CHAPTER XI

Excretion of Sodium and Other Strong Electrolytes

FLUID COMPARTMENTS OF THE BODY

In previous chapters emphasis has been placed chiefly on the excretion of waste products or foreign substances which are destined to be completely removed from the body, or on substances, such as glucose, for which the kidneys constitute a barrier preventing wasteful excretion. As we turn to the consideration of electrolytes, emphasis must be redirected from processes of excretion to processes of conservation and to the specific role of the kidneys in the regulation of the composition and volume of the body fluids.

Water is the chief constituent of the blood, body fluids, and tissues, and in reptiles, birds, and mammals the kidney, supplemented by the thirst mechanism, is the chief effector organ that regulates the concentration of water in the body by virtue of its capacity to excrete greater or lesser quantities of this substance.

The most fundamental consideration in this connection is the supposition that water, after distribution in the circulating plasma, moves freely into all tissues of the body and that, under conditions of equilibrium, it is distributed in such a manner that the vapor pressure (or osmotic pressure) of all tissues and internal body fluids is the same, except in so far as a difference may be maintained dynamically by hydrostatic pressure or tissue tension.

The digestive secretion of water is itself of a considerable order

of magnitude, as is shown by Gamble's[736] estimates quoted in table IV.

TABLE IV

Approximate 24-hour Quantities of Digestive Secretions

Blood plasma volume	3500 cc
Saliva	1500 cc.
Gastric secretion	2500 cc.
Bile	500 cc.
Pancreatic juice	700 cc.
Intestinal secretions	3000 cc
	8200 cc.

However, in most discussions of 'body water' these digestive secretions need not be considered, since no large quantity of fluid is present in the digestive tract at any one moment. For most purposes, the cerebrospinal fluid and secretions of the serous cavities can also be neglected. We are then left with three nominal compartments: the plasma fluid; the interstitial fluid and the intracellular fluid; the plasma and interstitial fluid together comprising the extracellular fluid. Numerous methods, at best approximations, have been used in the past to estimate the volume of these compartments, but recent investigations center attention upon the dye T-1824 for the measurement of plasma volume, inulin for the measurement of extracellular fluid volume, and heavy water (D_2O) for the measurement of total body water. The intracellular fluid volume is calculated by difference.

Data on these three compartments in dog and man are given in table V.[122,749,751 1808,1809,1810,1811]

TABLE V

Distribution of Body Water in Per Cent of Body Weight

	Plasma volume	Extracellular *fluid volume*	Intracellular *fluid volume*	Total body water
Method	T-1824 space	Inulin space	By difference	D_2O space
Dog	5 54 *	19 4	43 6	63 0
Man	4 31 †	16 0	37 0	53.0 ‡

* Average figure cited from Hopper *et al*[1032]
† Average figure cited from Gibson and Evans[772]
‡ Average figure cited from Berger *et al*[122]

Osmotic work on water is apparently never done within the confines of the body. The lymph, tissue fluids, gastrointestinal secretions, bile, cerebrospinal fluid, etc., are all essentially isosmotic with the plasma. The only exceptions to this rule are the saliva and sweat, both of which are hypotonic. The hypotonicity of the sweat possesses the physiological advantage of conserving sodium chloride, and the hypotonicity of the saliva is perhaps related to the role of this secretion in the control of water ingestion through the mechanism of thirst.

That water is uniformly distributed throughout the body in relation to osmotic pressure has been said above to be a supposition rather than a demonstrated fact. If the salivary and sweat glands can elaborate a hypotonic secretion, it is conceivable that at least some cells could metabolically maintain a positive or negative gradient in osmotic pressure between the cytoplasm and the interstitial fluid Indeed, it seems that such is actually the case in those cells in the renal tubule responsible for the elaboration of a hypertonic urine. The available information indicates, however, that the distribution of water throughout the body is conditioned by osmotically active substances [690]

The mere fact of the uniform distribution of water does not place any limitation upon the actual volume of water in the body as a whole or in any one of the fluid compartments. We are concerned with two problems: first, the regulation of the composition of the body fluids, and, second, the regulation of their volume through variation in the absolute quantity of solute (primarily sodium with its attendant anions) retained in the body. Retention or loss of sodium will lead to retention or loss of water and hence to expansion or depletion of extracellular fluid, without offense to the isosmotic principle.

The plasma serves as a medium for the transportation of water and solutes to all the tissues, or, more properly speaking, to the interstitial fluid, which separates the vascular bed from the tissues. Within the plasma is the subsidiary compartment of the blood cells. Between the blood cells and the plasma only a limited interchange of solutes occurs, so that in effect it is the plasma which is directly presented to the kidneys and upon which these organs operate.

The interstitial fluid, lying between the plasma and the tissues, is in almost free communication with the plasma, since all the diffusable constituents of the latter pass readily through the capillary endothelium, and it is by virtue of this free communication that the plasma is enabled to maintain continuous interchange between different tissues. The great speed of interchange between the plasma and the extravascular fluid is indicated by the fact that, as measured with D_2O, 73 per cent of the water in the blood is exchanged with extravascular fluid every minute in the guinea pig,[662] while, as measured by sodium[24], 60 per cent of the plasma sodium and 13 per cent of the extravascular sodium are transferred in either direction per min.,[1437] while 64 per cent of the plasma chloride is exchanged with extravascular chloride. That filtration plays a more important part than diffusion in this exchange is indicated by the fact that sulphate and sodium are distributed at about the same rate.[1871]

Less than 30 min. are required from essentially complete distribution of tritiated water in the body water of rabbits, and approximately 1 hr. in man.[1661]

Interchange between interstitial fluid and plasma is limited in only one respect: the capillary endothelium is poorly permeable to the plasma proteins and, since these with their attendant base are osmotically active, a limitation is thereby placed upon the free migration of water. Where the hydrostatic pressure of the plasma in the capillary tends to force water out of the vascular bed, the osmotic pressure of the plasma proteins (oncotic pressure) tends to draw water back into the vascular bed; were the hydrostatic pressure reduced to zero all the water of the interstitial fluid would theoretically be drawn into the vascular tree by the protein oncotic pressure; or, in the face of resistance to expansion of the plasma (or vascular volume) this movement would proceed until developing hydrostatic pressure came to equal oncotic pressure. Hence, the movement of water and its ultimate distribution between the capillary and the interstitial fluid are determined by the balance between hydrostatic and oncotic pressure. This generalization was formulated many years ago by Starling and, although difficulties arise in applying it in special instances because

of other superimposed factors, its fundamental validity cannot be impugned.[1574]

It is particularly important to note that the circumstances are generally such that filtration of water occurs in the arterial end of the capillary and reabsorption in the venous end (fig. 53), and that

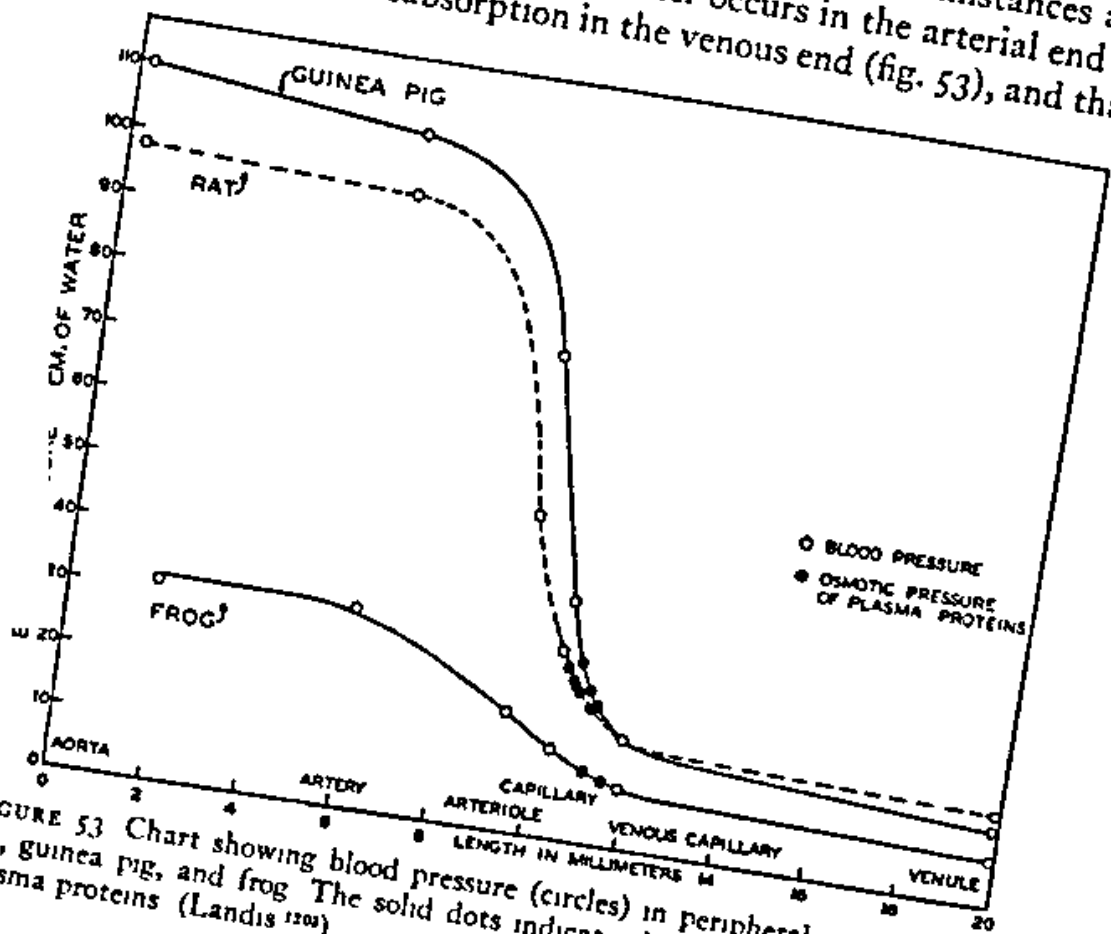

FIGURE 53 Chart showing blood pressure (circles) in peripheral vessels of the rat, guinea pig, and frog The solid dots indicate the osmotic pressure of the plasma proteins (Landis [1203])

the point of filtration equilibrium (hydrostatic = oncotic pressure) will shift toward or away from the venous end as capillary pressure is increased or decreased by dilatation or constriction in the arteriolar and metarteriolar bed. Although detailed knowledge — not available, it may be accepted that local vasomotor tone, under the control both of the nervous system and of humoral agents, plays an important part in determining the absolute quantity of interstitial fluid in any area. Thus, both the circulatory system and the kidneys are concerned in the regulation of the volume of interstitial fluid.

Beyond the interstitial fluid there is the compartment or compartments of the tissues. Between the tissues and the interstitial fluid there is such a *restricted interchange of electrolytes that for* most purposes they may be considered as isolated from each other except in respect to water itself. The restriction is applicable in two senses: first, in respect to the speed of interchange of cations and, second, in respect to their ultimate distribution. *The rate of* interchange of radioactive potassium between red cell and plasma is relatively slow and highly variable. Human red cells show 40 per cent exchange in 12 hr. *in vivo*, and the rate is even slower in the dog, while cat erythrocytes exchange 45 per cent of their potassium per hr.[1495] The erythrocyte exchange rate of potassium is lower in all mammals studied than is the exchange rate of sodium.[1875] When injected intravenously in the dog, about 9 hr. are *required for potassium and 24 hr. for sodium to reach equilibrium* or at least stable distribution throughout the body.[1230]

In the second sense, the ultimate distribution of cations is unique; the base of the tissues consists mostly of potassium and magnesium, there being little sodium in most tissues. That other electrolytes, however (chloride, bromide, thiocyanate), do penetrate some tissues to some degree is now generally accepted, the most recent evidence being derived from the so-called volume of distribution of radioactive isotopes as compared with the volume of distribution of inulin.[710, 1230, 1811] The data in table VI indicate that

TABLE VI

Gross Distribution of Sodium and Potassium in the Normal Dog[1230]

	Sodium mEq per liter of water	Potassium mEq per liter of water	Σ mEq per liter of water
Extracellular fluid	146	40	150
Intracellular fluid	35	115	150

about 20 per cent of the exchangeable sodium (exclusive of bone sodium) in the body is intracellular.

The nature of all the osmotically active particles within the cell that account for the intracellular osmotic effect is not known. The sum of the cations within the cell may not safely be used as an index of intracellular osmotic effect, despite the fact that they add

up to about the same molarity in the tissues as in the extracellular fluid. Redistribution of water between intracellular and extracellular fluids occurs in dogs treated with adrenal hormone or adrenalectomized, and the changes observed seem to be greater than can be explained in terms of electrolytes alone.

As has been said above, the regulation of the osmotic pressure of these compartments does not *per se* impose any limitation upon their respective volumes; so long as the vapor pressure of water is maintained uniformly, each compartment remains free to vary in volume. It must be concluded, therefore, that some regulation is superimposed upon the volumes of the plasma, interstitial fluid, and intracellular fluid independently of the regulation of their composition. There seems to be no better view than to suppose that in the tissues the number of osmotically active constituents is regulated by those as yet unknown processes which determine cell structure and other fixed cell characters, in a manner analogous to the regulation of cell volume in unicellular organisms. The regulation of the volume of the interstitial fluids and the plasma, on the other hand, is effected in part by the dynamic factors discussed above, by the regulation of the plasma protein concentration, and, no doubt, by tissue tension and other obscure factors, coupled with the active participation of the kidney.

The writer previously stated his belief that 'the kidney itself is not concerned with whether 2 or 5 liters of plasma are circulating in the vascular bed, so long as that plasma has the proper composition And this organ, in attempting to regulate the composition of the plasma, will frequently enlarge or reduce the volume of that fluid, and, indirectly, of the interstitial fluid, beyond physiological limits, and sometimes to fatal excess.' [1928] It is true that the kidney generally operates to regulate the composition of the plasma first, but the statement above must be corrected because in our present view the kidney is directly concerned in the regulation of the volume of the body fluids, perhaps chiefly the extracellular fluid, and thereby, if indirectly, the plasma.

ELECTROLYTE COMPOSITION OF THE PLASMA

The electrolyte pattern of the plasma is made up typically of the constitutents shown in table VII. The sum of the inorganic or fixed

bases is greater than the sum of the inorganic acids because about 22 mEq. of base are combined with the polyvalent protein anions or with organic acids. Sodium and potassium exist in a freely diffusable state in the plasma, as shown by the fact that their distribution between plasma and pleural, peritoneal, and subcutaneous

TABLE VII

Composition of Typical Human Plasma

(Gamble;[748] Margaria[128])

Base mEq/l.		Acid mEq/l.	
Na^+	142	Cl^-	103
K^+	5	HCO_3^-	27
Ca^+	5	$HPO_4^=$	2
Mg^+	3	$SO_4^=$	1
		Organic Pr^-	6
			16
			155
Total	155		

Osmotically equivalent NaCl solution, gm/100 cc. of water:
Men 0.9447, probable individual deviation: ±0.00495
Women: 0.9269, probable individual deviation: ±0.0059
Freezing point lowering (Δ)
Men: −0.553° C
Women: −0.543° C.

fluids is consonant with the Gibbs-Donnan equilibrium.[669] Calcium exists in the plasma in three forms, the first of which is a protein complex and not diffusable, the second is diffusable organic salts, and the third is ionic calcium. No data are available for magnesium. All the inorganic anions are believed to be freely diffusable.

The total electrolyte composition of the plasma is one of its most finely regulated features, despite the fact that the kidneys operate independently on the individual electrolytes and on water. Gamble and his associates[748] long ago suggested that the adjustments involved in the regulation of the acid-base balance of the blood have as their chief end the preservation of a constant total fixed base, but to the writer the terms 'fixed base' would seem to

indicate merely an arithmetic addition. The physiological desideratum is more probably either the ionic strength or the osmotic pressure of the plasma [1923] The former enters into and influences the reactivity of all electrolyte systems, and therefore of all physiological systems, and it is not difficult to imagine that the conservation of sodium, for example, is subordinate to this physi-

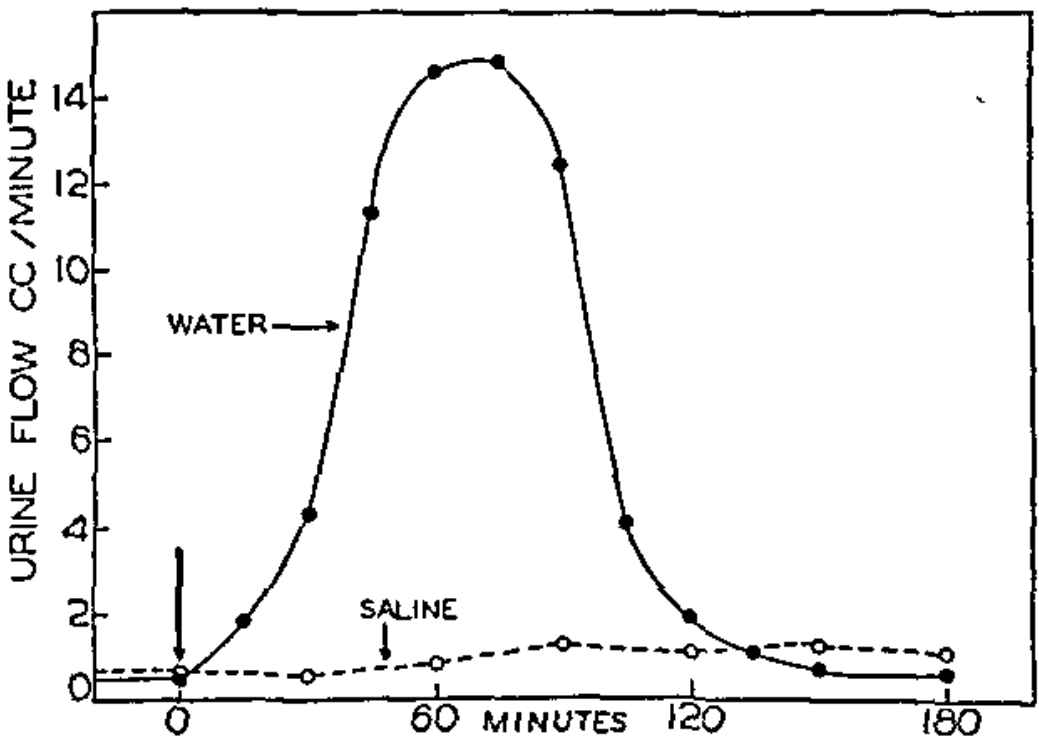

FIGURE 54. The diuretic response in man to 1000 cc. of water or, alternatively, 1000 cc of 1 per cent sodium chloride solution, ingested at zero time. In this experiment 92 per cent of the water was recovered within 180 min. (Smith [1926])

cal-chemical determinant. The evidence is clear that the conservation of water is immediately subordinated to the maintenance of a constant osmotic pressure in the plasma, but the evidence indicates that water conservation is both subsequent to and subordinate to the retention or rejection of sodium. Changes in osmotic pressure from the normal are corrected by the retention or rejection of water and not of sodium. From another point of view, it must be recognized that the conservation of sodium, the chief element in the fixed base and, thus, secondarily of water, is over the long run related or subordinated to the regulation of the extracellular fluid volume. So long as the osmotic pressure is preserved,

there is little immediate resistance to expansion of extracellular fluid volume because the regulatory mechanisms concerned with volume are more sluggish than are those which are concerned with composition. This difference is illustrated by the long-recognized difference in human response to the ingestion of water and of isotonic salt solution, as shown in figure 54. Water produces, after a short interval, a copious diuresis, the extra water excreted in a few hours being equal to the ingested volume. But, when isotonic salt solution is administered to man either *per os* or intravenously, little diuresis occurs; both the salt and water may be retained in the body for hours or days In the latter instance, there is little change in osmotic pressure of the plasma and the salt solution remains distributed throughout the extracellular fluid. On the other hand, if sodium is lost from the body, water will rapidly be sacrificed in the interests of constant osmotic pressure, and restitution of body fluid volume cannot be made until the salt deficit is corrected. Hence, in acute stresses (vomiting, diarrhea, excessive sweating, excessive salt loss or intake, partial renal failure, etc.), regulation of composition takes precedence over regulation of volume, leading to what Gamble called 'the mendicant position of the body fluids.' This mendicant position is largely a matter of rapidity and sequence of adjustment rather than physiological priority. The organism can apparently tolerate changes in volume better than changes in composition of the body fluids. But the relative importance of sodium *per se*, of fixed base, of ionic strength, of osmotic pressure, and of body fluid volume in this pattern of regulation cannot be assessed at the present time.

THE EXCRETION OF SODIUM

The excretion of electrolytes presents numerous complexities that do not enter into the excretion of non-electrolytes, for here we are dealing not with independent molecular species but with paired ions, the individual excretion of which is usually conditioned by some other obligation.

In view of the nature of strong electrolytes it is incorrect to treat any pair of ions, such as sodium and chloride, as though they existed in the plasma or urine in the form of a molecule. Yet because these two are frequently the predominant ions in both

plasma and urine, and because chloride always carries with it an equivalent quantity of cation, mostly sodium, we frequently but incorrectly speak of sodium chloride as a physiological entity. Because the analytical methods for chloride are simpler than those for sodium, nearly all investigations concerned with the excretion of sodium have, until the introduction of the flame photometer, followed the behavior of chloride, under the assumption that it is accompanied by an equivalent quantity of sodium. It is safer, where the nature of the cation is unknown, to designate the unidentified base as B^+.

The necessity of maintaining equivalent quantities of cations and anions in the blood and urine imposes a limitation upon the independent excretion of ions of any one charge. Within this limitation, considerable substitution of various ions is possible Interchangeability is particularly evident in the case of chloride and bicarbonate Loss of hydrochloric acid by vomiting may cause half the chloride to be replaced by bicarbonate and other anions. Vigorous exercise may replace half the bicarbonate with lactate. Increase in carbon dioxide tension may raise bicarbonate at the expense of chloride, while reduction of carbon dioxide tension may have the reverse effect Accumulation of keto acids during fasting or in diabetic acidosis may replace bicarbonate with the anions of these acids. Except as such substitution may cause a change in pH and carbon dioxide tension and thus lead to respiratory embarrassment, they apparently occasion no immediate distress. Indeed, chloride appears to play no specific role physiologically. By repeated centrifugation of blood and replacement of plasma by sulphate solution, Amberson, Nash, Mulder, and Binns [10] were able to reduce the plasma chloride in cats to 7 mM/liter, and to raise the plasma sulphate to 100 mEq/liter, while Hiatt,[102] by the repeated intravenous administration of sodium nitrate, was able to reduce the plasma chloride to 32.7 mEq/liter. In such animals the chloride concentration of the heart, stomach, lung, muscle, kidney, and other tissues and fluids, with the exception of the cerebrospinal fluid, was reduced proportionally below normal. From these studies, it appears that chloride is a physiologically indifferent ion. When sodium chloride is administered, the two ions may, over relatively short periods of time, be excreted at quite dif-

ferent rates because of readjustment of other anions and cations.[805]

Interchangeability is much less evident on the side of the cations, sodium, potassium, calcium, and magnesium; the normal concentrations of the last three are so small, relative to sodium, that permissible substitution extends through only a small absolute range.

