carbonic anhydrase inhibitor, and benzolamide, an agent considered to have effects largely on luminal carbonic anhydrase and less influence on the cellular enzyme. In virtually all species studied (man, dog and rat), both drugs have been demonstrated to show a reasonably consistent effect on renal blood flow and GFR, consisting of reductions in these parameters of from 25 to 30 % in the former measurement and from 10 to 50 % in the latter[49]. However, because, when they occur, the decrements in renal blood flow and GFR have generally been proportional, there has been no consistent change in filtration fraction[49, 52].

The mechanism of the alteration in renal hemodynamics produced by the carbonic anhydrase inhibitors has been carefully studied. Investigations by

Table III. Chronic effects of diuretics on systemic hemodynamics [a]

Study No.	Experimental Subjects	Drug/Dose/Route	Results										Author (Ref.)
			PV/BV	BP	CO	CVP	RAP	TPR	PCWP	PAP	LVFP	LAP	
A) Studies in Man													
1.	Hypertensive patients (n = 15)	CTZ, 500 mg BID p.o. × 26-60 days [b]	↔	↓									Lauwers et al. [26]
2.	Hypertensive males (n = 19)	CTZ, 25-100 mg/day p.o. × 1 mo.	↔	↓				(↑) [c]					O'Connor et al. [28]
3.	Hypertensive patients (n = 13)	CTZ, 50 mg BID p.o. × 6-8 weeks	↓	↓	↑			↓					Shah et al. [25]
4.	Hypertensive patients (n = 23)	CTZ, 500 mg BID p.o. × 1 mo. (or longer)	↔	↓	↔			↓					Conway and Lauwers [2]
5.	Hypertensive patients (n = 13)	HCTZ, 50-100 mg/day p.o. × 1-6 mos.	↓	↓									Leth et al. [27]
6.	Hypertensive patients (n = 11)	HCTZ, 75 mg/day p.o. × 1-2 weeks and 3 mos. [d]	↓	↓									Hansen [29]
7.	Hypertensive patients (n = 13)	HCTZ, 100 mg/day p.o. × 1-12 weeks [e]	↓	↓				↔					Van Brummelen [30]
8.	Hypertensive male patients (n = 9)	HCTZ, 50 mg BID p.o. × 1 week-4 mos. [e]	↓	↓									Van Brummelen [31]
9.	Hypertensive patients (n = 23)	HCTZ, 50 mg/day; patients studied at 1 mo. and 1 year (results were same at both time periods)		↓	↓			↓					Vardan et al. [32]
10.	Hypertensive patients (n = 12)	CTD, 50 mg/day p.o. × 2 mos. [f]	↓	↓									Dorhout Mees et al. [33]
11.	Hypertensive patients (n = 17) (Diabetics with "borderline to moderate" hypertension)	CTD, 100 mg/day p.o. × 6 weeks [g]	↓	↓									Weidmann et al. [34]
12.	Hypertensive patients	CTZ, 25 ,g BID p.o., or CTD 100 mg/day × 6 mos.-2 years [e]	↓	↓									Tarazi et al. [35]
13.	Hypertensive male patients (n = 38)	CTD, 100 mg q.o.d. (n = 6), or polythiazide, 1 mg q.o.d. (n 4 7), or HCTZ, 50 mg BID (n = 15), × 8 mos.	↓	↓				↓					Lund-Johansen [36]
14.	Hypertensive patients (n = 5)	F, 40-80 QID × several days to weeks	↓	↓									Dustan et al. [37]
15.	Edematous, mildly hypertensive patients	F, 120-200 mg and 100 mg spironolactone p.o. daily × 15-20 days [h]	↔		↓		↓	↓					Niarchos and Magrini [38]

[a] Abbreviations as in table 1.
[b] The investigators also reported decreased total body water but no change in ECF volume or total exchangeable sodium.
[c] Measured renal vascular resistance; found no change in RPF or GFR.
[d] Body weight was decreased at 2 weeks but returned to pre-treatment levels at 3 mos., while BP was reduced at both time periods.
[e] PRA increased.
[f] Body weight reported as decreased at both 1 week and 2 mo. time periods (see also table 2); BP decreased more greatly at 2 mo.
[g] Both PRA and aldosterone reported as increased.
[h] Since body weight fell but neither PV nor total BP decreased, the authors presumed that interstitial volume declined.