PROXIMAL REABSORPTION OF SODIUM AND WATER

The data cited in chapter II show that chloride is present in the capsular fluid of the Amphibia in approximately the same concentration as in plasma, implying the complete ultrafiltration of both sodium and chloride. We may assume that the glomerular filtrate carries its full complement of these ions, subject only to the conditions of a Gibbs-Donnan equilibrium arising from the presence of protein on one side of the glomerular membranes.*

In the Amphibia,[2136] reabsorption of water occurs along the proximal tubule to yield a glucose (phlorizinized) U/P ratio of *c.*1.40, indicating that about 30 per cent of the water of the glomerular filtrate has been reabsorbed (see fig. 2); the facts that the chloride U/P ratio and the osmotic U/P ratio both remain at 1.0 (see fig. 1) show that sodium and chloride are reabsorbed *pari passu* with water. In the distal tubule, sodium and chloride are removed from the urine to yield a hypotonic urine essentially chloride-free.

The micropuncture studies of Walker, Bott, Oliver, and MacDowell[2131] (figs. 4 and 5) show that the situation is qualitatively similar in rats and guinea pigs Creatinine is concentrated to a U/P ratio of 2.5 half-way down the proximal tubule (the most

* In a membrane system permeable to electrolytes but impermeable to proteins, at equilibrium the electrolytes will be distributed unequally on the two sides. Where the system contains a number of diffusible monovalent ions and an ionized salt of protein, NaR, the Gibbs-Donnan equilibrium may be written in the form of an equality of ratios of ion concentration.

$$\frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[HCO_3^-]_1}{[HCO_3^-]_2} = \frac{[Na^+]_2}{[Na^+]_1} = \frac{[K^+]_2}{[K^+]_1}$$

For mammalian plasma and glomerular filtrate, the Donnan factor for chloride, $[Cl^-]_F/[Cl^-]_P$, and bicarbonate, $[HCO_3^-]_F/[HCO_3^-]_P$, may be taken as 1.02,[930] for sodium, $[Na^+]_F/[Na^+]_P$, as 0.95, and for potassium, $[K^+]_F/[K^+]_P$, as 0.90[663] at 6 gm. of protein per 100 cc. of plasma.

distal point available in the mammalian kidney), but the authors calculate that by the end of the proximal tubule this ratio would reach 5.0, which would mean that 80 per cent of the glomerular filtrate had been reabsorbed. Since the urine remains isosmotic with the plasma, it follows that as much sodium has been reabsorbed as water. For reasons not clear, the chloride U/P ratio rises early in the proximal tubule to 1.4 and remains at this value throughout the first half of its length.*

Final sodium chloride reabsorption, to make a sodium and chloride-free urine, apparently occurs in the distal tubule (or collecting ducts) of the mammals, as in the Amphibia. It is apparently also in the distal tubule (or collecting ducts) that final reabsorption of water occurs to yield a hypertonic urine.

The difficulty in speaking of a sodium or chloride 'threshold' lies in oversimplification † The excretion of sodium (and chloride) is conditioned by a number of factors such as filtration rate, plasma sodium concentration, the natriuretic effect of ADH, and possibly one or more actions of adrenal cortical hormones on the

* Walker *et al* suggest that the chloride U/P ratio rises to 1.4 because chloride replaces bicarbonate as the latter is reabsorbed from the tubular urine; this suggestion implies that bicarbonate (with sodium) is reabsorbed more rapidly than is sodium paired with chloride, and that bicarbonate reabsorption in the proximal tubule is complete. At best, however, assuming 110 mM. of chloride and 25 mM. of bicarbonate per liter in the glomerular filtrate, if chloride replaced all bicarbonate the final concentration of chloride would be 135 mM/liter, which, allowing for the Donnan effect, would give a U/P ratio of $(110 + 25)/110 \times 1.02$, or 1.25 The observed ratio of 1 4 must have some other explanation

† Various investigators have attempted to define a 'threshold' for plasma chloride, because the urine may at times be practically chloride (and sodium) free. Thus Aitken[87] observed that, when the plasma chloride in man is reduced below 95 mEq/liter, excretion is fairly constant at about 5 mg. of sodium chloride per hr Rehberg[168a] also found that, when the plasma chloride falls below 106 mEq/liter, excretion is small and essentially constant. At higher plasma levels he believed that excretion, which may be substantial, is markedly affected by the rate of urine formation, but the converse proposition, that the sodium chloride load of the urine may have affected urine flow in his experiments, must be considered MacKay and MacKay[138a] showed that essentially chloride-free urine is usually excreted by the rabbit at plasma chloride levels below 85 mEq/liter, although, on other occasions, chloride excretion at this or lower levels may be substantial, a circumstance they attributed to the simultaneous excretion of potassium Equally important is the fact that ammonia will carry chloride into the urine independently of sodium excretion.

tubular reabsorption of this ion, and a simple definition of 'threshold' is even less possible than in the case of glucose. The problem of how sodium excretion is regulated can be approached only by a detailed analysis of all the factors involved.

The first of these is sodium reabsorption in the proximal tubule, where the greater fraction of both sodium and water is reab-

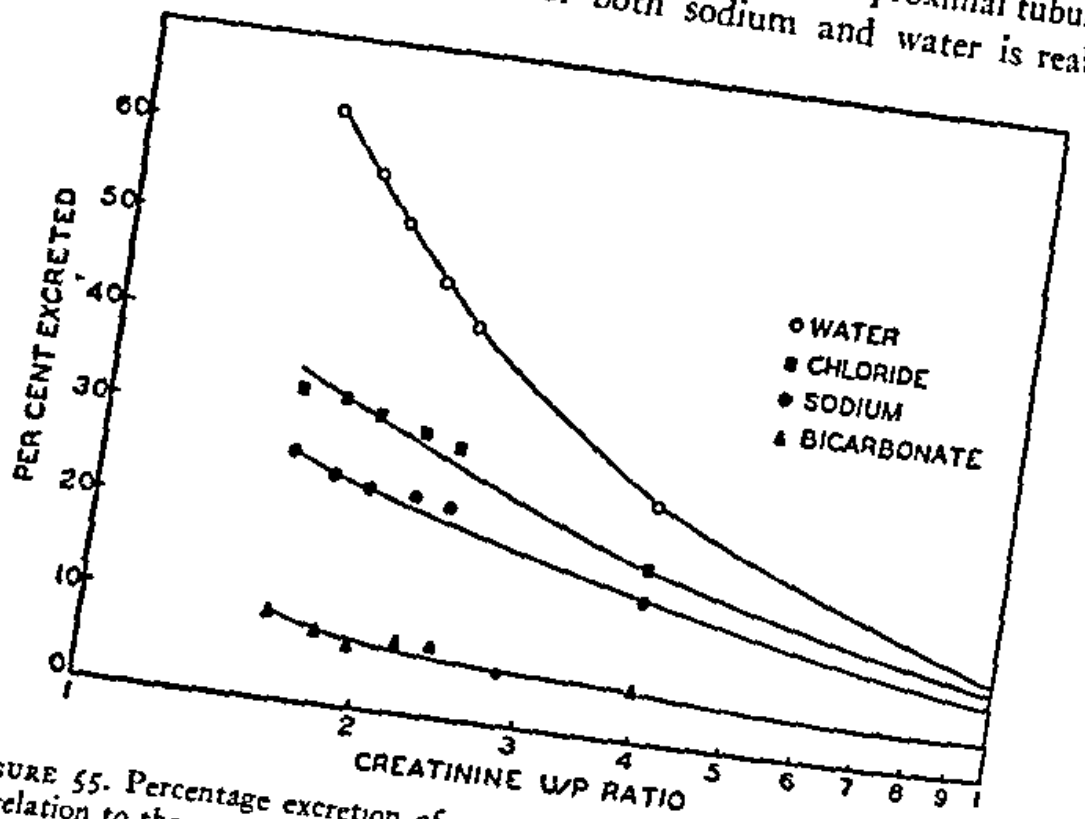

FIGURE 55. Percentage excretion of water, chloride, sodium, and bicarbonate in relation to the creatinine U/P ratio in a dog during osmotic (mannitol) diuresis. (Wesson and Anslow [171])

sorbed. Wesson, Anslow, and Smith [171, 172] have shown in the dog that, during osmotic diuresis induced by the intravenous infusion of hypertonic mannitol solutions, as much as 65 per cent of the water of the glomerular filtrate may be excreted in the urine at a time when only 13 to 27 per cent of the filtered sodium is excreted (fig. 55). Under the conditions of these experiments, the flow of urine is so great that any changes in composition of the urine effected by the distal tubule are relatively minor in magnitude, and the composition of the bladder urine can be taken to represent the composition of the tubular urine at the end of the thin limb.

The fact that much less sodium than water is swept out by osmotic diuresis shows, first, that the reabsorption of sodium in the proximal tubule is operationally independent of the reabsorption of water, and second, that sodium reabsorption is an active process rather than a process involving passive diffusion of sodium along with whatever water is reabsorbed. That sodium reabsorption is an active process is further demonstrated by the fact that sodium continues to be reabsorbed against a concentration gradient between urine and plasma of as much as 60 mEq/liter or more, so that the nominal sodium content of the reabsorbate (if all the reabsorbed sodium were dissolved in all the reabsorbed water) actually exceeds that of the plasma by 50 per cent or more.

Since the osmotic pressure of the urine closely approaches the osmotic pressure of the plasma during osmotic diuresis or deviates from it by being only slightly hypotonic, the authors conclude that the proximal reabsorbate is in the net isosmotic with the plasma.* The simplest explanation is that, as sodium and other constituents of the proximal tubular urine are reabsorbed, water diffuses back through the proximal tubule or thin limb to maintain an osmotic U/P ratio close to 1.0.

That osmotic diuresis causes decreased reabsorption of chloride has also been demonstrated by others Schou [1799] infused hypertonic sodium sulphate in anesthetized (urethane) rabbits, obtaining urine flows of 15 to 17 cc/min and creatinine U/P ratios of 1.5 or less, the lowest recorded figure being 1.2.† At a creatinine U/P ratio of 1.4 to 1.5, well over 50 per cent of the filtered chloride was excreted. Cisek and Holmes [281] have shown that chloride excretion increases *pari passu* with diuresis in the dog during the continuous intravenous administration of

* Correctly, one should refer again to the renal interstitial fluid rather than plasma, but for brevity we shall consider the interstitial fluid as invariably isosmotic with plasma

† Incidentally, it may be noted that there was marked increase in creatinine clearance and renal blood flow (as measured by a Rein thermostromuhr) in Schou's experiments, and a close correlation was observable between arterial pressure, renal blood flow, and filtration rate He calculates that the filtration fraction reached values exceeding 50 per cent, but in no case did the oncotic pressure of the postglomerular plasma exceed 66 per cent of the mean arterial pressure, i.e. a glomerular pressure of 66 per cent of the arterial pressure is adequate to effect the filtration of large quantities of fluid.

hypertonic sucrose, glucose, sorbitol, and urea,* the total chloride excreted being unrelated to the nature of the diuretic. They found that reabsorption of chloride is minimal at the peak of diuresis and is uninfluenced by pituitrin or desoxycorticosterone. Brodsky and Rapoport [266] have shown that osmotic diuresis in man, effected by glucose or mannitol, sweeps considerable sodium and chloride into the urine, *the effect again being unrelated to the nature of the osmotic diuretic.* Relman, Goodyer, and Peterson [1694] have shown that mannitol and glucose diuresis, induced simultaneously with copious water diuresis, increases sodium and chloride excretion. *The simplest interpretation here* is that osmotic diuresis sweeps sodium out of the proximal tubule faster than the distal tubule can handle it; this sodium appears in the urine irrespective of the rate of distal water reabsorption.

Wesson and Anslow [2171] attribute the decreased reabsorption of sodium during osmotic diuresis to dilution of sodium in the proximal tubule urine; as osmotic diuresis increases in magnitude, the retardation of passive water reabsorption effected by the osmotic diuretic lowers the concentration of sodium in the proximal urine and increases the concentration gradient between urine and plasma against which sodium reabsorption is occurring to a critical value, and thereby retards the reabsorptive process. They believe that, in any one experiment, this concentration difference approaches a critical value, despite marked variations in the absolute plasma and urine sodium concentrations, and that this critical value ranges in various experiments from 60 to 90 mEq/liter. The unreabsorbed sodium in turn contributes by its own osmotic action to retarding water reabsorption,† thus further promoting the excretion of water because, no matter what the proportions of sodium and mannitol in the urine, the latter remains isosmotic with the plasma.

The fact that a concentration gradient exerts a limiting action upon proximal sodium reabsorption is in marked contrast to the absence of such an effect in the distal system, where all except the

* The effect of urea appears to be comparable to that of other diuretics, if the load is large enough to establish an equal diuresis.

† The authors suggest that unreabsorbed urea may, by its osmotic action, retard the proximal reabsorption of water and contribute to the circumstance that only 85 per cent of the filtered sodium and water are normally reabsorbed in the proximal tubule

last trace of sodium may be removed from the urine. They infer that, in the proximal tubule, large quantities of sodium are normally reabsorbed against a small concentration gradient, a circumstance which permits the proximal tubule to reduce the gross bulk of the abundant glomerular filtrate and to concentrate, within certain osmotic limits, the waste products therein destined for excretion. In the distal segment, small quantities of sodium are reabsorbed against a much larger concentration gradient (as in the case of the proximal reabsorption of glucose), but from a much smaller quantity of fluid.

The fact that, by all the evidence, the urine delivered from the thin limb to the distal tubule * is isosmotic with plasma demands acceptance of the belief that some fraction of filtered sodium normally remains in the tubular urine at the end of the thin limb and hence is available for reabsorption by the distal tubule.† The size of this fraction depends upon the relative amount of sodium reabsorbed proximally. If we accept, from the evidence cited in the previous chapter, that about seven-eighths of the water of the filtrate is reabsorbed proximally and that one-eighth is available to the distal tubule for reabsorption, then we must accept that one-eighth of the sodium is also available for distal reabsorption.‡

So long as the fraction of sodium and water reabsorbed proximally remains large and fairly constant, changes in distal reabsorption will have but little effect upon the total reabsorption of either constituent. Two noteworthy consequences issue directly from this fact. As seen in the equation

$$P_{Na}C_F = T_{Na} + U_{Na}V \qquad (1)$$

* The use of the term distal tubule here and elsewhere does not exclude some sodium and water reabsorption by the collecting ducts.

† That nearly complete reabsorption of chloride can occur in the proximal tubule is shown by the chloride-free urine of the sculpin,[419] but that the U/P ratio of sodium is significantly below 1.0 can only be inferred from this fact. In any case, the urine is isosmotic with the plasma in the marine fishes, which

‡ The calculation neglects the osmotic pressure of urea and other less important solutes

the absolute amounts of both sodium and water reabsorbed will increase or decrease almost in direct proportion to the filtration rate, so long as $U_{Na}V$ is small in comparison with $P_{Na}C_F$, as it always is under normal conditions. Indeed $P_{Na}C_F$ and T_{Na} are normally so nearly equal that T_{Na} appears to vary in direct proportion to $P_{Na}C_F$.

Second, if we divide (1) by C_F,

(2)
$$P_{Na} = \frac{T_{Na}}{C_F} + \frac{U_{Na}V}{C_F}$$

and write $C_F = T_{H_2O} + V$

(3)
$$P_{Na} = \frac{T_{Na}}{T_{H_2O} + V} + \frac{U_{Na}V}{C_F}$$

i.e. the nominal concentration of sodium in the total reabsorbate T_{H_2O} will deviate from P_{Na} only in so far as U_{Na} or V is significantly large. Hence, in the overall operation of the kidneys, the composition of the plasma will undergo change as a result of urine excretion only in so far as V is significantly large and U_{Na} deviates from P_{Na}, which is to say, only in so far as sodium or water is preferentially excreted in the urine. This is, of course, self-evident, and yet failure to recognize the tautological pitfalls of equation (1) sometimes leads to semasiologic difficulties.*

With the proximal reabsorption of sodium an active process and that of water a passive process, one would expect the proximal tubular urine to be, at times at least, slightly hypotonic to the blood. Walker, Bott, Oliver, and MacDowell [2121] obtained a hypotonic urine from the proximal tubule of the rat in only 2 out of 21 instances, but their observations were made on unilaterally nephrectomized animals which were generally loaded with sucrose or saline, circumstances which might alter the conditions of proximal reabsorption. It is conceivable that, under some conditions, the proximal urine may be distinctly hypotonic. If such is the case, the present view affords an attractive explanation of the function of the thin segment in the loop of Henle. The older idea, that because this segment occurs only in the Classes (birds and mammals) where ADH promotes water reabsorption it is itself the locus of the formation of a concentrated urine and of osmotic work, has

* The R/P ratio of Hare *et al.*; [917] figures 2 and 3 of Mokotoff *et al.* [1449] on sodium reabsorption in patients in heart failure, the increased 'sodium reabsorption' reported in infants by Dean and McCance, [484] the correlation between $U_{Na}V$ and the 'tubular rejection fraction' of Green *et al.* [448]

never had strong appeal because the low epithelium of the thin limb does not, by contrast with the cuboidal cells of the distal tubule, seem cytologically constituted for such a function.* Perhaps the strongest argument against the formation of hypertonic urine in the thin segment is the fact that protein casts are never *found in this segment; casts first form in the ascending limb of the* distal tubule, with increasing precipitation in the distal convoluted tubules and collecting ducts In so far as cast formation is related to increasing concentration of protein, this circumstance indicates further water reabsorption in the distal system, which could scarcely be possible if the urine in the thin segment were already hypertonic to the plasma.

The present interpretation would be that the thin limb serves to promote osmotic equilibration by passive diffusion of water between tubular urine and plasma after the bulk of the sodium, etc., has been reabsorbed proximally.† Wesson, Anslow, and Smith [2173] accept the evolution of the thin segment as being related to the activity of ADH in promoting facultative water reabsorption (which they refer specifically to the distal tubule) and the capacity to excrete a hypertonic urine, but they see in the thin limb only an accessory adaptation facilitating the reduction to a minimum of the water load delivered to the distal tubule before final water and sodium reabsorption are effected. To deliver a variable excess of fluid having a variable osmotic pressure to this terminal segment would conceivably be disadvantageous to its precise operations in the critical retention of sodium and water, especially if either of these distal functions is itself limited by a critical rate

the present time.

† Shannon [1941] supposed, incorrectly we now believe, that all the sodium was reabsorbed in the proximal system and that a very dilute urine, equivalent to that excreted during water diuresis, was delivered to the distal tubule. The present evidence appears to controvert this view.

Mudge, Foulks, and Gilman [1488] have carried out similar studies of extreme osmotic diuresis in anesthetized (pentobarbital) dogs, using 50 per cent urea solutions instead of mannitol. Water balance was maintained by infusing sodium chloride solution at a rate commensurate with urine flow. These investigators confirm that at high rates of flow the urine becomes approximately isosmotic with the blood, indicating that under these conditions the distal system is incapable of altering the composition of the proximal urine significantly. The tubular reabsorbate is isosmotic and, since only small amounts of urea are reabsorbed, sodium salts provide the major osmotic constituent of the reabsorbate. Since urea contributes largely to the osmotic pressure of the tubular urine, it follows that the sodium concentration of the reabsorbate is greatly in excess of that in both the tubular urine and plasma. The existence of this sodium concentration gradient between the tubular urine and reabsorbate reaffirms the evidence that the proximal reabsorption of sodium is an active process. The authors accept that water is reabsorbed by passive diffusion to maintain the proximal osmotic U/P ratio at 1.0. In prolonged experiments the urine may become hypotonic to the plasma, as indicated by rough calculations from sodium chloride and urea concentrations The authors believe this reflects circumstances under which sodium and other osmotically active agents are reabsorbed more rapidly than water.

Where Wesson and Anslow [2171] believed that the proximal reabsorption of sodium was retarded by a limiting concentration difference between plasma and proximal urine of 60 to 90 mEq/liter (the figure varying in different experiments), Mudge *et al.* found that this concentration difference showed no apparent upper limit, ranging from 0 to 100 mEq/liter as diuresis increased, and varied widely in single experiments and from animal to animal. This concentration difference varies inversely with the filtration rate, indicating that, with lowered sodium loads, more complete reabsorption of sodium occurs even in the presence of isosmotic urine. The authors conclude that decreased sodium reabsorption occurs because of the continuous decrease in sodium concentration as each increment of the glomerular filtrate is reabsorbed along the prox-

imal tubule, a condition which only applies in the presence of an osmotic diuretic.

The administration of a mercurial diuretic at the height of urea diuresis further decreased the reabsorption of sodium, but did not alter the concentration difference between tubular urine and reabsorbate, indicating that mercurial diuretics decrease the functional capacity of the proximal tubule cells to transfer sodium without altering the fundamental mechanism of reabsorption.

Incidentally, Mudge *et al.* showed that osmotic diuresis does not cause the excretion of glucose even when 53 per cent of the filtrate is excreted in the urine, nor does it accelerate the excretion of bicarbonate or of phosphate if the plasma phosphate concentration does not increase. The reabsorption of these substances proceeds independently of the reabsorption of sodium and water.

TUBULAR REABSORPTIVE ACTIVITY

In any study of sodium excretion it must be recognized that the reabsorptive activity of the tubule (proximal or distal) may change in consequence of changes in the intrinsic activity of the tubule cells, of changes in the secretion of ADH or adrenal cortical hormones (ch. XII), or for other as yet unidentified reasons. Such changes in reabsorptive activity are commonly assumed to be present both in non-renal and renal disease but their evaluation at the present time presents many difficulties. Analysis of the problem can best be approached by reducing the number of variables to a minimum. It is known that the administration of isotonic saline or Locke's solution to the dog increases the filtration rate, presumably an effect related to the expansion of the extracellular fluid. Wesson, Anslow, Raisz, Bolomey, and Ladd [2172] have utilized the increase in filtration rate induced in this manner to examine the question of variability in sodium reabsorption. After the infusion of either saline or Locke's solution, the urine may have a diverse composition during various phases of the resulting diuresis, and protracted diuresis may therefore lead to significant and variable changes in plasma composition. To offset this factor, Wesson and his coworkers determined the urine pattern in preliminary tests, and then in subsequent experiments continuously infused

the animal at such a rate and with fluid of such a composition as to avoid any changes in the plasma electrolyte pattern, thus maintaining an expansion of extracellular fluid of 25 to 50 per cent for

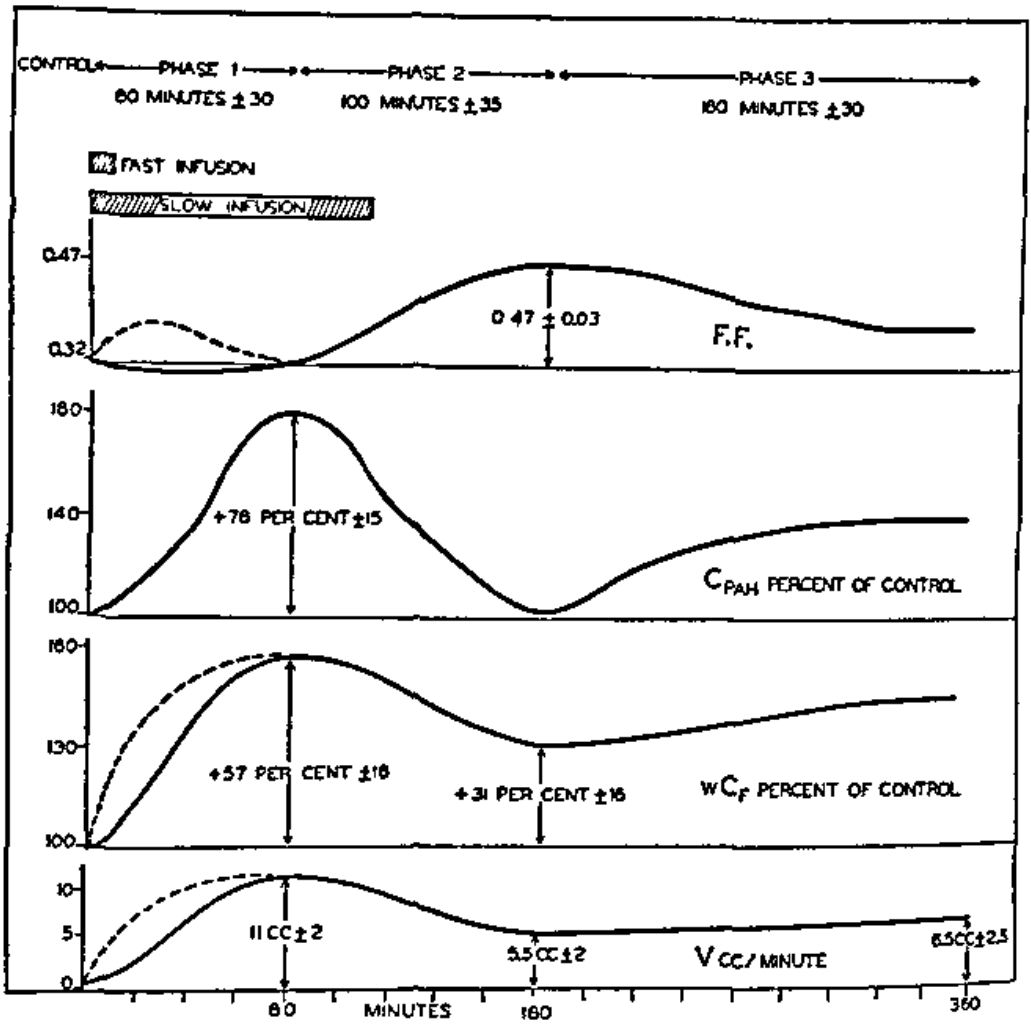

FIGURE 56. Average values for urine flow, filtration rate of water (wC_F), renal plasma flow, and filtration fraction following expansion of the extracellular fluid volume in 18 experiments on 6 normal dogs Numbers are means and ± mean deviations from the mean. Before averaging the individual curves, the time scales of the experiments on each animal were adjusted so that their inflections coincide with the average inflection times for all experiments (Wesson, Anslow, Raisz, Bolomey, and Ladd [2172])

6 to 8 hr. without change in composition, at least so far as the major electrolytes are concerned. Pitressin was also infused (20 milliunits/hr.) to promote to a maximal extent the reabsorption of water effected by this hormone.

These experiments reveal that the response of the dog to a sustained expansion of the extracellular fluid may be divided into

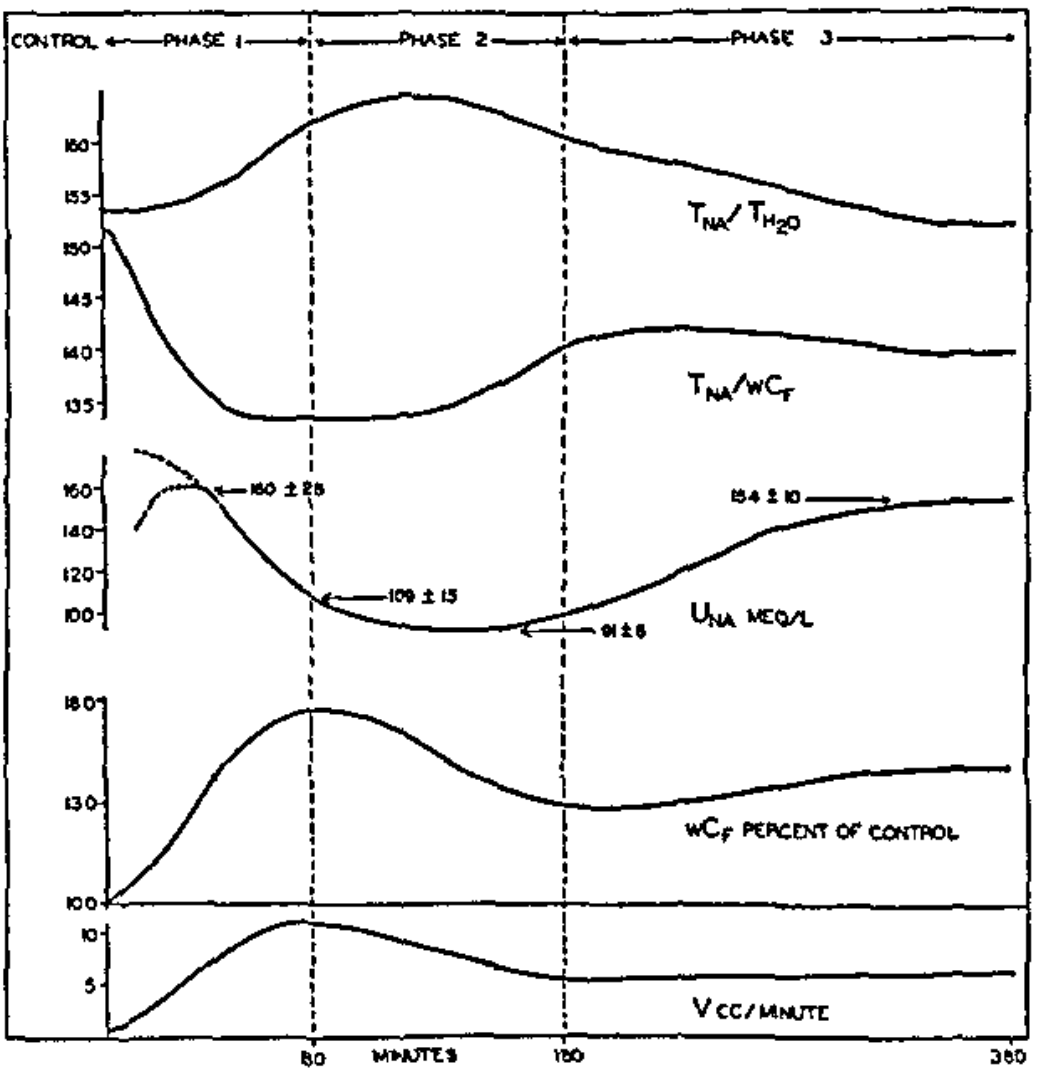

FIGURE 57 Urine sodium concentration, sodium reabsorption per unit of glo-

Ladd [illegible])

three phases (fig. 56). In phase I, the filtration rate and renal plasma flow increase on the average by 57 and 76 per cent, respectively. In phase II, these functions decline to reach minimal values at about the same time, thereafter increasing again to

the animal at such a rate and with fluid of such a composition as to avoid any changes in the plasma electrolyte pattern, thus maintaining an expansion of extracellular fluid of 25 to 50 per cent for

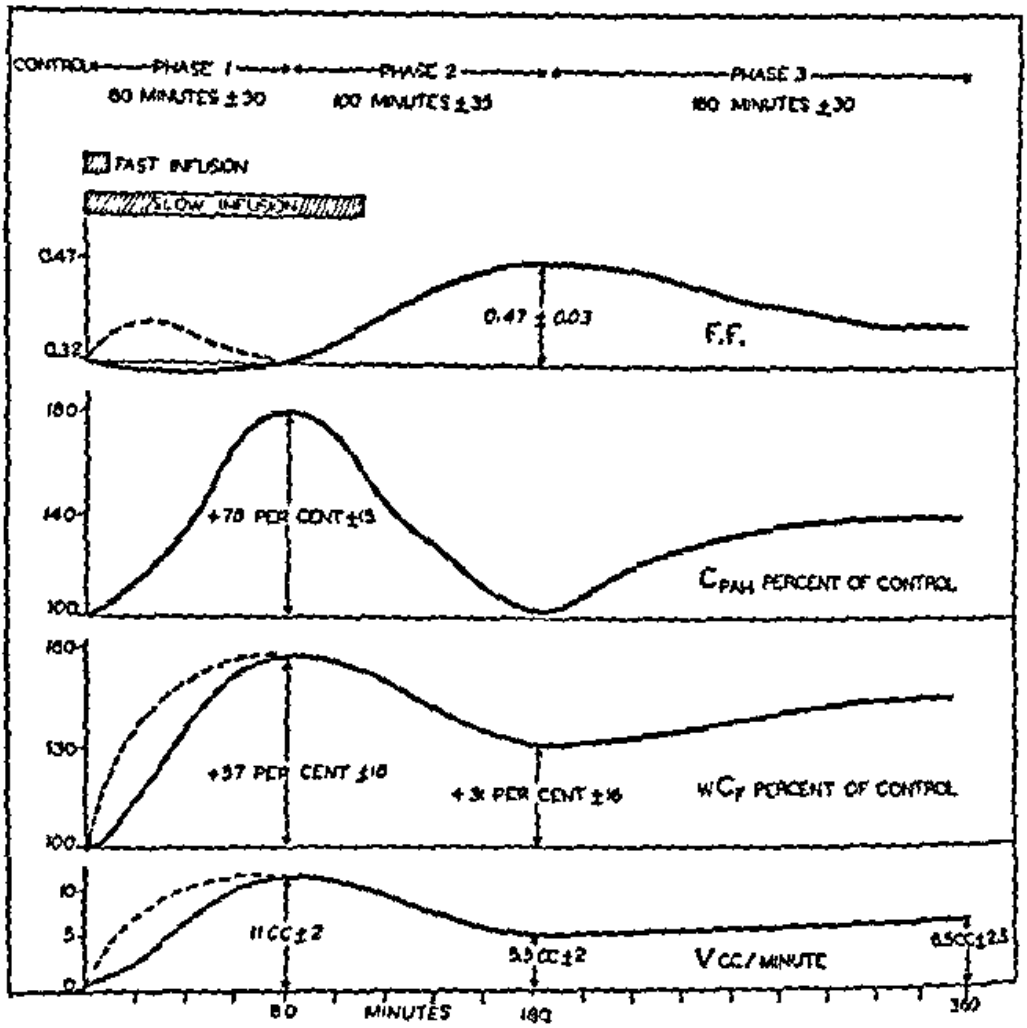

FIGURE 56. Average values for urine flow, filtration rate of water (wC_F), renal plasma flow, and filtration fraction following expansion of the extracellular fluid volume in 18 experiments on 6 normal dogs Numbers are means and ± mean deviations from the mean. Before averaging the individual curves, the time scales of the experiments on each animal were adjusted so that their inflections coincide with the average inflection times for all experiments. (Wesson, Anslow, Raisz, Bolomey, and Ladd [212])

6 to 8 hr. without change in composition, at least so far as the major electrolytes are concerned. Pitressin was also infused (20 milliunits/hr.) to promote to a maximal extent the reabsorption of water effected by this hormone.

These experiments reveal that the response of the dog to a sustained expansion of the extracellular fluid may be divided into

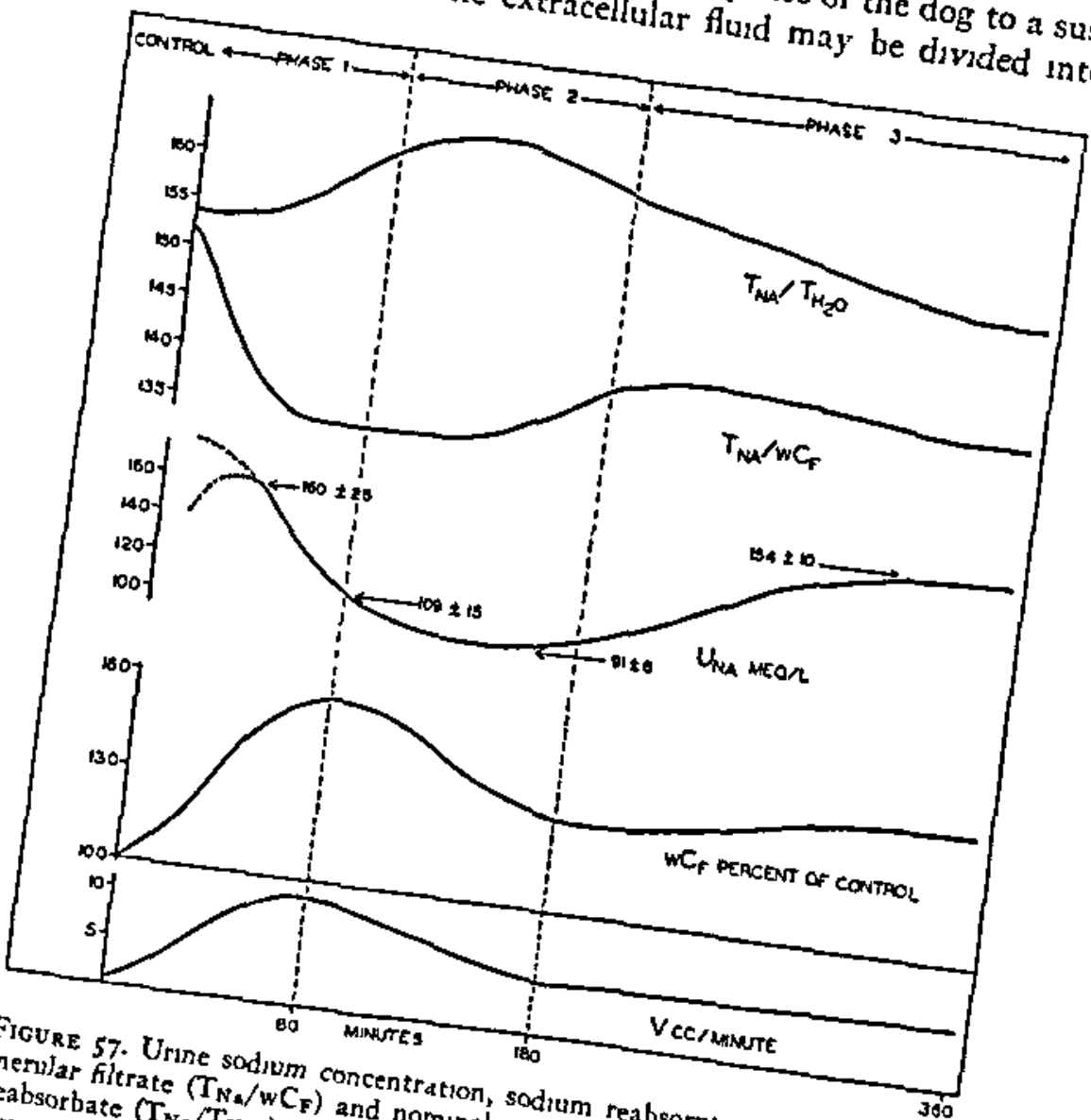

FIGURE 57. Urine sodium concentration, sodium reabsorption per unit of glomerular filtrate (T_{Na}/wC_F) and nominal concentration of sodium in the total reabsorbate (T_{Na}/T_{H_2O}) calculated from the mean values for the 6 longest experiments by the same procedure as the curves in figure 58. Urine flow and filtration rate are repeated from figure 56 for comparison. Numbers are means and mean deviations from the mean (Wesson, Anslow, Raisz, Bolomey, and Ladd 1951)

three phases (fig. 56). In phase I, the filtration rate and renal plasma flow increase on the average by 57 and 76 per cent, respectively. In phase II, these functions decline to reach minimal values at about the same time, thereafter increasing again to

the animal at such a rate and with fluid of such a composition as to avoid any changes in the plasma electrolyte pattern, thus maintaining an expansion of extracellular fluid of 25 to 50 per cent for

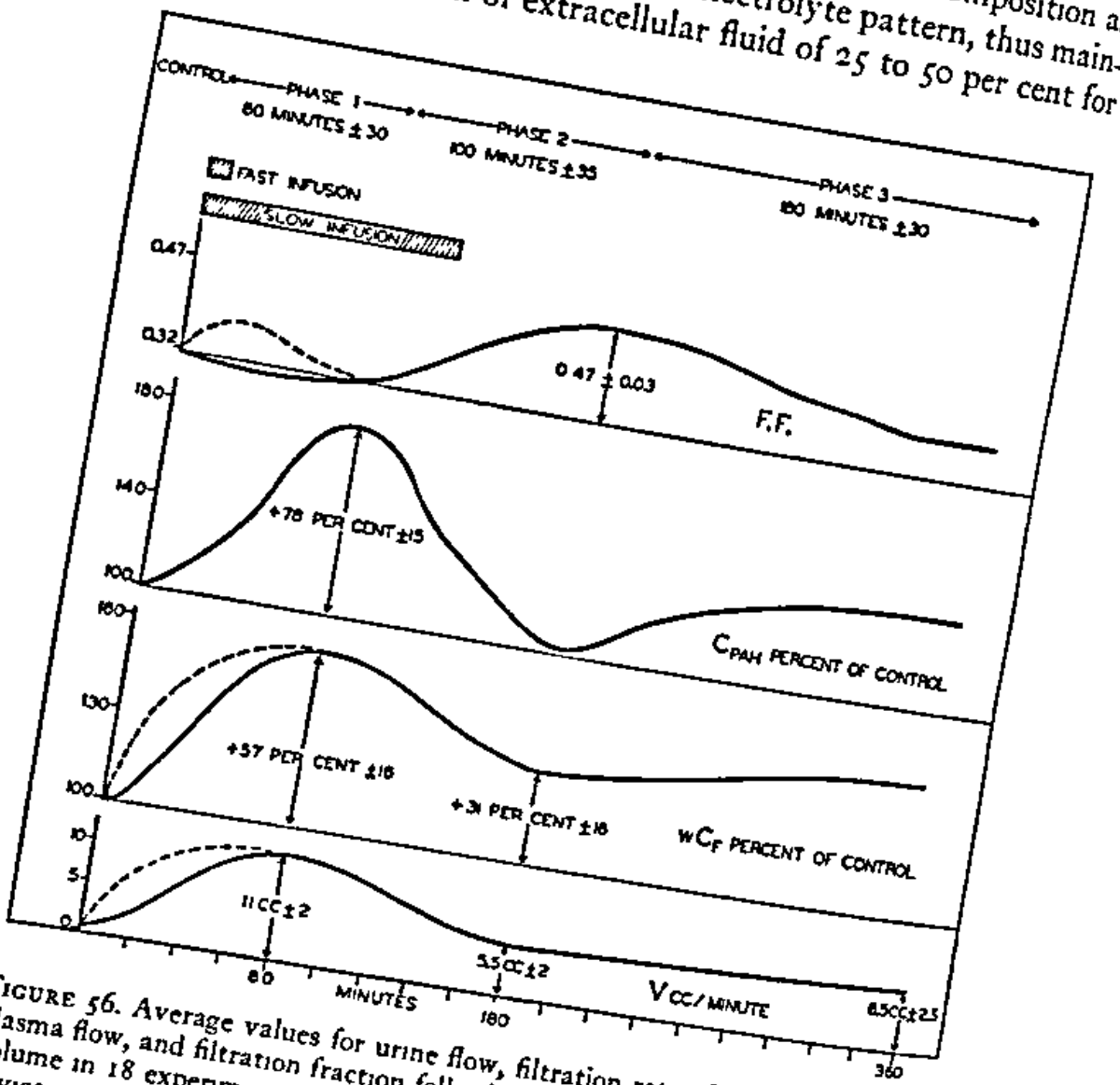

FIGURE 56. Average values for urine flow, filtration rate of water (wC_F), renal plasma flow, and filtration fraction following expansion of the extracellular fluid volume in 18 experiments on 6 normal dogs Numbers are means and ± mean deviations from the mean. Before averaging the individual curves, the time scales of the experiments on each animal were adjusted so that their inflections coincide with the average inflection times for all experiments. (Wesson, Anslow, Raisz, Bolomey, and Ladd [172])

6 to 8 hr. without change in composition, at least so far as the major electrolytes are concerned. Pitressin was also infused (20 milliunits/hr.) to promote to a maximal extent the reabsorption of water effected by this hormone.