Table IV. Renal hemodynamic effects of diuretic agents categorized by nephron site of action

Drug Category	Effect on Renal Blood/ Plasma Flow	Effect on Glomerular Filtration Rate	Effect on Filtration Fraction
A) Drugs that primarily inhibit transport in the proximal nephron:			
1. Carbonic anhydrase inhibitors	Reduce renal blood flow or nephron plasma flow by one fourth to one third that of control levels	Reduce GFR by -10-50 %	No change
B) Drugs that primarily inhibit transport in the loop of Henle:			
1. Sulfonamide Derivatives (furosemide, bumetanide, piretanide)	Increase (by -25-50 %) or no change	No change	Unchanged or decreased
2. Ethacrynic Acid	Increase (by -25-50 %) or no change	No change	Unchanged or decreased
3. Mannitol	Increase	No change	?
4. Mercurials	No change	No change	No change
5. Indacrinone	Decreased [a]	No change	?
C) Drugs that primarily inhibit transport in the early distal convoluted tubule:			
1. Thiazides	No change	No change or decreased	No change or decreased
2. Metolazone	No change	No change	No change
3. Indapamide	No change (or an increase) [b]		
D) Drugs that act primarily on the late distal convolution and collecting duct ("potassium sparing" agents):			
1. Spironolactone	No change	No change	No change
2. Triamterene	No change [c]	No change [c]	No change
3. Amiloride	No change	No change	No change

[a] Based on data from a single study, in the dog.
[b] Increased renal blood flow has been found only following the use of large doses of the drug in the dog.
[c] High doses of the drug (> 300/day) may reduce GFR and effective renal plasma flow.

Persson and Wright[53] and by Blantz and his colleagues[54, 55] have documented the fact that, by increasing distal delivery, these agents stimulate the tubuloglomerular feedback system, thereby reducing GFR. This system, originally described by Thurau and his associates[56], functions by sensing some component of flow past the macula densa area of the distal nephron. Thus, as either distal tubular flow rate or sodium or chloride concentration or content (or all of these) increase, single nephron plasma flow and GFR are reduced, probably as a consequence of the intrarenal release of angiotensin II and subsequent vasoconstriction[54, 55]. While it is clear from the data provided earlier in this chapter that volume contraction per se can also contribute to reductions in GFR, the latter phenomenon could not have accounted for the findings obtained in the studies of tubuloglomerular feedback just described. In the latter experiments, either volume depletion was not allowed to occur, or the changes occurred, temporally, prior to any significant diuresis[53-55].

An additional consideration with respect to the effects of diuretics on renal hemodynamics has to do with potential diuretic-induced alterations in the intrarenal distribution of renal blood flow. The possible importance of shifts in blood flow to cortical or to juxtamedullary nephrons on urinary sodium excretion rates was originally suggested by two kinds of evidence. First, in various experimental circumstances, electrolyte excretion could be modified either with or without an associated change in total RBF, but accompanied by changes in the distribution of blood flow within the kidney[57-59]. Second, cortical nephrons have short loops of Henle and lower filtration rates than do deep nephrons which have long loops and higher filtration rates[60, 61], suggesting that the latter may be salt-retaining while the former could have a lesser capacity for sodium reabsorption.

Indeed, in the studies reported by Barger[59], and by Earley and Friedler[57], natriuresis due to volume expansion was accompanied by a redistribution of blood flow to the superficial cortex. Therefore, even though the carbonic anhydrase inhibitors decreased total blood flow, the natriuresis they induced could be related, at least theoretically, to an effect of the drug to shift blood flow to the cortical regions of the kidney. This hypothesis has been tested with the finding that acetazolamide had only minor effects on renal blood flow distribution[52].

Drugs that Primarily Inhibit Transport in the Loop of Henle

1. *The Sulfonamide Diuretics*

The sulfonamide derivatives, furosemide, bumetanide and piretanide have been extensively studied as regards their effects on renal hemodynamics. In many (but not all) studies, these agents cause an increase in renal blood (and/or plasma) flow of from 25 to 50 % unassociated with any consistent alteration in GFR[49] (table 4). Whether the drugs caused an increase or no change in renal blood flow appears to depend importantly on the study design. When fluid and electrolyte losses were not replaced, enhacement of renal blood flow was les likely[49]. When renal blood flow did increase, it appeared to do so by virtue of a fall in renal vascular resistance[62, 63], and there were usually no changes in filtration fraction, although decreases have been reported when renal blood flow rose and GFR did not change[49]. Furthermore, study of the effects of the sulfonamide drugs on intrarenal blood flow distribution identified no consistent shift of renal perfusion to superficial cortical nephrons[52, 64, 65].