These experiments, though complicated in design, show that mere expansion of the extracellular fluid, accompanied at least by

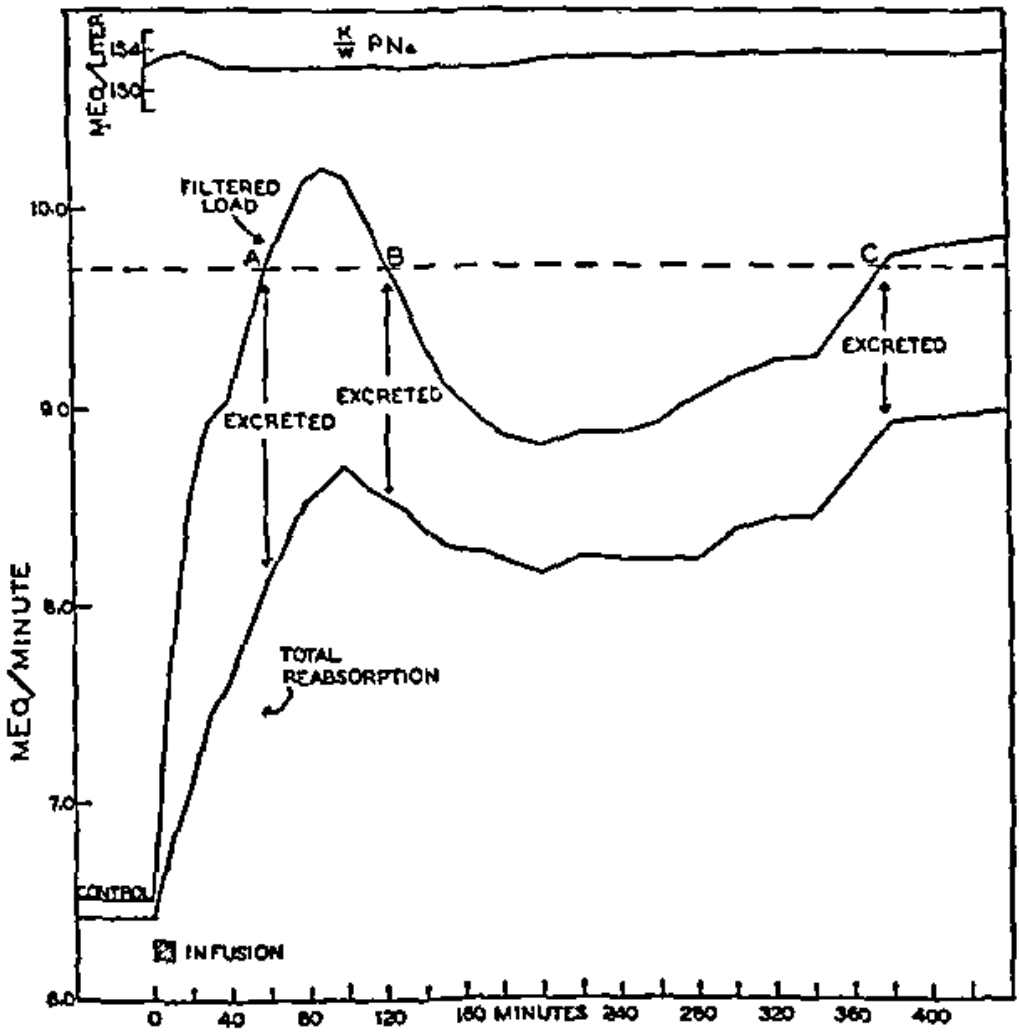

FIGURE 58 The filtered load of sodium ($k/wP_{Na} \times wC_F$) and rate of total sodium reabsorption in 2 dogs (2 experiments per dog) following fast infusion of Locke's solution The interval between load and reabsorption measures the

no changes in plasma electrolyte composition, increases the filtration rate and renal plasma flow, and the specific activity of the renal tubules in the reabsorption of both sodium and water at a constant filtered load of each. They reveal the difficulty of interpret-

fairly steady, supernormal values in phase III. These changes in filtration rate and renal blood flow were not related to blood pressure changes or dilution of plasma protein but, apparently, to expansion of the extracellular fluid volume as a whole or some part thereof.

The initial increase in filtration in phase I, figure 56, is accompanied by a marked increase in sodium excretion, which, the authors believe, is directly attributable to the increased load of sodium delivered to the tubules, since P_{Na} has remained constant.

In view of the general proportionality between the filtration rate and sodium reabsorption in the proximal system, there is no simple way in which one can express the reabsorptive activity of the kidneys for sodium when the filtration rate is changing. The absolute quantity reabsorbed, T_{Na}, is an unanalyzed function of the filtered load, $kP_{Na}C_F$, and, for this reason and because of possible (and here demonstrated) changes in water reabsorption mediated without relation to sodium reabsorption, the ratios T_{Na}/T_{H_2O} and T_{Na}/wC_F (fig. 57) afford no immediately useful information. Therefore, the only method of analysis now available is to compare T_{Na} under identical conditions of P_{Na} and C_F, and hence of the filtered load, $kP_{Na}C_F$. This can be done in these experiments at the points A, B, and C in figure 58, where the above-mentioned terms are constant. The data reveal that, at an identical load at these 3 points, T_{Na} averaged 8.12, 8.55, and 8.88 mEq/min.; i.e. tubular reabsorption increased by about 10 per cent. This increase, though slight in absolute terms, is sufficient at the existing filtered load of 9.70 mEq/min. to reduce the rate of excretion by one-half, i.e. from 1.58 to 0.84 mEq/min. The experiments throw no light on whether this increased reabsorption is attributable to the proximal or distal system, or on how it is effected.

During phase II, despite the continuous administration of pitressin in physiological doses, water reabsorption falls behind sodium reabsorption and the urine is for a time slightly hypotonic (fig. 57); this hypotonic state is followed by a hypertonic state in phase III. The data demonstrate that some factor other than ADH influences water reabsorption.

gard to the role of the osmotic pressure of the plasma in controlling sodium excretion Their argument, however, is based in part upon the assertion that, during osmotic diuresis caused by sodium sulphate and urea, chloride excretion is not increased, which is contrary to the evidence cited above. Nor is there *a priori* warrant for the statement that, if the action of mannitol and glucose were intratubular, the excretion of phosphate and potassium should also be increased; the mechanism of reabsorption of these substances, like that for glucose, is independent of the sodium mechanism. The arguments presented by the authors are inadequate to refute the intratubular locus of the action of osmotic diuresis in reducing sodium reabsorption.

Green, Bridges, Johnson, Lehman, Gray, and Field [849] report renal clearance and sodium excretion data on 60 hospital patients, all of whom had renal disease as judged by the filtration rate (41.5 ± 16 5 cc) and PAH clearance (228 ± 95 cc) The patients were chosen in order to afford a wide range of filtration rates. Ten were maintained on diets containing approximately 2 gm of salt per day. Mannitol was used to measure the filtration rate and was presumably administered in a salt-free solution. The authors examine particularly the per cent of filtered sodium which is excreted, which they call the tubular rejection fraction, TRF_{Na}. The total rate of sodium and water excretion during the experimental periods was much larger than was to be expected from the salt intake because of the clearance procedure. Since mannitol diuresis had substantially increased sodium and water excretion, the former to 33 gm sodium chloride per 1 73 sq m per day, the latter to 6.65 liters, sodium excretion under the conditions of the experiments has little bearing on the normal control of sodium excretion As the authors point out, in the presence of low filtration rates the per cent of filtered sodium excreted increases correspondingly, as must be the case if subjects with low filtration rates (essential hypertension, etc.) continue to maintain a constant plasma concentration on a normal salt intake The authors note that there is a high correlation between the rate of sodium excretion and the per cent of filtered sodium excreted, especially where $P_{Na}C_F$ is relatively constant This correlation is a tautological consequence of the fact that, where $P_{Na}C_F$ is constant, the ratio $U_{Na}V/TRF_{Na}$ is fixed thereby, and the demonstrated correlation merely reflects the narrow range of variation of P_{Na} and C_F in the subjects studied.

DISTAL REABSORPTION OF SODIUM AND WATER

Very little is known about sodium and water reabsorption distally. It cannot even be said to what extent these processes are restricted

ing changes in renal function in acute experiments where several variables are changing rapidly and simultaneously.

Selkurt, Hall, and Spencer [1825] have found that, when the filtration rate is reduced in one kidney of the anesthetized (pentobarbital) dog by reduction of local arterial pressure, moderate reduction of the filtration rate, to 63 per cent of the control value, leads to the rapid decline and cessation of sodium excretion Reabsorption is complete when the filtered load falls below 3·9 mM/min. per kidney (average weight 42 gm)

Green and Farah [850] examined sodium excretion in anesthetized (dial-urethane) dogs which were infused at a constant rate with strong sodium chloride solutions. Increase in the rate of sodium excretion necessarily reflected an increase in the 'tubular rejection fraction' (fraction of filtered load which was excreted), since, under the conditions of the experiment, $U_{Na}V$ varied through a much wider range than $P_{Na}C_F$ Water excretion paralleled that of sodium. The infusion of sodium chloride solutions did not produce consistent changes in the filtration rate in their experiments In 5 animals, infusion of the test solution was followed by a decrease in filtration rate, although sodium excretion increased, and in no instance did the greatest output occur during the period of maximal filtration The renal plasma flow consistently increased, but this increase did not invariably coincide with increased sodium excretion. No consistent relation was established between sodium excretion and plasma sodium concentration, sodium balance or sodium space (assuming only extracellular distribution equal to P_{Na}), water gain or loss, or hematocrit. The authors conclude that increased sodium intake influenced sodium excretion primarily by establishing an osmotic pressure difference between extra- and intracellular fluids, and that the major determinant in sodium regulation is not the preservation of sodium balance but the maintenance of osmotic homeostasis. The conclusion may be correct, but the data do not appear to establish the point experimentally The conclusion is based largely upon the calculation that the net change in sodium space was uniformly greater than the net water retention, indicating that water had been withdrawn from the tissues The calculation is suspect in the absence of evidence that changes in plasma sodium concentration were not reflected by changes in intracellular concentration and by the use of a single injection of mannitol to measure extracellular fluid volume, a method which is unreliable for this purpose.[1808, 1809]

Seldin and Tarail [1819] have arrived at a similar conclusion with re-

tion may be or under what circumstances it actually limits the reabsorption of water is not known. If physiologically significant, this maximal rate would only be attained under the influence of ADH, $T^d_{H_2O}$ falling below the maximal value and perhaps to zero in the absence of activation by this hormone.

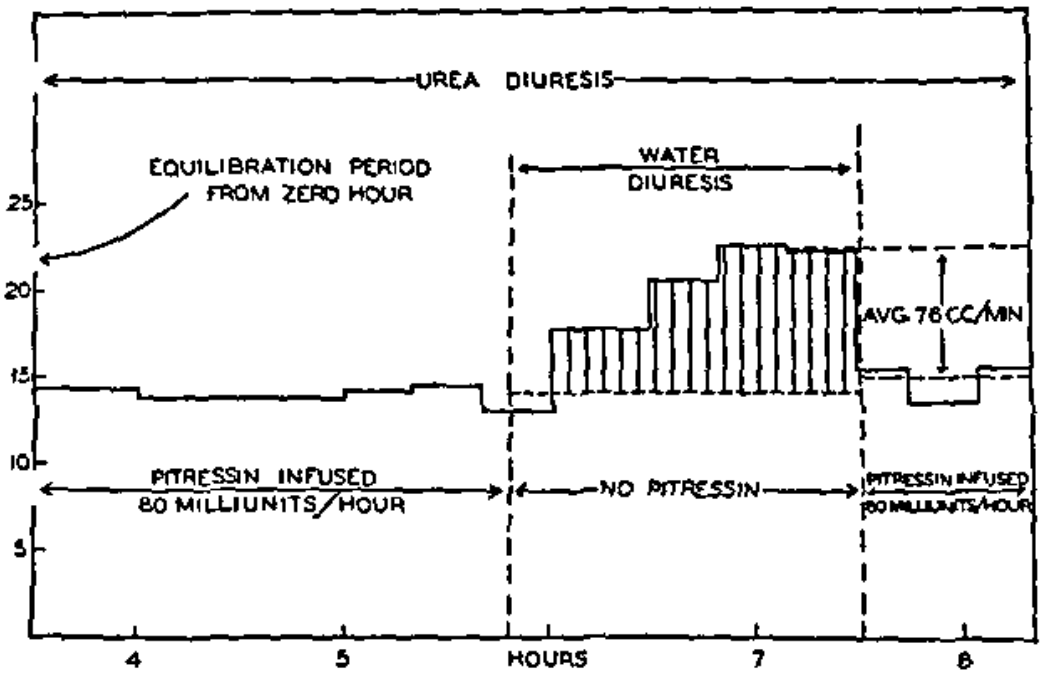

FIGURE 59 Facultative water excretion in a hydrated dog during osmotic (urea) diuresis After an equilibration period of some 6 hr (demonstrated by previous experiments to be necessary to obtain stable conditions with respect to sodium reabsorption), pitressin was withdrawn from the infusion, permitting the facultative water to be excreted in the urine.

Reasons are given in the text for believing that the water which must be abstracted from the urine (ΔV) during this diuresis in order to make it isosmotic with the plasma is quantitatively related to sodium reabsorption in the distal tubule Since the magnitude of ΔV is roughly constant at all levels of osmotic diuresis, this indicates that a constant quantity of sodium (T^d_{Na}) is reabsorbed distally under the conditions of the experiments (Wesson and Anslow, pers com)

Some intimations on the possible relations of distal sodium and water reabsorption have been sought by Wesson and Anslow (pers. com.) by examining the effects of pitressin on urine flow, with and without osmotic (urea) diuresis, the latter serving to increase the load of water and electrolyte delivered to the distal system. Here, as elsewhere, it is assumed, since there is no evidence to the contrary, that no water is excreted by any segment of the renal tu-

to the distal tubule or are carried on in the collecting ducts The data from micropuncture studies indicate that sodium reabsorption occurs in the former but they do not exclude the latter. That water reabsorption may occur in the collecting ducts is indicated but not proved by the formation of casts, as pointed out above.

It has been noted that systems involving tubular transport have, with few exceptions, been demonstrated to be limited by maximal rates, or, at least, by rates which do not change beyond the limits of experimental error with increasing load, once the load has exceeded some critical value. In general, these maximal rates (Tm) of tubular transport are at least roughly reproducible in a particular individual under basal conditions. That the distal reabsorption of sodium is an active process is indicated by the fact that sodium may be abstracted from the urine to the point where the urine is practically sodium-free. Indeed, without marked reduction in filtration rate, a normal subject will maintain himself in sodium balance on as little salt as 0.5 gm/day and, for short periods at least, the urine may be almost devoid of an analytical trace of sodium.

Rats maintained on a low chloride diet (0.5 to 1.2 mg as compared to a control excretion of 110 to 170 mg. of chloride per day), for periods of up to 15 weeks, show no striking outward signs of deficiency, although they gain less weight and eat more food per gm. of body weight than do controls. In such animals, whole blood chloride is reduced (252 mg/100 cc. as compared with 295 mg/100 cc. in controls) and bicarbonate is increased (72.3 as compared with 57.7 cc/100 cc. in controls).[881]

These considerations lead us to anticipate that distal reabsorption of sodium (T^d_{Na}) must be limited by a maximal rate (Tm^d_{Na}), as suggested by Wesson, Anslow, and Smith.[2172] How sharp this limitation may be and under what circumstances it actually limits the distal reabsorption of sodium remains to be determined.

Distal reabsorption of water, unlike proximal reabsorption, also appears at first sight to be an active process, inasmuch as water is here abstracted against the osmotic pressure of the urinary solutes to yield a hypertonic urine, a process requiring the local expenditure of energy by the tubule cells. It is therefore to be anticipated in theory that distal water reabsorption ($T^d_{H_2O}$) is also limited by a maximal rate ($Tm^d_{H_2O}$), but, here again, how sharp this limita-

diuresis) in the same proportions as osmotically active substances and water are presented to the distal tubule by the thin limb; i.e.

$$T^d_{Na}/T^d_{H_2O} = P_{osm} \text{ or } T^d_{Na} = T^d_{H_2O}P_{osm}.$$

Since ΔV remains fairly constant in any one animal in the type of experiment shown in figure 59 both in water diuresis and during osmotic diuresis, when the load of sodium and water delivered to the distal tubule is increased, it would appear that facultative water reabsorption is correlated with a specific quantity of reabsorbed sodium, which we will here call T^d_{Na}, and that T^d_{Na} itself remains constant under these fairly extreme conditions.*

Since, during uncomplicated water diuresis, the urine is very dilute, this sodium must be reabsorbed at some point in the tubule which is impermeable to water; i.e. T^d_{Na} must represent absorption at some point below the thin limb (in the distal system). Hence the facultative reabsorption of water ($T^d_{H_2O}$) (and the action of ADH) must likewise be assigned to the distal system, coexistent with or lower down the nephron than T^d_{Na}.

Distal water reabsorption may not, however, be limited to that which appears in the urine during a water diuresis when this is superimposed upon osmotic diuresis, as in figure 59, because, independently of distal sodium reabsorption, an additional quantity of water ($T^x_{H_2O}$) may be abstracted from an isotonic urine to yield a hypertonic urine. The magnitude of this process, which is given by the quantity of water required to dilute the hypertonic urine formed during maximal osmotic diuresis back to the osmotic pressure of the plasma, is small relative to ΔV during water diuresis; consequently, as the distal load of water increases during osmotic diuresis (and under maximal ADH activation), the osmotic U/P ratio approaches 1.0. It is conceivable that $T^d_{H_2O}$ and $T^x_{H_2O}$ represent a unitary process located at one region of the distal system, or $T^x_{H_2O}$ may represent an additional process occurring farther down the nephron than $T^d_{H_2O}$ (The latter appears to be the most attractive view.) Whether $T^x_{H_2O}$ is under facultative control by

* That sodium reabsorption may be decreased by the action of pitressin is well known (ch. x), whether this effect is on the proximal or distal system is as yet undetermined, but the natriuretic effect appears to amount to no more than some 10 per cent of T^d_{Na}

bule. Figure 59 represents an experiment in which a dog was hydrated with 85 cc/kg. of water orally at the zero hour, and pitressin was administered at the rate of 80 milliunits/hr. to prevent water diuresis. Simultaneously, osmotic diuresis was established by means of a priming injection of urea, the plasma urea concentration being kept constant by the reinfusion of the urine. Previous experiments have demonstrated that 4 hr. are required to establish a steady state with respect to urine volume and composition. After a control period extending from the fourth to the sixth hour, the pitressin infusion was withdrawn, permitting the urine flow to increase to the extent to which this hormone was promoting the reabsorption of water. During the ensuing water diuresis, the urine, which hitherto had been approximately isosmotic with the plasma, became hypotonic. On reinfusion of pitressin, the urine flow decreased and the osmotic pressure increased to their prediuretic levels.

In successive experiments, the urea load (or level of osmotic diuresis) was increased in order to increase the distal load of sodium and water. The observations on any one animal indicate that the osmotic magnitude of the water diuresis (ΔV) resulting from the withdrawal of pitressin during osmotic diuresis, regardless of the level of the latter, is approximately constant and equal to the water diuresis obtained in experiments carried out in the same way except for the omission of osmotic diuresis. Here ΔV represents the quantity of water which must be abstracted from the urine in order to make it isosmotic with the concurrent plasma.

Assuming (a) that the thin limb is permeable to water and that the urine delivered to the distal tubule is exactly isosmotic with the plasma during water diuresis (an assumption which remains to be established), a hypotonic urine such as is excreted during water diuresis requires that some osmotically active substance be reabsorbed by the distal tubule; excluding the back diffusion of urea, we may further assume (b) that the only substance reabsorbed here in significant quantities is sodium. It follows that the difference between the osmotic pressure of the plasma and of the diuretic urine reflects the quantity of sodium being reabsorbed during water diuresis. Or, conversely, facultative distal water reabsorption is related to distal sodium reabsorption (during water

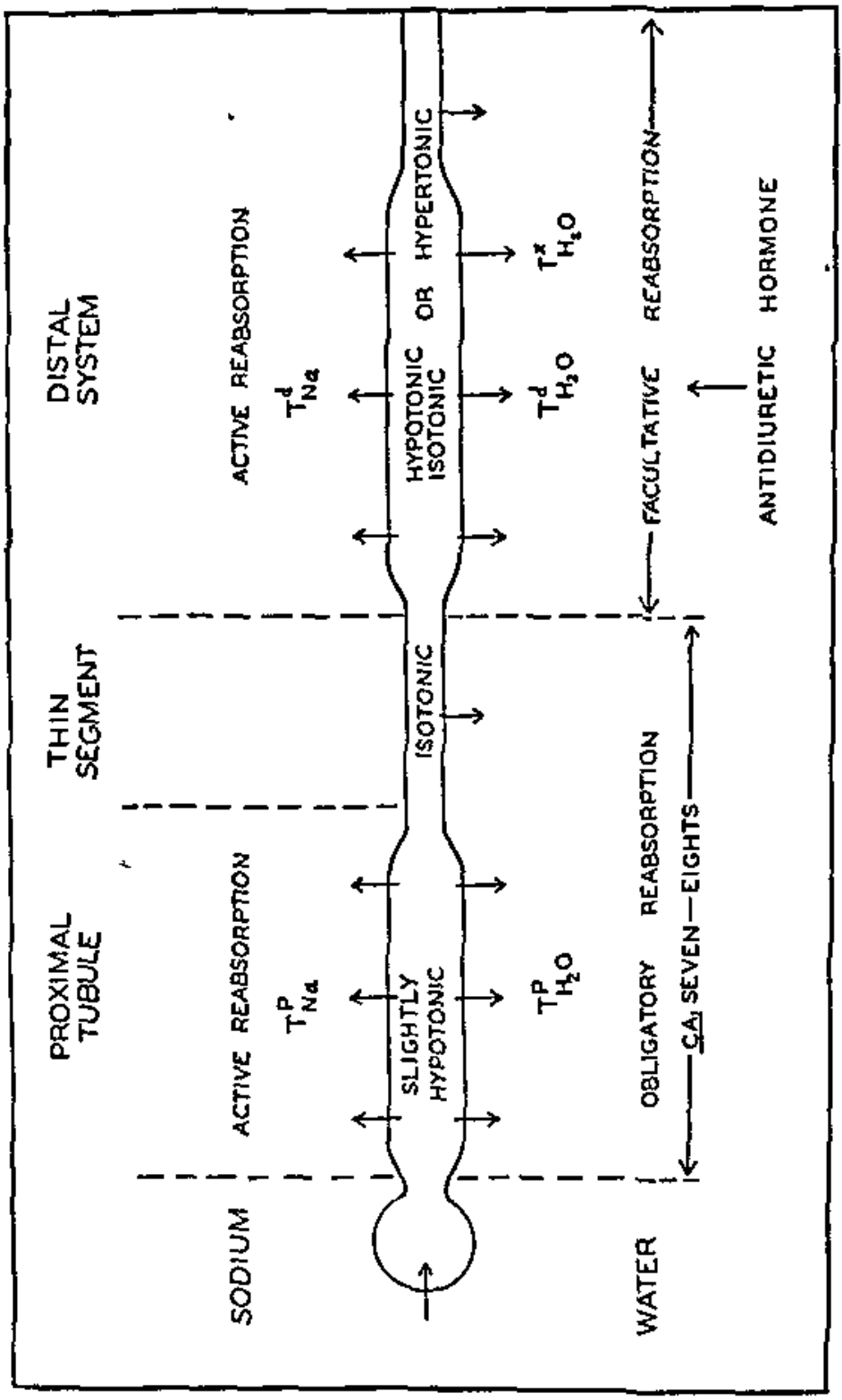

FIGURE 60 Schematic representation of sodium and water reabsorption.

ADH or is a continuous process which has little effect on the composition of the urine during water diuresis when $T^d_{H_2O}$ is small, is undetermined. In the first case, $T^x_{H_2O}$ does not appear in the calculation of T^d_{Na} since this computation is based upon P_{osm}, the theoretical osmotic pressure of the tubular urine before $T^x_{H_2O}$ was abstracted. In the second case, $T^d_{H_2O}$ is smaller than the water released by the absorption of T^d_{Na} by an amount equal to $T^x_{H_2O}$, and T^d_{Na} as calculated will be correspondingly less than the actual magnitude of distal sodium reabsorption.

In summary, it is clear that the facts are not available to answer with certainty several major questions relating to electrolyte reabsorption, and the following description is in some respects speculative. The theoretical formulation of Wesson, Anslow, and Smith,[2172] as modified by the studies cited above, represents as satisfactory a theory as any by which the known facts may be correlated.

The reabsorption of sodium is conceived as taking place in two stages (fig. 60): (1) a proximal process (T^p_{Na}) involving approximately four-fifths of the normal filtered load; (2) a distal process (T^d_{Na}) involving approximately one-fifth of the normal filtered load. To these we may add for completeness a small quantity (less than 1 or 2 per cent of the normal load) involved in independent ion [K^+, H^+, (NH_3^+?)] exchange processes. Water reabsorption involves a further process ($T^x_{H_2O}$) by which hypertonic urine is formed.

Proximal reabsorption is rapidly reduced when a sodium concentration gradient is developed between plasma and tubular urine. Normally, this concentration gradient remains small because of the rapid, passive reabsorption of water, but during osmotic diuresis the reabsorption of water is retarded and the sodium in the tubular urine is diluted, impeding its reabsorption. The fact that the proximal reabsorption of sodium is incomplete under normal filtered loads and that roughly 20 per cent is passed on to the distal system is possibly attributable to the circumstance that the diffusion of water does not proceed fast enough to maintain osmotic equilibration, and the resulting sodium concentration gradient acts to limit sodium reabsorption, this limitation being

tion as a bulk transfer mechanism, serving to reduce the gross volume of the glomerular filtrate, the distal process effects fine adjustment upon a small volume Since the ultimate excretion or retention of sodium depends upon this distal process, it is reasonable to suppose that this is the locus of such sodium reabsorption as is susceptible to hormonal control (corticosteroid, pituitary, etc.), and in this sense it is facultative, as in the case of water.

A small volume of isotonic fluid (of which about 10 per cent of the total osmotic pressure is attributable to urea and most of the rest to sodium salts) enters the distal tubule. Here the distal process reabsorbs sodium until the urine is sodium-free, or the distal reabsorptive capacity (T^d_{Na}) (conditioned in part by hormones) is exceeded. Such sodium as is reabsorbed distally liberates an osmotic moiety of water which, in the absence of ADH, contributes to the production of a hypotonic urine, the decrease in urine osmotic pressure being equivalent to the distal reabsorption of sodium.*

In the absence of ADH, the hypotonic urine left after the reabsorption of sodium continues into the bladder without further important changes In the presence of ADH, the facultative water reabsorptive process ($T^d_{H_2O}$) is activated. The water osmotically liberated by the reabsorption of sodium is now reabsorbed to produce an isosmotic urine. Further water reabsorption ($T^x_{H_2O}$) from the urine, which now has a small bulk, leads to the formation of a hypertonic urine, the limiting factor here being apparently the maximal osmotic U/P ratio. $T^x_{H_2O}$ is not only small but is apparently limited in rate, so that urine of maximal osmotic pressure is formed only at low urine flows. Whether $T^d_{H_2O}$ and $T^x_{H_2O}$ are referable to the same portion of the distal tubule, or whether $T^x_{H_2O}$ is referable to a lower portion of the nephron (collecting ducts?) than $T^d_{H_2O}$, is as yet undetermined

Changes in sodium excretion may be brought about in two ways: (1) by changes in the distal load of sodium effected by changes in the rate of filtration; (2) by changes in the rate of

* The theory up to this point would serve to explain the excretion of an osmotically dilute urine in those Classes which have only a proximal and distal segment in the nephron, and in which ADH is not active with respect to water reabsorption.

supplemented by the presence of osmotically active substances (urea, sulphate, etc.) in the urine, which retard water reabsorption.

In this view, the proximal tubule is always *maximally engaged* in sodium reabsorption within the limits imposed by the composition of the tubular urine at each point along the tubule. Elevation of the filtration rate will, however, by increasing the volume of fluid delivered to the tubule, serve to abolish concentration differences from whatever cause, so that the absolute rate of sodium reabsorption will tend to increase *pari passu* with the filtration rate. Conversely, a decrease in filtration rate exaggerates the proximal concentration gradient, so that the absolute rate of reabsorption will tend to decrease. Hence there is an approximate though not strict proportionality between filtration rate and proximal reabsorption. The absolute rate of reabsorption may be expected to approach an asymptote as the filtration rate increases and, conversely, with decreasing filtration rate, reabsorption may be expected to become much more complete, so that, at half the normal filtration rate, perhaps more than 90 per cent of the filtered sodium may be reabsorbed. The effect of changes in the sodium concentration in the glomerular filtrate upon proximal reabsorption may be conceived as qualitatively but not quantitatively similar to the effect of changes in filtration rate * At low plasma sodium concentrations, it may be expected that a larger fraction of the filtered sodium will be reabsorbed proximally than at normal concentrations, and *vice versa*.

The thin segment is conceived as a region that is highly permeable to water, wherein the variably hypotonic proximal urine is brought to osmotic equilibrium with the plasma. If an isotonic urine issues from the thin limb, we must accept that sodium can be reabsorbed distally. This distal process is characterized by the facts that it is capable of extracting virtually the last trace of sodium from the urine, and that the magnitude of the reabsorptive process, when fully engaged, is much smaller than that of the proximal process Whereas the proximal process appears to func-

* As a consequence of the probable difference in the response of the kidney to the two factors, volume and concentration, it is unrealistic to describe sodium excretion in terms of the total load, or the product of volume and concentration.

visions a pattern of glomerular-tubular balance in which both glomerular and tubular activity are variable, but through appropriate compensatory changes the system can maintain salt and water balance through a wide range of activity in either component.

The foregoing considerations lead us to speculate whether there exists in the body a mechanism by which expansion or contraction of the extracellular fluid tends automatically to increase or decrease the filtration rate, or otherwise influence the reabsorption of sodium. Some evidence on this point will be discussed in the following sections.

EFFECT OF SALINE UPON THE FILTRATION RATE IN THE DOG AND RAT

It has long been recognized that the administration of isotonic saline increases the filtration rate in the dog Schmitz [1193] observed increases of 27 to 89 per cent in the dog after the intravenous administration of quantities no larger than 100 to 150 cc., and Shannon [1861] utilized this phenomenon in his interpretation of how the diabetes insipidus dog maintains itself on salt and water balance on a low and high salt intake. The phenomenon is apparent in the studies of Hare, Hare, and Phillips [917] in both diabetes insipidus and normal dogs, and in those of Wesson, Anslow, and Smith, [2172] where its possible relation to the maintenance of normal salt and water balance was emphasized

Baldwin, Kahana, and Clarke [11] record that the infusion of 0.9 per cent saline at a rate of 1 to 3 cc/mm. in 2 dogs increased the filtration rate from a mean of 67 8 cc (range 41.6 to 91.5) to the range of 80 9 to 94 8 cc , and the PAH clearance from a mean of 209 cc (range 124 to 295) to the range of 218 to 399 cc. Ten per cent saline (2 to 5 cc/min.) had even more marked effects on both functions The filtration fraction in both instances remained fairly constant

Green and Farah [850] did not observe an increase in filtration rate in dogs infused with 1 7 M sodium chloride, but this function nearly doubled in a dog infused with 0.147 M. Why the more concentrated solutions should be without effect on glomerular activity in their experiments is not clear.

(distal?) reabsorption under hormonal control. The maintenance of salt and water balance probably involves both factors. Expansion of the extracellular fluid without change in composition in respect to the important electrolytes is known to increase the filtration rate; this increased filtration first increases the distal load to a point of overloading T^d_{Na} (phase I, figs. 56–58) and more slowly (phase II) leads through unidentified mechanisms to an increase in T^d_{Na} itself, the latter causing decreased excretion at a constant load (see fig. 58). Both mechanisms are probably operative in maintaining the volume of the extracellular fluid and salt and water balance. Conversely, reduction of body fluids is known to decrease the filtration rate; this decreased filtration reduces the distal load of sodium to a level less than T^d_{Na}, leading to sodium retention. Reduction of extracellular fluid may also set in operation mechanisms that increase T^d_{Na}. Where the reduction in filtration rate is extreme, irrespective of slight variations in T^d_{Na}, it will lead to excessive retention of sodium. In any instance, loss or retention of sodium, operating through the osmotic pressure of the plasma and the supraopticohypophysial system, will lead to loss or retention of water until the homeostatic osmotic pressure of the plasma is restored. The slowness with which glomerular and tubular activities are adjusted in man would explain the slowness with which saline diuresis is initiated, and the relatively small increase in the filtration rate, together with the fact that the distal process operates upon only a fraction of the total filtrate, would explain the relatively small magnitude of the diuresis.

The present value of any theory in this field must be sought not in the completeness with which it encompasses all the facts, but in its agreement with most of them and in the extent to which it can guide or suggest further investigation to affirm or disprove it. The notable advantage of the present interpretation is that, by physiologically integrating the renal mechanism controlling the excretion of sodium, the supraopticohypophysial mechanism controlling the excretion of water, the glomerular apparatus controlling the filtration rate, and the action of the hormones of the adrenal cortex and neurohypophysis on the distal (?) system, one would have a system that would regulate not only the composition of the extracellular fluid but its volume as well. This theory en-

subject, who showed no increase in filtration rate, showed no increase in sodium or chloride excretion, while in a third there was no correlation between the filtration rate and the excretion of sodium. Sodium citrate was without effect upon the filtration rate, partly because of conversion to and preferential excretion of sodium as bicarbonate.

Among the variable factors involved in determining the response to saline in man (and possibly in the dog) is the previous history of the individual with respect to hydration. Ladd [118] has found that if normal subjects are hydrated with 2000 cc. of tap water 9 to 11 hr before the administration of saline (3000 cc. of 0.9 per cent sodium chloride intravenously at 45 to 65 cc/min), they respond with a transient, paradoxical water diuresis, in that large quantities of dilute urine are excreted during the later part and shortly after saline administration At the peak of diuresis the U/P ratio of inulin or endogenous creatinine chromogen falls to the range of 5 to 8 (average 6 0). This seems to involve a water diuresis rather than a pure saline diuresis because the osmotic U/P ratio decreases to the range of 0 3 to 0 7 (average 0.4); whereas in saline diuresis, as observed in non-hydrated subjects, this ratio remains above 1 0 at the highest urine flows.

The preliminary dose of water, of course, produces a typical diuretic response, as revealed by chromogen U/P ratios of 6 to 9 and by the excretion within 4 hr. of some two-thirds of the administered water. One notable feature of this phenomenon is that it fails to occur in subjects hydrated with the same dose of water less than 7 or more than 14 hr. before the injection of saline. It appears that this period of hydration has left some trace or hysteresis effect in the body which transmutes a saline diuresis into a water diuresis. A second notable feature is that during the administration of saline the osmotic pressure of the plasma (as measured by freezing-point depression) increases; i.e. water diuresis occurs in the face of the signal stimulus which should induce maximal water reabsorption. This paradoxical diuresis may be prevented or arrested by the intravenous administration of pitressin in physiological doses and fails to occur after the intravenous administration of hypertonic saline (3000 cc of 1.2 per cent sodium chloride solution), indicating failure of response of a still active supra-

jects; in 6 instances the filtration rate decreased by 5 per cent or more. The results were no different in 4 patients who had been maintained for a week on a high salt diet. In only 6 instances did the PAH clearance increase after saline by more than 10 per cent (12, 16, 16, 20, 28, and 123 per cent). Hypertonic saline (500 cc. of 5 per cent salt solution) was slightly more effective but still unimpressive; the filtration rate increased in 3 instances (16, 19, and 98 per cent), remaining essentially unchanged in the other 3 (−2, +6 and 7 per cent); the PAH clearance increased in 5 instances (11, 22, 26, 39, and 90 per cent) and decreased in 1 (7 per cent).

In the face of the effectiveness of saline in increasing glomerular activity in the dog and rat, and in the face of the all but firmly established relationship between extracellular fluid volume and glomerular activity (with reference to glomerular-tubular balance and sodium excretion), these negative results are at least disquieting. They imply to the writer that glomerular activity in man is stabilized to a greater degree than in the other species studied, or that its regulation involves undiscerned factors which are of less importance in the other species. It is significant, as Crawford and Ludemann emphasize, that isotonic and hypertonic saline are retained in man for long periods, only some 25 per cent at best being excreted within three and a half hours, in contrast to the dog, in which, after the administration of isotonic saline, a return of 75 per cent or better within this period may be expected. The marked increase in filtration rate and rapid excretion of saline in the dog and the absence of such an increase and the sluggish excretion in man are doubtless causally related.

Crawford and Ludemann find no correlation between the changes in filtration rate and sodium excretion. In 7 out of 11 instances, the rate of sodium excretion increased after isotonic saline by more than 10 per cent (16 to 282 per cent) despite no change or a decrease in filtration rate. This circumstance can only reflect changes in the reabsorptive activity of the tubules Leaf, Couter, and Newburgh [1220] report that when a normal subject changed from a low to a high salt diet the filtration rate and endogenous creatinine chromogen clearance increased by about 33 per cent, and were accompanied by increased sodium excretion; a second

The fact that sodium retention in man leads to water retention is clearly demonstrated The question whether water retention leads directly to sodium retention is not so clearly answered. As noted in chapter x, chloride excretion increases abruptly during the transient polyuria and the onset of permanent polyuria in diabetes insipidus animals, but neurohypophysectomy appears to produce no specific change in the manner in which the kidney handles sodium, for permanently diabetic animals soon come back into normal sodium balance [1768, 2245] In view of the trauma associated with the production of experimental diabetes insipidus, this transient excretion of chloride is difficult to interpret.

Short-term water diuresis experiments are equally difficult to interpret. Eggleton [879] found that, during water diuresis, chloride excretion decreased in 8 out of 9 subjects, the average decrease being 30 per cent, confirming earlier investigators cited by her During the diuresis induced by alcohol (which apparently inhibits ADH secretion) a similar decrease in chloride excretion occurred [888] Crutchfield and Wood [457] report that water diuresis usually decreased sodium excretion; however, the difference in the mean excretion of 41 patients selected without regard to the control output (330 8 mg/hr during diuresis as compared with 336 0 mg in the controls) is so slight that its significance is questionable The authors state that, if the control urine flow is 'low,' sodium excretion may be increased by diuresis, but their division of patients with respect to 'low' and 'adequate' urine flows is somewhat arbitrary Opposed to these reports are the data of Barclay, Cooke, Kenney, and Nutt,[82] which show no consistent pattern of chloride excretion during water diuresis. Kattus *et al*,[1093] in well-controlled but short-term (3 hr) experiments, noted that large variations in urine flow did not appreciably modify the pattern of sodium excretion, but inspection of their data reveals that water diuresis (during their control periods before exercise) was almost invariably accompanied by increased sodium excretion, never by decreased excretion.

It would seem that, if short-term water diuresis *per se* does affect sodium excretion, the effect is easily obscured by unrelated variations in sodium balance, filtration rate, and other factors The evidence as a whole can scarcely be said to support the belief that hydration of the body leads directly or indirectly to sodium retention.*

* The point assumes importance in view of the implicit assumption by several workers that increased excretion of ADH or other antidiuretic factors in

opticohypophysial system under conditions that normally activate it. Whatever the explanation, Ladd's observations may help to clarify some of the irregularities in the response of man to saline, as well as the fact that the diuretic response to water itself is quite variable.

The sluggishness of the human kidney in respect to its response to saline can be observed in other studies presenting no specific information on renal function. Stewart and Rourke[2008] report the administration of 0.9 per cent saline to the extent of 6.5 liters/day to postoperative patients expanded thiocyanate space by approximately 90 per cent and plasma volume by 60 per cent. The daily increments, however, become progressively smaller and by 3 to 5 days a maximal expansion was followed by a gradual subsidence. Increase in the quantity of plasma protein maintained a protein concentration at nearly 6 gm/100 cc. Similar quantities of 5 per cent glucose reduced the volume of the thiocyanate space, possibly, as the authors suggest, because of the failure of the kidneys to conserve sodium in the face of the (glucose and ?) water diuresis. Unfortunately, since these observations were made in postoperative patients, neither the accumulation data nor the apparent compensation of the body to repetitive administration can safely be transferred to normal subjects.

Perera and Blood[1589] have shown that normal subjects, when deprived of salt, undergo diuresis and loss of weight (*c.*1 kg) in 24 hr., while Grant and Reichsman[843] report that subjects taking 20 to 30 gm of salt per day with water *ad libitum* show within 48 hr. a similar gain in weight, the plasma volume, blood volume, venous pressure, and thiocyanate space also being increased.* Lyons, Jacobson, and Avery[1285] report an average weight gain of 1.9 kg. in 7 subjects taking 40 gm. of salt in 48 hr. In 6 of these the plasma volume increased by a mean of 15.6 per cent Sodium bicarbonate had a similar but significantly smaller effect on weight

Eichelberger and Roma[590] report that, when hypotonic saline (77 mEq/liter) was infused in large volumes into dogs, the average urine excreted contained 90 mEq/liter of sodium and chloride, while the concentration in the retained fluid ranged from 60 to 76 mEq/liter. The resulting hemodilution leads to a movement of extra water into the muscles, liver, skin, erythrocytes, and brain.

* Hypertensive subjects do not show this abrupt change in weight,[1589] but weight loss is evident when they are kept on a low salt diet for longer periods.[355]

to interpret experiments on the effects of drugs and hormones on chloride excretion without further data.[1179, 1180, 1181]

DIURNAL VARIATIONS IN GLOMERULAR ACTIVITY AND IN ELECTROLYTE AND WATER EXCRETION

It has long been known that there is a diurnal rhythm in water and electrolyte excretion in man [1379, 1898, 1899] The urine volume and urinary sodium, potassium, and chloride excretion are substantially greater during the day than at night, the larger urine volume of the day being associated with a negative water balance counterbalanced at night by a positive water balance Only slight fluctuations are evident in urinary phosphate, sulphate, titratable acidity, and ammonia, although there is almost uniformly a larger excretion of all these solutes during the day than at night No significant shift in calcium and magnesium was observed The excretion of water and electrolytes reaches a maximum from 6·00 A M. to 12 00 noon, declines in the afternoon, and falls off sharply at night to reach a minimum from 12:00 midnight to 6·00 A.M The specific gravity, attributable largely to the nitrogenous fraction, is highest at night because of decreased urine volume, in spite of the fact that the total amount of nitrogen excreted is slightly diminished De-hydration and fasting do not markedly affect this diurnal rhythm in sodium and water excretion, although fasting may reverse potassium excretion

The mechanism involved in maintaining this diurnal rhythm appears to be related to the sleeping and waking states rather than to changes in physical activity, although the influence of the latter has not been wholly excluded If the individual sleeps during the day and is active at night, the rhythm is reversed.[1833] Simpson [1899, 1900] had earlier shown that the excretion of phosphate and chloride is lower during sleep than during the waking hours in fasting subjects resting in bed under circumstances which do not disturb phosphate metabolism. Short periods of sleep during the day caused a decrease in urine volume in only 1 out of 17 subjects, showing the persistent tendency of the diurnal rhythm.

The studies of Popper and Brod,[1645] and Brod [258] indicate that this diurnal rhythm is accompanied by a qualitatively parallel variation in filtration rate, as judged by the endogenous creatinine chromogen clearance, which increases during the morning and decreases at night, and particularly during sleep The rhythm is reversed in chronic congestive heart failure (ch. XXII)

Sirota, Baldwin, and Villarreal,[1904] using a constant intravenous low-speed infusion pump with a flexible plastic intravenous catheter, have

It is of interest that Eggleton [879] found that, in the same individuals, tea (560 cc.) increased chloride excretion by 150 per cent while water decreased it by 70 per cent. The diuretic response was itself 30 per cent greater with tea than with water. This may in part be related to an increase in filtration rate produced by caffeine, but more important is the fact that xanthine derivatives increase sodium excretion by specifically reducing tubular reabsorption (ch XXVII).

EXERCISE

Barclay and his coworkers [82] report that chloride excretion is consiently reduced during exercise, and Sinclair-Smith, Kattus, Genest, an Newman [1902] have shown that mild exercise (walking 3 m.p.h. on a motor-driven treadmill) causes significant retention of sodium and chloride, independently of changes in filtration rate as measured by the endogenous creatinine or inulin clearance. The fraction of filtered sodium excreted was reduced by 17 to 65 per cent (average 63) of the value obtained during the control period, increased reabsorption persisting for an average of 37 min after the end of exercise. Standing quietly had a slight effect in promoting sodium and chloride retention Variable but typical antidiuresis was associated with exercise. The excretion of potassium and phosphate showed no predictable correlation with changes in sodium excretion Sodium retention is not related to loss of sodium in sweat or to elevation of blood lactic acid; the authors note that it may reflect changes in the secretion of the adrenal cortex or neurohypophysis.