Examination of the effects of this group of agents on tubuloglomerular feedback has been extensive[49]. All three drugs can be shown to interfere with the tubuloglomerular system which is involved with GFR autoregulation. These agents ar believed to interfere with tubuloglomerular feedback because of their ability to inhibit transport in the loop, thus reducing absorption across the macula densa cells[66]. Therefore, instead of a decline occurring in single nephron filtration rate as would be expected from an increase in distal tubular flow, no such decrease occurs.

The sulfonamide drugs have been widely studied to determine if their renal hemodynamic effects are, at least in part, the result of interactions with the synthesis of the prostaglandins or with the functional effects of this group of eicosanoids. Because the prostaglandins can themselves cause an increase in renal blood flow[49], and because furosemide administration can lead to a stimulation of prostaglandin synthesis[67-69], the possibility that the renal hemodynamic effects of the drug might be modulated by the prostaglandins was evaluated[70]. By inhibiting prostaglandin synthetase, they were able to show that although the capacity of furosemide to increase renal blood flow was dramatically reduced, this hemodynamic alteration did not interfere with the natriuretic properties of the drug[70]. This conclusion regarding furosemide was shared by Ayano et al.[71] and by Bailie et al.[72]. While the inhibition of prostaglandin synthetase likewise appears to obviate the increase in renal blood flow caused by bumetanide, the results differ in that with the latter drug, there is also a decrease in its natriuretic activity in the dog[73, 74]. Interference by indomethacin with the natriuretic potency of bumetanide has also been reported in man[75].

One final consideration with respect to the sulfonamide diuretics has to do with the facts that these drugs stimulate prostaglanding synthesis (vide supra) and that the prostaglandins can themselves stimulate renin production[49]. Thus, the diuretics might stimulate plasma renin activity irrespective of their effects on ECF volume.

In summary, the sulfonamide derivative loop of Henle agents tend to increase renal blood flow, especially if ECF volume contraction is avoided. When volume depletion is allowed to occur, however, a fall in renal blood flow may be noted. The increase in renal blood flow, when it occurs, is associated with an increase in prostaglandin synthesis and can be obviated by inhibition of prostaglandin synthetase, suggesting that the renal blood flow effect is mediated, as least in part, by prostaglandin-promoted vasodilatation. An important mechanism also is the interruption of the tubuloglomerular feedback mechanism which would ordinarily cause SNGFR to fall. It is postulated that the mechanism of the diuretic effect on tubuloglomerular feedback is mediated by an inhibition of transport across the macula densa cells. In general, the sulfonamide drugs do not alter GFR, and, in general, interference with the renal blood flow effect of furosemide with indomethacin does not alter the drug's natriuretic potency, suggesting that the hemodynamic effects of the drug do not contribute in a major way to its natriuresis. However, the natriuretic effect of bumetanide does appear to be reduced by prostaglandin synthetase inhibition, suggesting an effect of the prostaglandin on either the hemodynamic or tubular actions of the drug (or both). Thus far, however, the consensus of opinion favors the former, rather than the latter mechanism.

2. *Ethacrynic Acid*

Ethacrynic acid, a substituted phenoxyacetic acid, is structurally dissimilar from the sulfonamide group. Like the sulfonamide derivatives, however, it may cause either an increase or no change in renal blood

flow, but generally does not alter GFR. Accordingly, filtration fraction either remains unchanged or falls (table 4). A reduction in filtration fraction, should it occur, would cause the forces favoring reabsorption to predominate and lead to increased rates of excretion of sodium and water.

The mechanism of the increase in renal blood flow caused by ethacrynic acid has been difficult to study in the rat model of tubuloglomerular feedback because the rat nephron is resistant to the effects of the drug. However, intraluminal perfusion of the loop of Henle with ethacrynic acid has been performed with the result that no effect of the drug on tubuloglomerular feedback could be detected[66]. Alternatively, it may be that the lack of any effect was related, instead, to a requirement of the drug to be complexed with cysteine before becoming active[76]. In the studies by McNay and Abe[77], ethacrynic acid increased total blood flow but did not preferentially redistribute intrarenal blood flow to the superficial cortex[52].