De Muylder and his coworkers [499, 500, 501, 502, 503, 504, 505, 506] have reported sodium chloride and potassium clearances in rabbits, including observations after the injection of pitressin in small and large doses, and of isotonic saline and glucose, as well as observations of the effects of such injections and of the subcutaneous injection of hypertonic glucose on the inulin clearance and minimal inulin U/P ratio. They develop the theory that oliguria or anuria is the result of a reduced filtration rate, which is itself a compensatory reaction to increased oncotic pressure and hyponatremia. In view of the ease with which reflex oliguria can be established in the rabbit, uncertainties with respect to variations in glomerular activity in relation to hydration and the complications presented by osmotic diuresis, these experiments are difficult to interpret. The complexities presented in the excretion of sodium make it difficult hepatic cirrhosis, cardiac failure, etc, leads first to water retention and then to sodium retention and the production of edema The assumption seems at present to have no evidential foundation

Baldwin, Villarreal, Sirota, Schreiner, and Wesson (pers. com.) found that in 4 of the subjects above in whom the N/D inulin clearance ratios were 1.02, 1.13, 0.97, and 0.94, respectively, the N/D ratios for sodium excretion were 0.77, 0.79, 0.71, and 0.59. In a fifth, in whom the N/D inulin clearance ratio was 0.97, the N/D sodium ratio was 1.81. Despite constancy in the filtration rate, there appears to be a definite increase in sodium reabsorption at night, except in the 1 patient noted.

CONTINUOUS DIURESIS

Coon, Noojin, and Pfeiffer[401] gave 100 to 300 cc/kg of fluid orally to dogs in doses of 50 cc/kg every half hour. The rate of onset of diuresis was largely independent of salt content but the maximal urine flow (8 cc/min. in a 10 kg dog) was obtained with 0.4, 0.5, and 0.6 mg per cent of sodium chloride, lower urine flows being obtained with stronger (0.7, 0.9 per cent) and weaker (0.2 or 0.1 per cent) solutions; 0.2 per cent sodium chloride produced the least change in chloride balance, as shown by lack of cumulative action and minimal change in serum chloride. They suggest that 0.5 per cent sodium chloride is most diuretic because it is more rapidly absorbed from the gastrointestinal tract than are more concentrated solutions, but once the fluid is absorbed the kidney cannot (?) excrete more than 0.2 per cent sodium chloride in diuretic quantities. This interpretation may be questioned in favor of differential effects on the filtration rate and on the several systems involved in the excretion of salt and water. Pfeiffer *et al.*[1602] report the effects on diuresis in dogs of adding calcium, magnesium, and potassium to 0.45 per cent sodium chloride. Their results must await further knowledge for interpretation.

Wolf[2258, 2267] has shown that, when salt solutions of various concentrations are given intravenously to dogs at a rate of 2.3 cc/min., excretion of salt and water ultimately approaches a steady state which in most instances is reached by the seventh hour. Two concentrations of infusate yield a urine with about the same chloride/water ratio as the infusate, 170 mEq/liter (which Wolf calls the non-limiting isorrheic * concentration), and *c* 500 mEq/liter (which he calls the limiting isorrheic concentration). In similar studies on man, Wolf defines a third, or minimal, isorrheic concentration of *c* 40 mEq/liter, which presumably is also applicable to the dog. The non-limiting isorrheic concentration

* An isorrheic concentration is one at which, during a steady state, relative input of salt and water is equal to relative output of salt and water. The term was first used by Eggleton, Pappenheimer, and Winton[588] in their studies of the isolated kidney.

followed the filtration rate and renal plasma flow throughout a 24 hr. period. The mean night to day (N/D) or sleeping/waking ratio for urine flow in 18 normal subjects was 0.83 ± 0.39, for inulin U/P ratio 1.40 ± 0 41, for inulin clearance 0.96 ± 0.07, for endogenous creatinine chromogen clearance 0.97 ± 0.06, and for PAH clearance 0 98 ± 0.06,

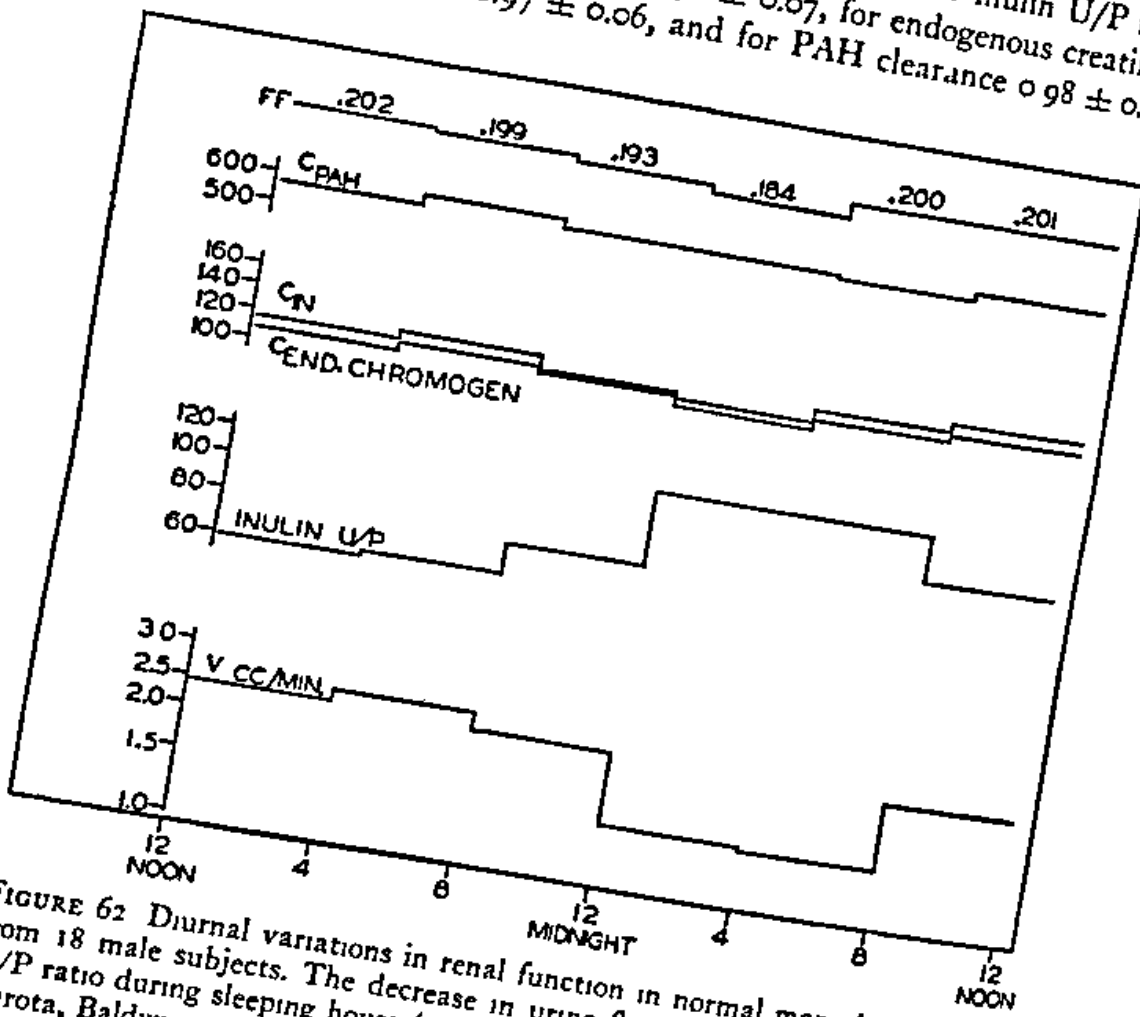

FIGURE 62 Diurnal variations in renal function in normal man. Average data from 18 male subjects. The decrease in urine flow and the increase in inulin U/P ratio during sleeping hours (12 P M. to 8 A M) are statistically significant. (Sirota, Baldwin, and Villarreal 1904)

the data indicate a significant decrease in urine flow, a significant increase in tubular reabsorption of water, and a relatively constant filtration rate and renal plasma flow. However, during the 4 hr. period from 12.00 midnight to 4·00 A M, corresponding to the period of deepest sleep, there was a slight but significant fall in filtration rate with no change in renal plasma flow (fig 62). The decrease in urine flow at night is almost wholly attributable to increased tubular reabsorption of water. Simpson 1898 has shown that antidiuresis occurs even when the fluid intake at night equals that of the day.

body fluids, the experiments are not designed to throw any light upon the mechanisms involved.

Wolf[2258] reports that, when protracted water diuresis is maintained in man by repetitive drinking at rates varying from 6 to 10 cc/min, the rate of excretion of water comes ultimately to exceed the rate of intake by an average of 8 per cent The total output, including insensible loss (0 7 cc/min.), may exceed intake by 15 to 25 per cent During this maintained diuresis, the chloride concentration of the urine decreases to a minimum of *c* 34 mEq/liter, the rate of excretion leveling off at *c* 0 28 mEq/min. The reasons for continued chloride excretion are unknown, and no information is available relative to sodium balance, but the data are interpreted as showing that sustained water diuresis of sufficient magnitude has both a dehydrating and chloruretic effect.* Wolf finds that the chloride lost during diuresis, if referred to the excess water excretion plus water lost by insensible perspiration, has the proportion of about 170 mEq/liter, a figure identical with the non-limiting isorrheic concentration in dog and man, implying that the excess water is excreted because of the loss of chloride from the body. (This relationship breaks down when the water intake exceeds 10 cc/min., presumably because the kidneys are unable to excrete water as fast as it is ingested and the condition of a 'steady state' cannot be maintained.) One might infer that the addition of salt to the ingested fluid to the extent of 40 mEq/liter results in an equalization of the relative rates of salt and water intake and output (minimal isorrheic concentration), compensating for the disturbance in sodium balance occasioned by water diuresis.

Wolf and Ball[2261] have studied the 'steady states,' with respect to sodium and sulphate excretion, which are reached in the dog as a result of the prolonged infusion of various sodium sulphate solutions. They find the infusion of isotonic sodium sulphate (134 mM/kg. water at 4 1 cc/min.) leads ultimately to a urine flow close to the rate of infusion

In the absence of more detailed knowledge of the effects of such solutions on glomerular and tubular activity, the data collected during sustained infusions throw no light on the fundamental renal operations or upon non-renal factors which may be important in controlling sodium excretion. The analysis of renal function must necessarily progress slowly, but it seems doubtful to the writer that it will be accelerated by the empirical approach

*The dehydrating and chloruretic effects are not demonstrated at diuretic rates as low as 5 liters/day of water (3 cc/min), as recommended for the treatment of cardiac edema [1779]

of 170 mEq. presumably represents a fluid upon which, after prolonged infusion, the body performs no changes in its overall operations of salt and water conservation. This figure is not far from the isosmotic concentration of sodium chloride (0.945 gm/100 cc. of water, or 161 mEq/liter) and it is not clear whether or not the difference is significant.

At infusion concentrations above c.500 mEq/liter, relatively more water than salt is excreted, so that dehydration and salt retention occur. Such infusions are rapidly injurious, leading to intense thirst and sodium intoxication * Between concentrations of 170 and 500 mEq/liter, the kidney operates to convert such fluid as is retained to a concentration of 170 mEq/liter by excreting more salt than water. This is essentially the 'threshold' plasma concentration (106 mEq/liter) described by Rehberg,[1659] at which water and salt were reabsorbed (and therefore excreted) in exactly the same proportions as they are present in plasma. Conversely, between 40 and 170 mEq/liter the kidney operates to convert the retained fluid to a concentration of 170 mEq/liter by excreting more water than salt. At 40 mEq/liter, the urine again has the same concentration as the infusate This is virtually a state of water diuresis with salt loss which is perfectly compensated by the simultaneous excretion of infused salt, as described below. Below 40 mEq/liter, more water than salt is excreted—the response is that of simple water diuresis. For urea, the only isorrheic concentration is 35 mg/cc., which appears to reflect a maximal urinary concentration during the steady state of Wolf's experiments. Wolf[2259] has applied his overall balance studies to the excretion of potassium chloride, potassium bicarbonate, ammonium chloride, and sodium bicarbonate, and presented certain 'constants' which he believes to be physiologically significant. He has also presented a method of calculation of the osmotic changes in the extracellular fluid induced by varying loads of solute.[2259]

Wolf's non-limiting isorrheic concentration for sodium chloride (170 mEq/liter) is, as noted above, nearly identical in osmotic pressure with the plasma (161 mEq/liter). One might infer that, at this level, the complex mechanisms for conservation or rejection of water and salt are minimally activated, and with infusions of lesser concentrations the complex adjustments of the glomerular apparatus and of sodium and water reabsorption are operating to restore the plasma sodium concentration to this value. Although affording an interesting approach to the ultimate consequences of changing the volume and composition of the

* The value of 500 mEq/liter is not the maximal sodium chloride concentration of the urine, which reached 725 mEq/liter in some of Wolf's studies on the dog and 610 mEq/liter in those of Adolph on man.[27]

of the filtration rate (range 6.2 to 13 0), and the chloride U/P ratio fell from 2 or above down to exactly 1 0. Glucose excretion was only slightly increased. Although the author does not suggest this interpretation, the results are suggestive that cyanide may have a specific action on the distal tubule, blocking the distal reabsorption of sodium and water and the acidification of the urine by H^+ ion exchange; in the proximal tubule the only indicated action is the arrest of tubular excretion; the proximal reabsorption of glucose and of sodium appeared to be unimpaired.

HISTOCHEMICAL STUDIES OF CHLORIDE DISTRIBUTION

Several cytological and histochemical studies have been made of the distribution of chloride in the renal medulla and cortex by Feyel and Vieillefosse,[641] Glimstedt,[787] Ljungberg,[1256] and others before them These studies have been reviewed by Ljungberg and the present discussion will be limited to the observations reported by this investigator.

Ljungberg has applied the Linderstrom-Lang technique to the microanalysis of sections 18 75μ thick cut from a 3 mm. core of rabbit kidney. He finds that the chloride concentration in such a column shows a characteristic concentration curve increasing from cortex to medulla (fig 63) In the outermost zone of the cortex the chloride concentration averages some 2 5γ per section (142 mg/100 gm.), the concentration increases slightly within the cortex, to drop abruptly to a minimal value at 3.50 mm from the surface, and to rise again progressively to figures in excess of 90γ per section (1000 mg/100 gm) at the apex of the medulla This figure exceeds the chloride concentration in any other known tissue The minimal value at 3 50 mm. depth coincides with the boundary between the cortex and the outer zone of the medulla, the region in which the thin limb begins to appear in significant numbers among the straight segments of the proximal and distal tubules and collecting ducts That the progressive concentration of chloride in the medulla is not attributable to urine in the collecting tubules is indicated by the facts, first, that the total area of these lumina and the thin segments is only some 8 per cent of the medullary cross section; and, second, the chloride content is apparently unrelated to the urine chloride concentration, which in Ljungberg's experiments ranged from 81 to 1089 and averaged 418 ± 64 mg/100 cc

When parallel sections are stained with a silver reagent, 'argentophilia' is practically absent from the thin segment, and only faintly present in the proximal tubule and thick descending limb, it is pronounced, however, in the distal convoluted tubules and more particu-

Nelson, Rosenbaum, and Strauss (pers. com) have not confirmed Wolf with respect to the excretion of chloride during prolonged water diuresis. They find that, in normal subjects taking water at a rate of 20 cc/min. (300 cc. every 15 min.), diuresis begins within an hour and reaches a peak of 10 to 15 cc/min. within 2 hr., thereafter tending to decrease to as little as half the peak level despite the fact that water is accumulating in the body, as demonstrated by weight increase and dilution of plasma electrolytes, protein, hemoglobin, and hematocrit by as much as 10 per cent. In these experiments, prolonged water diuresis is accompanied by water retention rather than excess water excretion, but the intake exceeds the anticipated magnitude of facultative water excretion by a significant amount.

The urine chloride concentration and the rate of chloride excretion decreased to 5 mEq/liter and 0 03 mEq/min. at urine flows of 6 cc/min , and to 7 mEq/liter and 0 07 mEq/min. at flows of 10 cc/min., figures in sharp contrast to the figures of 34 mEq/liter and 0.28 mEq/min. reported by Wolf. Nelson *et al.* suggest that the maximal rate of diuresis depends on the salt load available for excretion; when salt has recently been ingested, or after preloading the day before, peak diuretic levels were attained almost twice as high as were ordinarily observed, and a diuresis of 10 cc/min. or higher was maintained for as long as 9 hr. Only by increasing the salt content of the body was it possible to avoid accumulating a positive water balance, and then this was accomplished only for the first few hours. This interpretation conforms with the view that the water available for facultative excretion is related to the distal load of sodium, as expressed above.

CYANIDED KIDNEY

Nicholson [1324] has perfused one dog kidney *in situ* with cyanided blood while using the other kidney as a control The inulin and creatinine clearances remained unchanged and identical, but the reabsorption of water was greatly reduced, the U/P ratio of creatinine decreasing from the range of 50 to 191 down to 7.4 to 17.5. There was no evidence of back diffusion of creatinine, but the urea/inulin clearance ratio fell in the average from 0.58 to 0 33, showing excessive back diffusion of urea, and revealing that this ratio (at adequate urine flows) is a sensitive indicator of tubular integrity. The tubular excretion of phenol red was entirely abolished, this clearance falling to the level determined by unbound dye. The pH of the urine changed from acid (5.57 to 6.76) or alkaline values (7.92 to 7.98) to that of the blood (7.40 to 7.55). The urine volume increased from low levels (0 35 to 1.13) up to some 10 per cent

of the filtration rate (range 6.2 to 13 0), and the chloride U/P ratio fell from 2 or above down to exactly 1.0. Glucose excretion was only slightly increased. Although the author does not suggest this interpretation, the results are suggestive that cyanide may have a specific action on the distal tubule, blocking the distal reabsorption of sodium and water and the acidification of the urine by H^+ ion exchange; in the proximal tubule the only indicated action is the arrest of tubular excretion; the proximal reabsorption of glucose and of sodium appeared to be unimpaired.

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Ljungberg has applied the Linderstrom-Lang technique to the microanalysis of sections 18.75μ thick cut from a 3 mm core of rabbit kidney He finds that the chloride concentration in such a column shows a characteristic concentration curve increasing from cortex to medulla (fig. 63) In the outermost zone of the cortex the chloride concentration averages some 2 5γ per section (142 mg/100 gm.), the concentration increases slightly within the cortex, to drop abruptly to a minimal value at 3.50 mm from the surface, and to rise again progressively to figures in excess of 90γ per section (1000 mg/100 gm.) at the apex of the medulla. This figure exceeds the chloride concentration in any other known tissue. The minimal value at 3 50 mm depth coincides with the boundary between the cortex and the outer zone of the medulla, the region in which the thin limb begins to appear in significant numbers among the straight segments of the proximal and distal tubules and collecting ducts. That the progressive concentration of chloride in the medulla is not attributable to urine in the collecting tubules is indicated by the facts, first, that the total area of these lumina and the thin segments is only some 8 per cent of the medullary cross section; and, second, the chloride content is apparently unrelated to the urine chloride concentration, which in Ljungberg's experiments ranged from 81 to 1089 and averaged 418 ± 64 mg/100 cc.

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larly in the collecting tubules.* The specificity of this method for the demonstration of intracellular chloride has been questioned by Lison,[1251] and the final interpretation of Ljungberg's studies must await further information on this point.

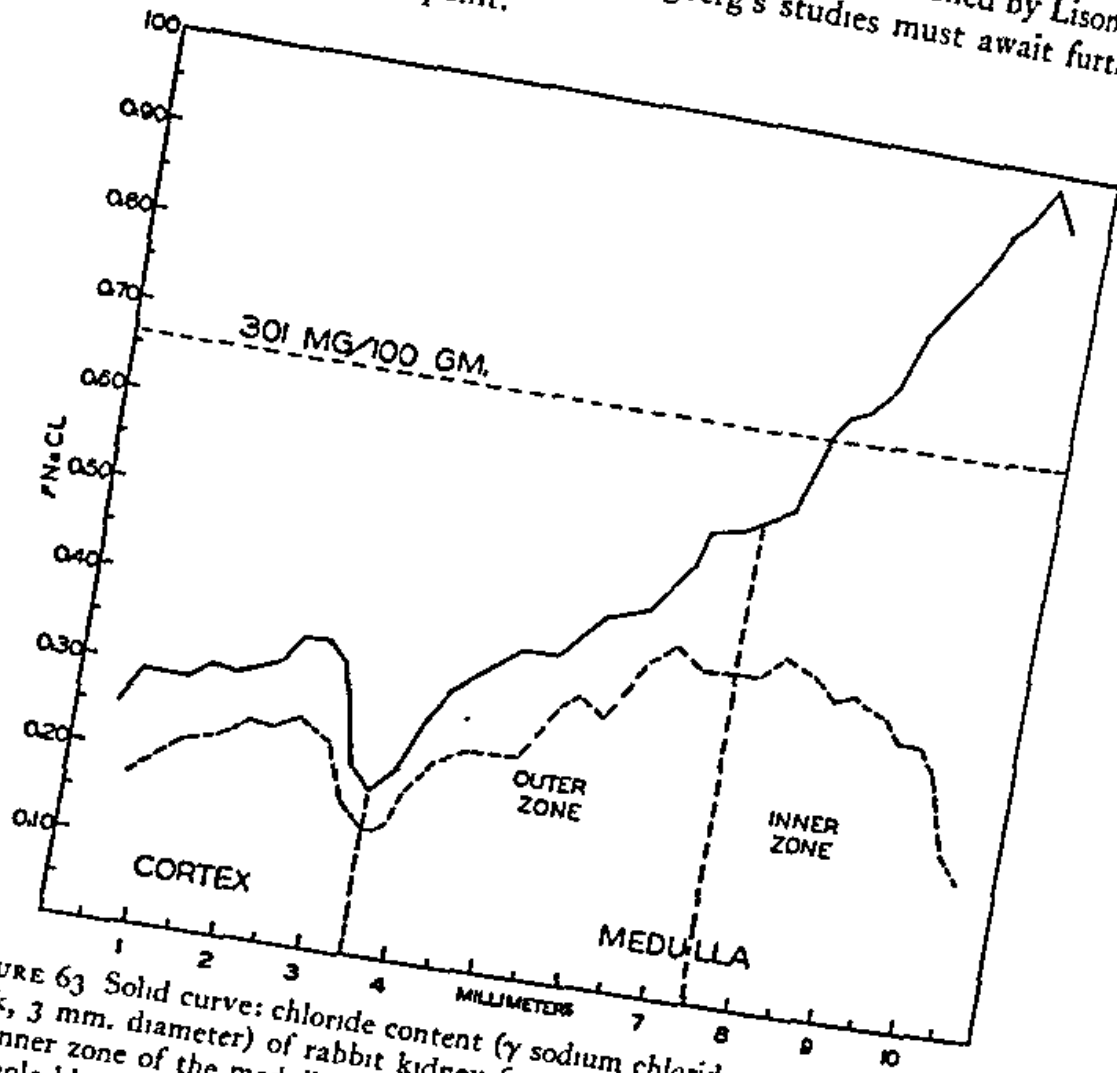

FIGURE 63 Solid curve: chloride content (γ sodium chloride per section 18.75 μ thick, 3 mm. diameter) of rabbit kidney from cortex to medullary papilla. In the inner zone of the medulla the concentration per unit volume exceeds that in whole blood (301 mg/100 cc.).
The dotted line shows the chloride distribution in the cyanide poisoned kidney. (Ljungberg [1251])

If it is accepted, as Ljungberg argues, that the intracellular argentophilic substance is chloride, it appears that the concentration of this ion in the collecting ducts reaches remarkable proportions. By various assumptions he calculates the intracellular chloride concentration to be

* The density of silver impregnation increases distally in the collecting tubules when chloride excretion is minimal, and recedes proximally when excretion is maximal. This observation presents difficulty in any interpretation.

less than 99 to 111 mg/100 gm. in the cells of the proximal tubules, and between 2500 and 2700 mg/100 gm., or 25 times more, in the cells of the collecting ducts. The plasma chloride in the rabbits with which he worked averaged 361 mg/100 cc., so that the calculations indicate an intracellular concentration in the collecting ducts some 7 times that of the plasma.