As with certain other loop of Henle agents (vide supra), ethacrynic acid has been reported to increase prostaglandin synthesis[78]. Furthermore, it appears that the prostaglandins participate in the mediation of the enhancement in renal blood flow due to ethacrynic acid-induced vasodilatation[79]. The possibility that ethacrynic acid may stimulate renin production through its actions on prostaglandins synthesis and independent of its effects on ECF volume, has not been studied directly. However, Imbs et al.[80] performed experiments in the dog, in which they documented an increase in renin secretion that was instantaneous, and occurred despite the prevention of salt and water loss.

3. *Mannitol*

Mannitol tends to increase renal blood flow without much change in GFR. Accordingly, filtration fraction should fall. The problem with concluding that this parameter does so is that, unfortunately, measurements of all of these variables in the same study have not been performed[49]. Although whole kidney GFR is unchanged by the drug, micropuncture studies performed in the rat reveal an increase in SNGFR in superficial nephrons[81, 82], which seems to be matched by an equivalent reduction in deep nephrons[82]. In his studies, Blantz[81] found that the SNGFR of superficial nephrons in the Munich-Wistar rat rose by about 30 % following the infusion of mannitol. This alteration was the result of two factors which combined to raise net ultrafiltration pressure: an increase in nephron plasma flow as well as a decline in afferent oncotic pressure.

McNay and Abe[77] have determined that blood flow in all zones of the kidney rises following mannitol infusion, reflecting an increase in total blood flow, and that there is no shift or redistribution of blood flow to any zone. While the increase in renal blood flow often seen with mannitol infusion is accompanied by an increase in the urinary excretion of prostaglandin E2[83], no studies have been performed demonstrating an increase of this material in the renal venous effluent, so that prostaglandin *production* cannot be assessed. Rather, the rise in urinary PGE2 could be a function of urine flow rate. Furthermore, the increase in renal blood flow is not interfered with by cyclooxygenase inhibitors unless the kidney is underperfused[84]. Based on these data, it seems unlikely that a significant proportion of the hemodynamic effects of mannitol are mediated by prostaglandins, except, perhaps, in specific and special circumstances. Mannitol also increases renin production[85] but whether this is an intrarenal effect, a prostaglandin effect, or is due to systemic factors, is currently unknown.

4. *The Mercurials*

In evaluating any potential hemodynamic effects of the mercurial diuretics, one must take into account the fact that many of the studies involving these agents utilized combination drugs which also contained one of the theophylline preparations. Except for rather transient alterations, therefore, the bulk of the data indicate that the mercurials have no consistent effect on renal blood flow or GFR[49].

5. *Indacrinone*

Unfortunately, measurement of renal blood flow following indacrinone administration has been performed only in a single study, in the dog. In these experiments, the drug reduced renal blood flow by about 15 %, but urinary losses were not replaced and volume contraction most likely occurred[86]. In several studies, however, in the rat and chimpanzee, no consistent alteration in GFR occurred[49]. The effect of the drug on renal hemodynamics has been studied after cyclooxygenase inhibition. These studies revealed that inhibition of prostaglandin synthesis had no effect on the response to indacrinone in the rat, but that when dogs were pre-treated with 4 mg/kg of indomethacin, renal blood flow was reduced by 17 %, in addition to which, the diuretic response to indacrinone was diminished[86].

Drugs that Primarily Inhibit Transport in the Early Distal Convoluted Tubule

1. *The Thiazides*

A voluminous literature has developed with respect to the thiazides. Careful review of the available data

reveals that the effects of drugs upon renal blood flow and GFR are importantly affected by several factors including: the ECF volume status at the time of drug administration; whether the urinary losses are replaced (thus averting volumen contraction); and the dose of the diuretic administered. Because these variables have not always been well-controlled in the numerous investigations that have been performed over the years, and probably also related to both species and biological variation, differing and sometimes conflicting results have been obtained [49]. However, the majority of the studies conducted in the dog and rat have shown that the thiazides cause no consistent change in renal blood flow, GFR or filtration fraction (table 4). However, in man, in many (but not all) studies, an acute reduction in GFR occurs, which value often, then, returns to baseline within a few hours. Furthermore, this decline in GFR is unaccompanied by a reduction in renal blood flow. Accordingly, therefore, there was an acute decrement in filtration fraction [48]. Although studies of glomerular hemodynamics have not been performed following administration of the thiazides, we do know that reductions in whole kidney GFR, when they occur, are associated with parallel declines in SNGFR [87]. While there have been no studies of glomerular hemodynamics in which either renal or nephron plasma flow has been measured, the data available suggest that, in those situations in which the thiazides cause renal hemodynamic changes, they do so by effecting postglomerular vasodilatation. Krause and his colleagues have reported that the fall in GFR following hydrochlorothiazide administration is associated with an increase in proximal tubular pressure [88]. In the latter study, nephron plasma flow was not measured, but whole kidney filtration rate declined in proportion to increased free-flow intratubular pressure, while intratubular stop flow pressure was unchanged after the injection of hydrochlorothiazide. Therefore, since pre-glomerular capillary dilatation is not suspected to play a role in the renal hemodynamic effects of the thiazides, one would not expect the prostaglandins to be involved. In studies performed in man, Favre et al. found that normal human subjects pre-treated with indomethacin demonstrated no evidence of any alteration in the potency of hydrochlorothiazide. Creatinine clearance bean to fall during the pre-treatment phase and continued to decline during diuretic administration [89]. Kirchner and his colleagues, utilizing simultaneous micropuncture and clearance techniques in the rat, found no effect of indomethacin on GFR during hydrochlorothiazide administration, but they did find that the fractional excretion of sodium and chloride was reduced by indomethacin pre-treatment [90]. In the chimpanzee, Fanelli and his coworkers could demonstrate no effects of the interaction between indomethacin and hydrochlorothiazide on either GFR or effective renal plasma flow regardless of which agent was administered first [91]. Thus, if in some instances, the inhibition of prostaglandin synthesis interferes with the natriuresis due to the thiazides [60, 90, 92, 93], it appears to do so by some process unrelated to alterations in renal hemodynamics [90].

2. *Metolazone*

Although, like the thiazides, metolazone is a sulfonamide derivative, its chemical structure places it in the category of a quinazoline compound. This drug, like the thiazides, is effective as a natriuretic agent primarily because of its ability to inhibit sodium transport in the early distal convolution. However, it has distinctive features that distinguish it from the thiazide group [94, 95]. As indicated in table 4, studies with metolazone have generally demonstrated that the drug causes no alterations in either renal blood (or plasma) flow, GFR or filtration fraction. In the majority of the studies performed in the dog and man, urinary losses were replaced [49], which may account, in part, for the lack of any reduction in GFR. Metolazone, likewise, causes no changes in intrarenal blood flow distribution [52].

3. *Indapamide*

Another sulfonamide agent, this drug differs from the thiazides in that it is an indole derivative [96]. In the majority of the studies, both acute and chronic, in which its actions have been examined in the experimental animal and in man, no consistent effect on renal hemodynamics has been discovered [49]. When the drug has been given in high dosage, a reduction in GFR has been noted [97-99], but in an occasional study [97], especially in hypertensive patients [100, 101], a beneficial effect on GFR has been reported (perhaps related to the control of blood pressure, per se). As is the case with the thiazides, indapamide stimulates the renin-angiotensin system [102-104]. In the study by Weidmann et al. [104], the drug caused substantial increases in plasma renin levels without any significant alteration either in blood volume or total exchangeable sodium. These observations suggest that, as described above, some other pathway leading to stimulation of the renin-angiotensin-aldosterone axis is causative. An obvious possibility is the enhancement of prostaglandin synthesis leading to an increase in renin production (vide supra). Grose et al. have shown that indapamide, like the thiazides and furosemide, can cause the stimulation of prostaglandin synthesis *in vitro* [105], while LeBel and coworkers have reported a simultaneous increase in urinary PGE2 and plasma renin activity following indapamide [106]. While these data support the thesis that the prostaglandins may be involved, observations regarding *in*

vivo prostaglandin synthesis in this experimental circumstance have not been reported. Weidmann's study [104] ruled out alterations in adrenergic activity as etiologic.

Drugs that Act Primarily in the Late Distal Convolution and Collecting Duct ("Potassium-Sparing" Agents)

1. *Spironolactone*
2. *Triamterene*
3. *Amiloride*

Because these are so few observations concerning the renal hemodynamic effects of this group of agents, they will be considered together. Spironolactone's effects on renal hemodynamics have been difficult to critically assess, because the drug or its metabolites can interfere with the colorimetric determination of creatinine [107]. Both indomethacin and aspirin pre-treatment can interfere with or obviate the diuretic effect of spironolactone [108-111], while the drug can increase the excretion of prostaglandin E2 [68]. However, spironolactone and an *in vivo* and *in vitro* competitive inhibitor of prostaglandin synthetase have been reported to exhibit similar properties in increasing urinary flow rate and in decreasing prostaglandin metabolite excretion in the rat [112]. Accordingly, it has been suggested that they may have related mechanisms of action [112]. At the moment, these conflicting observations regarding the interaction of spironolactone with the prostaglandin system cannot be resolved. However, because measurements of renal hemodynamics were generally not performed in these studies, it is impossible to know whether the findings obtained were related to glomerular or tubular effects, or both.