In rabbits killed 1 hr. after the injection of 2 cc. of 0 05 per cent potassium cyanide, the concentration of chloride, both as shown by histochemical analysis and silver staining, is reduced in the kidney as a whole and particularly in the distal system (fig. 63). Similar reduction is observed in Masugi nephritis [1237]

Ljungberg interprets his data as indicating that chloride reabsorption in the proximal tubule is a matter of passive diffusion, while reabsorption in the distal system is an active process and involves a step wherein chloride is concentrated within the cell However, the evidence for active reabsorption of sodium (with chloride as a passive anion) in the proximal tubule is so firmly established that it cannot be lightly set aside, and the *a priori* inference that active reabsorption requires cellular concentration is refuted (if we accept the specificity of Ljungberg's results) by the absence of a high intracellular chloride concentration in the proximal tubule Also negating this inference are the functional data on the failure of tubule cells to concentrate intracellularly substances which are actively excreted (phenol red, diodrast, and hippuran).

The intracellular concentration of chloride in the distal tubule and collecting ducts may be related to active chloride reabsorption as Ljungberg supposes; if so, it would seem that the mechanism concerns the reabsorption of sodium and not of chloride because, in the absence of an exchange anion (for which there is no evidence), chloride could not be reabsorbed without sodium, and indeed the evidence cited earlier in this chapter leads to the conclusion that it is sodium which is operated upon by the tubules and that chloride is an indifferent anion.

An alternative view, admittedly without evidential support but enticing as a speculation, is that an extraordinarily high intracellular concentration of (sodium? potassium? protein?) chloride is involved in the distal system in the reabsorption of water to form a hypertonic urine Under appropriate conditions water would diffuse into such an intracellular system by osmotic pressure to form a urine with an osmotic U/P ratio in excess of 1.0 In this theory, the water, once in the cell, would of course have to be disposed of, but this may be accomplished by metabolic disposal or by an osmotic pump that reconcentrates the intracellular electrolyte. Vaguely, the interpretation is more attractive

than the supposition that isotonic tubule cells abstract water molecules *per se* against the osmotic pressure of a hypertonic urine.

POTASSIUM

The potassium clearance under normal conditions is less than filtration rate [2259] and, since potassium is completely ultrafiltrable, it h been generally accepted that only tubular reabsorption is involved i its excretion. A potassium U/P ratio less than 1.0 has never been recorded, but this fact does not exclude active reabsorption.[2046] The regulation of the excretion of this cation is, however, very obscure. The clearance at normal plasma levels in man is independent of urine flow down to 0.6 cc/min, below which the clearance falls, possibly because of a reduction in filtration rate.[187, 655] It is said that in infants the clearance paradoxically varies inversely with the plasma level, but an abrupt increase in clearance, accompanied by a reduction in plasma level, is said to occur immediately after the oral administration of potassium salts [2232]

Isolated records of potassium clearances greater than inulin clearances [1109 1301] aroused no special interest until recently. Wirz [2149] records potassium/inulin clearance ratios in adrenalectomized cats of 1.41 and 1.55 at a time when the inulin clearance was very low, and he observed numerous ratios close to 1.0 when the inulin clearance was more nearly normal Subsequently Mudge, Foulks, and Gilman [1457] and Berliner and Kennedy [130] have independently shown that, under certain conditions in dogs, potassium-creatinine clearance ratios substantially above 1.0 may be obtained for protracted periods of time, an observation which has been confirmed by Wesson and Anslow (pers. com.) during osmotic diuresis. Mudge *et al.* found that the clearance ratio increased from 0.05 to 0.10 at normal rates of urine flow to 0.80 to 0.90 during marked urea diuresis, when the creatinine U/P ratio was about 2. At still lower creatinine U/P ratios the potassium/creatinine clearance ratio rose to 1.36. Similarly high ratios were obtained during the infusion of potassium chloride. The highest clearance ratio reported by Wesson and Anslow [2171] during mannitol diuresis was 0.95, but the ratio reached 1.91 during urea diuresis. Berliner and Kennedy found that with the preliminary oral administration of potassium chloride during the experiment, clearance ratios of 1.15 to 1.33 could be obtained for many successive periods.

It is assumed that extensive potassium reabsorption occurs in the proximal tubule, supplemented by tubular excretion in the distal system, and that the distal process, normally small, is increased during potassium overload in the body. This is the first instance in which it

has been necessary to postulate the simultaneous reabsorption and tubular excretion of any substance The physiological implications of such a double system are not clear.

The high potassium/creatinine clearance ratios are abolished by mercurial diuretics (Wesson and Anslow, pers. com.).[1458]

Berliner, Kennedy, and Hilton [132] find that, during the excretion of non-reabsorbable anions (ferrocyanide or thiosulphate), infusion of potassium regularly results in ratios of excreted to filtered which are higher than can be obtained during the excretion of chloride; the minimal tubular excretion of potassium so far exceeds the possible tubular excretion of anions that a cation exchange mechanism must be postulated.

Neutral potassium chloride and bromide when given intravenously lead to the excretion of a highly alkaline (pH 8.0 to 8 5) urine containing large amounts of bicarbonate [2219 2258] The potassium clearance in normal cats appears to be generally independent of urine flow except under conditions of extreme oliguria where emptying errors may be large.[2249]

Conway, Fitzgerald, and MacDougald [399] have shown that the proximal tubule in the isolated frog kidney contains little intracellular sodium, although it can accumulate potassium against a gradient to upwards of three times its normal concentration They believe that the cells of the proximal tubule are 'impermeable' to sodium, but freely permeable to potassium and chloride. The distal tubule, which normally contains little potassium, does not accumulate potassium over the external concentration The authors argue against the interpretation that sodium and water are reabsorbed in the proximal tubule, because sodium does not accumulate in the cell. There is no reason to expect accumulation of sodium in the proximal tubule, however, if this ion is actively reabsorbed by this segment Substances undergoing tubular transport are not stored in the tubule cells. Phenol red, for example, is excreted by proximal tubules *in vitro* against a concentration gradient greater than 100 to 1, and yet no phenol red accumulates in the cell and the evidence is against the accumulation of diodrast or hippuran in the proximal tubule during excretion in man [1955] The absence of sodium from the proximal tubule implies active transport rather than otherwise.

CALCIUM, MAGNESIUM, AND STRONTIUM

Little is known concerning the specific features of calcium excretion except for the facts that the total excretion can be increased or decreased by varying the calcium and phosphorus intake, the acid-base forming properties of the diet, and by certain physiological means such as the

administration of parathyroid hormone. The deficiency in our knowledge on how calcium is handled by the kidneys arises in part from the complexity of the physical-chemical state of this substance in the plasma.

The total calcium content of normal human plasma ranges from 9 to 11 5 mg/100 cc. (2 3 to 3 0 mM/liter). Only about half of this is diffusible,[1279] the rest being combined with plasma proteins. Calcium and magnesium proteinates are probably much less completely ionized than are the corresponding sodium and potassium salts. The dissociation of calcium proteinate is affected by the protein and calcium ion concentration, and also by pH, temperature, albumin/globulin ratio, etc. In addition, the physiological activity of the diffusible calcium depends upon its electrochemical condition. It is well known that citric, tartaric, glycerophosphoric, and other hydroxy or dicarboxylic acids form poorly ionized calcium salts, while Greenwald [856] has adduced evidence that calcium and magnesium carbonates and phosphates are not completely dissociated, and that calcium, but not magnesium, forms a complex with carbonate and phosphate having the composition $Ca_2 \cdot PO_4 \cdot CO_3$. Calcium chloride may be thought of as nearly completely dissociated into calcium and chloride ions, the former being physiologically active, but the calcium in the organic complexes is not available in an ionic condition. Most investigators have favored the belief that a significant fraction of the plasma calcium is in the form of a non-ionized, non-protein salt of such a nature as calcium citrate,[694, 1134, 2068] a fraction which is sometimes designated as calcium-X. The physiological activity of calcium-X has been investigated by McLean and Hastings,[1347] using the excised frog heart, which is extremely sensitive to the ionic composition of the perfusion fluid, as a test for calcium ions. With this biological method they have concluded that the quantity of calcium-X is normally no greater than 0.5 mg. per cent; of the remaining calcium about half is present as calcium-proteinate and half as calcium ion.

It is to be expected that the excretion of calcium will not be related in any simple manner to the total calcium of the plasma. That portion combined with protein is unavailable for filtration, as perhaps is also much of the (colloidal?) phosphate complex, and it is probable that calcium-X and other complexes formed with carbonate and phosphate, as well as poorly ionized salts of organic acids with free phosphate groups, would not be handled by the kidney as are calcium ions. Hence, clearance studies must remain ambiguous until the state of calcium in the plasma is subject to better analysis.

Physiological control appears to be such as to maintain not so much a constant concentration of total calcium in the plasma as a constant concentration of physiologically active calcium.[2068] One of the chief mechanisms involved in this regulation is the hormone of the parathyroid glands, which influences the equilibrium between plasma calcium and the calcium in the bones.

Calcium differs from sodium and potassium by the fact that when ingested much of it escapes through the bowel, only a small part appearing in the urine. This is due to the circumstance that it is precipitated as insoluble salts in the alkaline intestinal fluids. For this reason calcium chloride produces acidosis, in the net ionic balance it is as though hydrochloric acid were absorbed and calcium excreted as the carbonate, phosphate, or soap. The belief that calcium and magnesium are excreted into the bowel is challenged by McCance and Widdowson[1302] on the grounds that during prolonged intravenous administration both salts are almost completely recovered in the urine without any increase in the fecal salt. However, the intestinal secretions probably contain not less than 1 mM/liter of calcium, and the total volume of these secretions is probably not less than 8 liters/day; if this salt is precipitated like orally administered calcium, it would be lost in the stool. In this sense, it might be better to speak of the unavoidable loss of calcium, rather than its excretion, by way of the intestinal tract.

Nothing is known about the renal excretion of magnesium and strontium except that the kidney roughly distinguishes calcium from strontium, the latter being excreted more rapidly.[1018] Only one-third to one-half of the intravenously administered strontium is rapidly excreted,[1303] but, of that which is excreted, 90 per cent appears in the urine. That portion not excreted is deposited in the bones.

The administration of parathyroid hormone to normal dogs raises the total serum calcium and the filtrable calcium, and increases both the rate of tubular reabsorption and the rate of excretion. The increased reabsorption can be attributed to the increased filtered load, and it is inferred that the hormone has no specific effect on tubular activity. The hypercalcemia and hypercalcuria produced by the hormone are the results of its extrarenal actions in mobilizing calcium from body stores.[1067]

Dogs receiving steady intravenous infusions of calcium chloride or gluconate for 5 hr show no specific diuretic responses. The excretion of calcium under these conditions has been described by Wolf and Ball,[2260] but in the absence of data on plasma concentration these data are amenable only to empiric description.

IODIDE, ETC.

In experiments uncontrolled with respect to sodium excretion, the iodide clearance in the dog, at plasma levels of 5 mEq/liter, averaged about 17 per cent of the filtration rate.[600] But, on a low sodium chloride diet, the iodide clearance, at plasma iodide concentrations of 1.6 mEq/liter or less, ranged from 0.05 to 0.79 cc/min. Administration of sodium chloride increased the clearance to 17.7 cc/min., the iodide/chloride clearance ratio always being greater than 1.0.[1729] Inorganic radioactive iodide was cleared at a rate averaging 31 cc/min. of plasma in 7 normal subjects. Exclusive of observations 3 hr. or more after administration, the average clearance was 27 cc/min. in 11 patients with thyrotoxicosis. After 3 hr the plasma contains radioactive thyroxine, which invalidates renal clearance determinations.[1498]

The thiocyanate clearance in dogs is likewise very low (0 1 to 7.1 cc/min.) and related to the simultaneous excretion of (sodium) chloride, as shown by an increase in clearance after sodium chloride administration and by a positive correlation (P = +0.92) between thiocyanate excretion and chloride excretion.[2066] In man, Berger (pers com.) finds a chloride/thiocyanate clearance ratio ranging from 0.3 to 3 0, roughly scattered above and below 1 0. Breed (pers. com.) in 10 hypertensive subjects obtained thiocyanate-mannitol clearance ratios averaging 0.077 (0.038 to 0.20). The bromide clearance is likewise low, 22 observations in the dog (Berger, pers. com.) giving a bromide/chloride clearance ratio of 0.6.

Nitrate and chlorate are excreted very slowly, but no quantitative data are available

It may be recalled that iodide, nitrate, and thiocyanate are excreted by the aglomerular kidney (ch. 11).

CHAPTER XII

The Adrenal Cortex and Addison's Disease

In 1855, Thomas Addison identified the disease that bears his name with the complete destruction of the adrenal glands. Subsequent investigations have shown that the physiological disturbances in Addison's disease are apparently due to the deficient secretion of incompletely identified hormones elaborated by the adrenal cortex. A syndrome comparable in nearly all respects with Addison's disease can be produced in mammals by bilateral removal of the whole glands, or of the cortex alone. Complete bilateral destruction of the adrenal medulla is not lethal and is not related to adrenal insufficiency or Addison's disease. The most notable physiological defect in acute adrenal insufficiency is failure of sodium conservation by the kidneys, with consequent loss of sodium and water from the body, and progressive reduction of the extracellular fluid volume approaching lethal limits within a few days. Symptomatically, acute adrenal insufficiency is marked by the development of weakness, anorexia, prostration, vomiting, hypotension, dehydration, oliguria, and shock.

Most of the physiological disturbances in Addison's disease and in adrenalectomized animals appear to be secondary to oligemia (circulatory insufficiency, hypotension, tachycardia, feeble pulse and cyanosis, hepatic hypoxia and insufficiency, impaired glucose and fat absorption, elevated serum calcium, oliguria, azotemia)

since they can be partly or wholly alleviated by the administration of sodium chloride Some may, however, be related directly to impaired carbohydrate and protein metabolism, or to the unbalanced effects of other endocrine organs.

Bloody diarrhea is commonly present in the adrenalectomized dog, but even bloodless diarrhea is relatively infrequent in man Chronic adrenal insufficiency in man is characterized by acute exacerbations which punctuate a progressively downward course These 'adrenal crises' are most likely to occur following stress. Even in the absence of acute symptoms, the chronic Addisonian patient usually manifests asthenia, unusual susceptibility to fatigue, and a characteristic brown pigmentation of the skin and mucous membranes of the oral cavity, attributable to an increased production of melanin.[1974]

Baumann and Kurland [100] first called attention to a marked decrease in the plasma concentration of sodium and chloride and a rise in plasma potassium in adrenalectomized cats. Loeb [1258] showed that a significant decrease in plasma sodium concentration was characteristic of crisis in Addison's disease, and that the patient could be kept symptom-free by the addition of large amounts of salt to the diet. Loeb and his associates [1260, 1261] and later Harrop and his coworkers [926] demonstrated that the decrease in plasma sodium in the adrenalectomized dog resulted from an abnormal loss of this cation through the kidney. It is now established [1965] that the sequence of events in acute adrenal insufficiency is referable in considerable measure to progressive reduction of body fluid as a result of failure of the renal tubules to reabsorb sodium, with secondary loss of water. This dehydration is reflected by an increase in hematocrit and some increase in serum protein concentration, and by a reduction of plasma and interstitial fluid volume. With increasing dehydration, renal function decreases and nitrogen, sulphate, and phosphate retention, fixation of urine specific gravity, and failure of ammonia formation follow. In untreated patients the plasma sodium may decrease 10 to 15 mEq below the low normal value of 140 mEq/liter, and during crisis to 100 mEq/liter. Plasma chloride usually decreases more than bicarbonate. During acute adrenal insufficiency, the plasma potassium may increase from the normal value of 4 to 5 mEq/liter to

double this value, and potassium intoxication is potentiated by excessive retention.

Even in the earlier stages of adrenal insufficiency, when sodium concentration and hence the osmotic pressure of the plasma is reduced, water shifts from the extracellular to the intracellular compartment, leading to increased water content in the tissues and aggravating the reduction in plasma and extracellular fluid volume [887 1259 2034 2035 2074]

The adrenal cortex is the source of many steroid compounds, some 28 or more having been isolated, while other active compounds of unknown composition remain in the amorphous residue. These compounds appear to have two general functions. The desoxycorticosterones, i.e those lacking a keto- or hydroxy-group at carbon 11, appear to be concerned primarily with the regulation of electrolyte balance, a function which (we presume on the present evidence and contrary to a number of earlier opinions) is mediated entirely by promoting the reabsorption of sodium in the renal tubules The pure compound which has been most extensively studied is the synthetic desoxycorticosterone acetate (DCA) It has not been demonstrated that desoxycorticosterone is a normal product of the adrenal cortex, the only substance isolated from the adrenals that has strong sodium-retaining power is chemically wholly unlike desoxycorticosterone and has no effect on potassium excretion * [2060] Some of the cortical steriods exist in chemical union with ascorbic acid. The increased reabsorption of potassium characteristic of adrenal insufficiency may be related to failure of sodium reabsorption, or it more probably reflects an independent renal disturbance.[921 1729 2299] It is significant, however, that potassium retention does not occur if the sodium intake is adequate to maintain sodium balance.

That the renal conservation of sodium is, so far as short periods of time are concerned, the most important action of the adrenal cortex is demonstrated by the fact that adrenalectomized animals can be maintained in a moderately good state of health for indefinite periods simply by increasing the dietary intake of salt.

* The synthetic compounds, corticosterone and dehydrocorticosterone, though less effective than desoxycorticosterone, have a similar action on the renal conservation of sodium and the excretion of potassium

Conversely, the clinical picture of acute adrenal insufficiency can be induced in the Addisonian patient by restricting the intake of salt to about 1.5 gm/day, and corrected, except in its terminal stages, by increasing the salt intake.

The second established function of the adrenal cortex concerns the intermediate metabolism of protein and carbohydrate, especially under conditions of emergency demand. The synthetic compound E of Kendall (11-dehydro-17 hydroxycorticosterone, cortisone) is highly potent in this respect.[1263] It is not know whether or not this compound is normally elaborated by tl adrenal cortex. That it is not essential for life is shown by the fac that Addison's disease can, except for emergencies, be treated as successfully either with DCA or dietary salt as with whole cortical extract. Compound E induces moderate retention of salt and water.[1592] It has attracted attention because of the dramatic relief of rheumatoid arthritis and other conditions effected by its administration in relatively large and probably unphysiological doses.

The adrenal cortex also elaborates androgenic and estrogenic substances, but so far as is known these have no relation to renal function.

Selye [1831] has reported extensive studies of the role of the adrenal cortex in what he calls the 'alarm reaction.' Adrenalectomized animals are especially susceptible to many forms of stress such as cold, anoxia, hemorrhage, burns, acute infection, etc. Such trauma regularly cause enlargement of the adrenal glands in normal white rats in the course of a few hours, while some of them at least have been shown to bring about rapid depletion of the ascorbic acid content of the glands, perhaps indicating rapid excretion of a 'mother compound.' In such traumatized animals there is also a decrease in the cholesterol content of the glands and an increased excretion in the urine of material which prolongs the life of adrenalectomized rats, and which increases the storage of glycogen in the liver of fasted, adrenalectomized rats. This urinary corticoid material is presumed to be of adrenal origin. During these 'emergencies,' the requirement for adrenal steroids of the compound E type is increased, and adrenalectomized animals or patients with severe Addison's disease main-

tained only with DCA or salt continue to be susceptible to severe spontaneous hypoglycemia and other metabolic disturbances which may prove fatal under conditions of stress.

ADRENOCORTICOTROPHIC HORMONE (ACTH)

The adrenal cortex is under the trophic influence of the adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland, and hypophysectomy leads to atrophy of the cortex unless ACTH is administered. Dougherty and White [440] have shown that both ACTH and adrenal cortical extract cause disintegration of lymphoid tissue, a process which is accompanied by an increase in circulating gamma globulin believed to be liberated from this tissue. This increase in gamma globulin results in an increase in circulating antibodies. There is simultaneously an increased excretion of uric acid, presumably resulting from accelerated nucleoprotein metabolism. Thorn, Prunty, and Forsham [1075] have devised a test for adrenal competence based upon the administration of a single dose of ACTH to stimulate cortical secretion; the test is considered positive if the uric acid/endogenous creatinine ratio is increased in a urine sample collected during a period of 1 to 3 hr. after injection of 25 mg. of ACTH, and if the eosinophil count shows a sharp drop. 11-Hydroxycorticosterone gives a positive Thorn test, but DCA is without effect. Adrenalin has a similar action on the eosinophil count and the lymphoid tissue, since it stimulates the secretion of ACTH. It is not yet established that the increased excretion of uric acid is a result of increased production rather than decreased tubular reabsorption.*

GENERAL EFFECTS OF DCA IN NORMAL ANIMALS

Because of the ready availability of the pure synthetic preparation, DCA has been more extensively studied than any other compound related to the cortical steroids. As noted above, it is not yet determined that desoxycorticosterone is a normal product of the adrenal gland.