The effects of triamterene on renal hemodynamics have been studied only infrequently, and in these studies, the experimental subject was either normal man or patients with edema [113, 114] or non-cardiac medical problems [115]. Because the drug can cause reductions in cardiac output [114, 115], its effects, in high dosages, to decrease both GFR and effective renal plasma flow [113] could well have resulted from systemic rather than intrarenal hemodynamic alterations. An interesting and potentially clinically important series of interactions have been reported between triamterene and the cyclooxygenase inhibitors [89, 116-118]. First of all, Favre and his coworkers [89, 116, 117] and Olsen [118] have reported that triamterene is a potent stimulator of prostaglandin synthesis. Second, cases of acute renal failure have been reported when indomethacin has been administered to normal subjects who are simultaneously receiving triamterene [89, 117].

In the study by Favre in normal subjects, triamterene had no significant natriuretic effect, yet the drug stimulated renin and aldosterone secretion, and caused a 2-to 4-fold increase in the urinary excretion rate of PGE2 and PGF2α [116]. Because of their previous experience with the combined administration of the two drugs [117], the authors did not challenge their subjects by adding indomethacin. Since the administration of triamterene resulted in elevations in plasma renin activity and urinary aldosterone in the absence of volume depletion, and since urinary prostaglandin excretion rose despite the lack of an increase in urine sodium excretion, it is tempting to conclude that the renin and aldosterone effects of the drug are mediated by increase prostaglandin synthesis. While the exact nature of the relationship between the two drugs remains unknown, its seems reasonable to postulate the following sequence of events: triamterene may induce a situation in which renal perfusion is dependent upon or at least related to an increased level of prostaglandins, counteracting an increased secretion of renin. Under these circumstances, interference with prostaglandin production could tip the balance toward vasoconstrictor forces, resulting in severely compromised renal perfusion and, subsequently, dramatic reductions in GFR [119].

Nether in the experimental animal nor in man does amiloride cause any alterations in effective renal plasma flow or in GFR unless the drug, over time, induces volume depletion [49]. As is the case with the other two potassium sparing agents, amiloride stimulates plasma renin activity and urinary aldosterone excretion [89, 116]. This is most likely a consequence of its natriuretic effect, since urinary prostaglandin excretion was not increased by the administration of the drug [89 116]. At this writing, interactions of amiloride and inhibitors of cyclooxygenase have not been reported.

Tubular Transport Consequences of Diuretic-Induced Hemodynamic Effects

The systemic and intrarenal hemodynamic consequences of duretic administration appear to influence tubular fluid and electrolyte transport and, therefore, both natriuresis and diuresis, by two major mechanisms; 1) effects of ECF volume changes, and 2) alterations in GFR. Thus, both ECF volume contraction and declines in GFR limit diuretic effectiveness. Furthermore, volume contraction can, itself, lead to reductions in GFR. Both mechanisms, in addition to effects on filtered sodium load, as described above, can promote the reabsorption of salt and water both in proximal and distal nephron segments. The mechanism by which volume depletion does so

in the distal nephron includes stimulation of the renin-angiotensin-aldosterone axis with both direct transport effects related to mineralocorticoid mediated enhancement of sodium reabsorption and, indirectly, associated with increases in filtration fraction. The exact details of the enhancement of proximal reabsorption are unclear. Possibilities include disruption of glomerulotubular balance, alterations in physical (Starling's) forces controlling reabsorption (for example, increased filtration fraction) and, perhaps, the direct consequence of the effect of angiotensin on proximal reabsorption [120, 121]. In addition to the effect of volume depletion, the decline in GFR seen with the administration of certain diuretic agents may result from direct effects of the diuretics to cause vasoconstriction, interference with tubuloglomerular feedback mechanisms (as described extensively above), and. perhaps in some cases, alterations in the coefficient of ultrafiltration related to volume depletion itself [122, 123].

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