Administered in excessive amounts to normal animals and men, DCA induces sodium † and water retention, increased potassium excretion,

* It will be recalled that a wide variety of compounds interferes with the tubular reabsorption of uric acid.

† Contrary to its usual action in normal subjects, DCA increases sodium excretion in patients with Cushing's syndrome [1000].

and a decrease in plasma potassium.[2072, 2073] Plasma sodium may be elevated some 5 or more mEq/liter. Prolonged administration of DCA to normal dogs leads to muscle weakness with replacement of as much as 30 per cent of the muscle potassium by sodium. The blood pressure is increased in patients in whom hypertension had been present before the onset of acute adrenal insufficiency, and the development of hypertension has been reported[1691] in patients treated with DCA in whom there was no evidence of previous hypertensive disease, while hypertension, and cardiovascular and renal lesions have been produced in normal rats treated with massive doses of DCA and salt.[1825] This hypertensive effect has not been confirmed, however, in dogs on a high salt diet.[2024] Woodbury, Cheng, Sayers, and Goodman[2270b] find that the effects of large doses of DCA in elevating the plasma concentration of sodium and decreasing that of potassium is antagonized by ACTH, and they believe that large doses of DCA produce a deficiency of adrenal cortical secretion by inhibiting the adrenocorticotrophic activity of the anterior pituitary. They suggest that hypertension, increased size of the heart and kidney, nephrosclerosis, and other cardiovascular changes produced by DCA in experimental animals are toxic manifestations resulting from excess exogenous DCA and a deficiency of 11,17-oxysteroids consequent to inhibition of pituitary activity

Massive doses of DCA in normal dogs and rats lead to the development in a few weeks of polydipsia and polyuria, which are exaggerated by the dietary administration of excess salt (potassium chloride is without specific effect) Polyuria cannot be produced in DCA-treated rats on a low salt diet.[754, 1176, 1494, 1668] In neither species does the rate of fluid excretion approach the magnitude reached in diabetes insipidus, however, and, unlike diabetes insipidus, pitressin has only a moderate antidiuretic effect This polyuric action is exaggerated by hypophysectomy.[432, 636, 1668, 1833, 2242] Water and saline diuresis are accelerated by DCA and cortical extract, but the return of water is not increased.[754, 1494] DCA in doses up to 30 mg/day does not increase the water exchange of normal cats, and in this species it does not exaggerate diabetes insipidus.[2242] Normal man, given smaller doses than necessary to produce polyuria in dogs, responds to DCA by retaining sodium and water.[2071, 2292]

The increased urine flow induced by large doses of DCA (other adrenal corticoids are apparently not active in this respect) is frequently likened to diabetes insipidus, but the parallel is unsafe Gaunt, Birnie, and Eversole,[754] in reviewing this and related problems, note that two factors are involved: (a) augmentation of thirst as a result of sodium re-

tention; and (b) an assumed inhibition of tubular reabsorption of water. The evidence for the latter is, however, based largely upon the damping of water diuresis in adrenal insufficiency, the presumption being that this is due to the absence of some 'diuretic' potency in the adrenal gland. The problem is too complex for so simple an interpretation The questions of electrolyte distribution between tissues and extracellular fluid, the concentration of sodium in the plasma, changes in the filtration rate and sodium load delivered to the distal tubule, and a possible toxic effect of large doses of DCA on the tubules themselves, all require further investigation before a physiologically specific 'diuretic' activity can be attributed to DCA or any of the naturally occurring adrenal hormones.

Rusznyak, Foldi and Szabo [1763] report that desoxycorticosterone glucoside (percorten), administered intravenously, greatly increases T_{mG} They suggest that this effect results from an increase in phosphorylation in the renal tubules The phenomenon was absent in alloxan-treated animals [667] However, Lambert, Lebrun, and de Heinzelin de Braucourt [1194] report that in 10 patients the administration of percorten intravenously decreased T_{mG} by an average of 30 per cent The filtration rate, as measured by thiosulphate, was not altered Five control experiments showed that the repeated intravenous injection of glucose did not change T_{mG}, and the solvent (acetamide-glucose) was without effect The authors are examining the question whether this action of percorten is to be attributed to the fact that it is a glucoside.

Friedman, Polley, and Friedman [721] report that DCA pellets, subcutaneously implanted in rats, produce hypertension, cardiac hypertrophy, and altered renal function, the concomitant feeding of 1 per cent saline intensifies the renal changes The plasma concentrations of potassium and chloride are initially decreased, the sodium concentration and the sodium/chloride ratio are increased, and finally both sodium and potassium concentration are increased. Calcium excretion is unaffected Their interpretation of alterations in renal function following DCA administration are not completely validated by their data. They state that the alteration in renal function consists first of a reduction in the PAH clearance, but that the blood flow to each unit of functioning excretory tissue is normal so that no ischemia is present * Later the quantity of functioning tubular tissue decreases, while the renal plasma flow decreases even more, so that relative renal ischemia occurs

* The C_{PAH}/T_{mPAH} ratios appear to be incorrectly calculated in some instances, but estimations from the means of the two terms would not alter this conclusion

In this stage, gross interference with filtration is assumed to be present. However, examination of their data reveals that DCA alone had no apparent effect on renal function. The animals treated with DCA and saline did not differ from the untreated or saline controls at the end of the second week; at the end of the fourth week C_{PAH} had decreased, but only at the end of the sixth week was there a probably significant decrease in C_{PAH} and Tm_{PAH}. Apart from the interpretation of the data as presented, the normal data on C_{PAH} and Tm_{PAH} presented elsewhere (ch. XVII) by Friedman and his coworkers differ significantly from the data reported by other investigators for this species. It should be noted that the technique of renal clearance determination in rats is not satisfactory to all investigators, and observations in this species must at the present time be accepted with reservations.

Swingle and Remington [2035] concluded that DCA and related hormones directly influence the distribution of electrolytes and water between the extracellular fluid and the tissues. Gaudino and Levitt [750] have re-examined the question, using isotopic, Na^{24} and K^{42}, inulin as a measure of extracellular space, and D_2O as a measure of total body water. They find that the administration of DCA to two normal dogs led to expansion of the extracellular space (+40 to +53 per cent) at the expense of the intracellular space (−33 to −43 per cent), the intracellular concentrations of sodium and potassium being reciprocally elevated at the peak of the response. The filtration rate increased (+37 to +53 per cent), as did the renal plasma flow (+23 to +42 per cent), while Tm_{PAH} decreased (−26 to −74 per cent). Serum potassium fell to nearly half its control value, plasma sodium remaining unchanged. Total body sodium increased by 30 per cent over a period of 16 days, with a simultaneous increase in the average intracellular concentration of this ion.

Administration of cortical extract led, conversely, to expansion of the intracellular space (+25 to +39 per cent) and total body water (+30 to +49 per cent), with no alteration in the extracellular space and with no consistent changes in filtration rate or renal plasma flow. Tm_{PAH} showed marked but contradictory changes. Plasma sodium, potassium, and NPN did not change significantly. The effects of DCA and cortical extract in normal animals were transient, all variations tending to return toward normal on continued treatment, as others have observed *

That DCA in large enough doses increases the filtration rate and renal plasma flow in normal dogs has also been reported by Collings, Down-

* The effects of DCA in the adrenalectomized dog were, however, persistent, suggesting that the adrenal gland may itself destroy DCA.

ing, and Hodges,[297] who attribute these effects to increased circulating blood volume (increased extracellular fluid?).

RENAL FUNCTION IN EXPERIMENTAL ADRENAL INSUFFICIENCY

Harrison and Darrow [921] first showed that bilateral adrenalectomy in dogs is followed by reduction in filtration rate and urea clearance to some 25 per cent of the control values, an effect only partly corrected in their experiments by salt or cortical extract. They attributed the high concentration and consequent excessive excretion of sodium in the urine of the adrenalectomized dog to failure of tubular reabsorption. On the other hand, the 'maximal' U/P ratio of potassium was reduced from 40 to 75 in the normal to 10 after adrenalectomy, and they believed that this circumstance, combined with oliguria, led to potassium retention. The administration of salt, in their view, by replacing the sodium deficit in the body fluids, increases the filtration rate and urine flow and thus permits the excretion of greater quantities of potassium at a low U/P ratio, reducing the plasma potassium concentration. Cortical extract, on the other hand, not only increases urine volume but also the maximal potassium U/P ratio (from 10 up to 20 to 35) Roemmelt, Sartorius, and Pitts [1139] also conclude that the retention of potassium is a manifestation of increased specific reabsorption of this cation and not directly related to diminished sodium excretion.

The evidence seems convincing that, in the untreated animal, adrenalectomy rapidly leads to reduction of the filtration rate and modification of other renal functions Friedman *et al* [719] report that 1 day after adrenalectomy in the rat the PAH clearance and T_{mPAH} are reduced but the inulin clearance is unaffected Renal function returns to normal in 6 days. The data were, however, obtained by comparing sham-operated animals with adrenalectomized animals Boss, Birnie, and Gaunt [216] report a 33 per cent decrease in filtration rate in rats 5 days after adrenalectomy

Wirz [1249] reports marked reduction in the filtration rate in adrenalectomized cats, and Gaudino and Levitt [730] find a marked and rapid reduction in filtration rate, renal plasma flow, and T_{mPAH} in adrenalectomized dogs These, and all clinical studies in man, support the inference that the adrenal-deficient organism is delicately poised with but a small margin of safety in salt and water balance and, without perfect maintenance of the latter, slips quickly in exsiccation with significant reduction in renal function merely because of this exsiccation The im-

portance of more adequate knowledge on the filtration rate in this problem cannot be overemphasized.

If maintenance therapy with either sodium chloride, DCA, or cortical extract is adequate, the filtration rate is apparently not reduced by adrenalectomy *per se*.[719, 2205, 2249] Lotspeich [1274] found that the creatinine clearance in adrenalectomized rats maintained on a high salt diet averages 0.490 cc/100 sq. cm, as compared with 0.513 cc/100 sq. cm in controls fed *ad libitum* and 0.467 cc/100 sq. cm. in salt-fed controls; while Roemmelt, Sartorius, and Pitts [1739] found no reduction in filtration rate in adrenalectomized dogs maintained with cortical extract It seems probable that Harrison and Darrow's dogs did not receive adequate maintenance therapy.

The filtration rate, renal plasma flow, and Tm_{PAH} are not changed when calculated on a surface-area basis in normal or adrenalectomized rats treated with DCA and saline, but are decreased on the basis of kidney weight because of renal hypertrophy.[717]

The administration of adrenal cortical extract had no marked effect on Tm_D in normal or 'puncture' dogs (the slight changes were negative), or in hypophysectomized dogs, in which this function is reduced to low levels. It also had no effect on the diodrast clearance in normal, puncture dogs or hypophysectomized dogs, and only slight positive effects on the inulin clearance.[946]

Very mild adrenal insufficiency, asymptomatic and with normal blood volume and NPN, sodium, and potassium levels, was, however, accompanied by decreases in the diodrast clearance and Tm_D as marked as those observed after hypophysectomy, with small decreases in the inulin clearance. DCA pellets restored renal function toward normal The asymptomatic, adrenal-deficient dog did not respond, as did the normal or the hypophysectomized dog, to anterior lobe extract with increases in clearances and Tm_D, despite the fact that the action of the hypophysial hormone is directly on the kidney and not mediated through the adrenotrophic hormone [2204, 2206]

In Gaudino and Levitt's study,[750] during adrenal insufficiency the intracellular space increased (+15 to +30 per cent) while the extracellular space decreased (−59 to −61 per cent) * Plasma volume is said to have remained fairly constant at mild degrees of insufficiency, when changes in the other compartments were prominent (the specific gravity of the plasma and the hematocrit were increased, however). The usual

* Similar qualitative changes are reported in adrenalectomized dogs by Flanagan and Overman,[461] using the less reliable methods of thiocyanate for total body water and the single injection of mannitol for extracellular fluid.

signs of adrenal insufficiency were present: plasma sodium decreased and plasma potassium and NPN increased. The filtration rate, diodrast clearance, and T_{mPAH} all decreased.

Gaudino and Levitt conclude that the adrenal cortex has a primary influence on the equilibrium distribution of fluid between the extracellular and intracellular compartments. DCA produces a decrease in the intracellular and an increase in the extracellular space; adrenalectomy has the reverse effect Cortical extract simulates adrenalectomy in increasing the intracellular space, but it does not significantly modify the extracellular space If DCA reflects the action of an adrenal hormone, the dissimilar actions of DCA and cortical extract may reflect a possible opposing role on the part of the physiological hormones.*

The shifts of water between the intracellular and extracellular compartments cannot be related solely to the concentration of electrolytes in these compartments In normal dogs during DCA treatment, water moved out of the cells at a time when the plasma sodium was unchanged, and against an increased intracellular cation concentration; while treatment with cortical extract led to expansion of the intracellular space with no change in plasma sodium concentration At the height of adrenal insufficiency, water again shifted into the cells despite an unchanged plasma sodium concentration Assuming that osmotic equilibrium between plasma and tissues obtains at all times (an assumption that has not yet been proved), these facts indicate that adrenal activity influences the osmotically active constituents within the cell, other than sodium and potassium, so as to alter the effective intracellular osmotic pressure

These investigators note that in the normal animal some mechanism operates to maintain the volume of the extracellular space remarkably constant After adrenalectomy, it may be conceived that continued loss of sodium and water make it impossible for this mechanism to operate, that there is no specific impairment of the regulatory mechanism is indicated by the fact that the extracellular space is approximately preserved by the administration of salt alone, and changes in extracellular fluid volume are still reflected in changes in filtration rate and renal plasma flow, as in the normal animal. Apparently the adrenal gland is not necessary for the regulation of the filtration rate in relation to extracellular fluid volume. But, in DCA-treated animals, both normal and adrenalectomized, the extracellular space is excessively expanded, indicating that DCA somehow disturbs the mechanism regulating the volume.

* The adrenal cortical extract used did not contain significant quantities of DCA.

ume of this compartment without specifically blocking the control of glomerular activity.

On DCA injection, plasma volume did not increase in 2 out of 3 dogs, despite 60 and 52 per cent increase in extracellular space, and in severe insufficiency the decrease in extracellular fluid on a percentile basis was about twice the decrease in plasma volume. This dissociation indicates that plasma volume is not a sensitive index of extracellular space.

Under conditions of dehydration, the maximal concentration of urine of the adrenalectomized dog, as judged by specific gravity chloride content, is considerably less than normal.[1152] So, too, in pers with Addison's disease the maximal concentration of sodium in nig (oliguric) urine samples is less than in normal subjects, while the co centration tends to remain fixed after the ingestion of water because c damped water diuresis. These two circumstances lead to fixation of uri nary concentration at an intermediate value, a phenomenon which has been made the basis of diagnostic tests for Addison's disease.[1697, 1734]

In adrenalectomized animals and Addisonian patients, water diuresis is typically diminished in extent and water excretion delayed in time.[753, 754, 757, 1182, 1734, 1878] This blunting of diuresis is said to be uncorrected by the administration of salt, despite the fact that, in adrenalectomized dogs maintained on a high sodium, low potassium diet, the urine formed at the peak of water diuresis is as dilute or nearly as dilute as that obtained in intact animals. Abrupt water diuresis is in part restored by cortical extract, compound E, and the 11-oxygenated cortical steroids, but DCA is less effective.[216, 754, 1274, 1739] It seems probable that the blunting of water diuresis is attributable in great part to reduced filtration rate, which results in reduced load of sodium and therefore water delivered to the distal system, supplemented perhaps by continuous secretion of ADH.

Diminished water diuresis in adrenal insufficiency is not related to the absence of the adrenal medulla. Bilateral demedullation in rats has no effect on the course of diuresis, even though the injection of adrenalin into normal animals under certain circumstances augments the diuresis to such an extent that dehydration may result even while water is being administered.[756]

Adrenalectomized animals develop water intoxication after the retention of less water than is required in normal animals, a sensitivity corrected to some extent by adrenalin, which increases the diuretic response in the rat; by DCA; and, more effectively, by compound E.[611, 752, 944, 2036] The protective action of DCA is in part attributable to the promotion of diuresis,[176] (possibly because of an increase in the filtra-

tion rate) and possibly in part because of changes in the electrolyte content of the tissues and extracellular fluid

Unilateral adrenalectomy moderately increases renal function on the operated side, but apparently only by interfering with the renal innervation.[1171]

Plasma urea and NPN are reported to rise in adrenalectomized dogs maintained on DCA, while plasma sodium and potassium and the filtration rate are still normal. There is no decrease in the urea/inulin clearance ratio, and hence elevation of plasma urea implies increased protein metabolism [2205]

ACTION OF DCA ON SODIUM REABSORPTION BY THE RENAL TUBULES

It has been widely assumed that DCA acts directly on the renal tubule to promote sodium reabsorption, and that it is simply the absence of this positive effect that leads to increased sodium excretion in adrenal insufficiency. Some investigators, however, have suggested a more complicated interpretation.

Silvette and Britton [1893] reported that adrenalectomized opossums do not excrete sodium as readily as do controls and, consequently, they show a greater rise in serum sodium and chloride concentration after saline administration. Cortical extract increased sodium excretion in both normal and adrenalectomized animals receiving distilled water, though the effects were variable when saline was given Posterior pituitary extract increased sodium excretion in adrenalectomized animals, an effect evident to a lesser if not negligible degree in normal animals. Oliguria is characteristic of adrenalectomized opossums as of other mammals, and during oliguria there is a general tendency for the urine flow to vary with sodium excretion; since the urine flow was increased by cortical extract in both normal and adrenalectomized animals (perhaps more so in the latter), Silvette and Britton spoke of this extract as being 'diuretic,' and concluded that there is a specific hormone of the adrenal cortex that acts in the kidney to produce (water) diuresis, antagonizing the influence of ADH. Their interpretation clearly defines the antagonism in terms of the reabsorption of water by the renal tubules, a view which then and now is unwarranted, since the filtration rate may have been increased in both normal and adrenalectomized animals (more so in the latter), thus delivering more sodium and water to the distal system and promoting either sodium or water diuresis. Because ADH inhibits water diuresis, Silvette and Britton spoke of a

physiological antagonism between the adrenal gland and the neurohypophysis. Such antagonism has also been inferred from the circumstance that adrenalectomy prevents transient polyuria in hypophysectomized rats.* [434] The demonstration that DCA reduced sodium excretion, whereas pitressin increased it,[433] shifted the supposed antagonism between the adrenal cortex and the neurohypophysis to the reabsorption of sodium, rather than water, a view which has recently received support from Pitts and his coworkers.

Roemmelt, Sartorius, and Pitts [1739] have shown that the adrenalectomized dog, when given saline, concentrates sodium to as great a degree or greater than does the normal animal, showing that a reduction in the limiting maximal concentration of the urine *per se* cannot explain the renal deficiency in reabsorption. They find, however, that in the adrenalectomized dog the capacity to excrete sodium after saline administration is reduced, as is the capacity to excrete water. The depression of water diuresis they attribute to overproduction of ADH and/or increase in sensitivity of the renal tubules to this hormone, since Birnie *et al.*[176 754] have reported an increased quantity of antidiuretic and chloruretic substance in the blood of adrenalectomized rats.† In their view, increased secretion of ADH (or increased sensitivity of the tubules to ADH) leads to excessive water reabsorption, and the resulting oliguria leads, by a mechanism that is not clear, to an increased reabsorption of sodium; this is in turn reflected in an inability to excrete this ion with normal effectiveness after loading the body with saline. They attribute the loss of sodium from the body at normal loads, the cardinal feature of adrenal insufficiency, to the natriuretic effect of ADH, present in maximal concentration in this condition; the hypothesis in this form thus shifts the explanation of the failure of the kidney to conserve sodium from a deficiency of DCA and its positive action on sodium reabsorption to the excessive natriuretic effect of ADH. This theory of a reciprocal or antagonistic action between ADH and DCA is extensively developed by Gaunt, Birnie, and Eversole [754] in the interpretation of the symptom complex of adrenal insufficiency.

* The blunting of polyuria in hypophysectomized animals has an adequate explanation in the marked drop in filtration rate (ch. xv) without further complicating a surgically and physiologically involved situation by adrenalectomy

† The questionable significance of such tests is discussed in chapter x

Certain observations of Winter and his colleagues are of interest in this connection. The injection of 3 units of pitressin 3 times daily leads to a strongly negative sodium and chloride balance in cats, but the effect is temporary and is followed by a compensatory retention whether the injections are continued or not. Salt excretion is said to be much less affected in diabetes insipidus animals than in normals, a circumstance which appears to apply to man (ch x).

The transient polyuria and the onset of permanent polyuria in diabetes insipidus cats are both accompanied by abrupt, parallel increases in chloride excretion, but compensation occurs within 2 or 3 days so that ultimately chloride balance is re-established despite the absence of ADH

After adrenalectomy, cats with diabetes insipidus show an early negative sodium balance similar to adrenalectomized animals with intact neurohypophysis. Since the neurohypophysectomized-adrenalectomized animals die sooner than do animals with intact hypophysis, their postadrenalectomy loss of electrolyte is, in the total, not so great. Such animals do not show the decreased plasma sodium and chloride concentration characteristic of adrenalectomy, presumably because of concurrent loss of water, but the characteristic increase in potassium still occurs.

The facts that adrenalectomy leads to a negative sodium balance in the diabetes insipidus animal, as in the animal with intact neurohypophysis, and that pitressin has little or no natriuretic activity in patients or animals with diabetes insipidus require reconciliation with the theory of Roemmelt *et al.*, i.e. that natriuresis is attributable to excess secretion of or increased sensitivity to ADH.*

Sartorius and Roberts [170] re-examined the problem in the dog and found that, in well-hydrated dogs (40 cc/kg. *per os*), pitressin in single doses of 0.8 to 8.0 milliunits/kg. produced, after a latent period of about 15 min., an increase in sodium excretion which at the larger dose amounted to a maximum of 100 microEq/min. and

* The fact that when pitressin is given to adrenalectomized cats the excretion of sodium is not increased as in the normal animal [169, 170] is compatible with the theory of pre-existing maximal ADH activity, if such maximal activity can be firmly established

lasted for 80 min. or more. Antidiuresis was present for the first 30 min. and was succeeded 1 to 1½ hr. later by an increase in urine flow of undetermined origin, which on occasion reached 4 to 5 cc/min. The intravenous administration of DCA (80 microgm/kg.) in a sesame oil-aqueous emulsion to hydrated dogs excreting sodium at rates within 10 and 30 microEq/min. led, after a latent period of 45 min., to a sharp decrease in sodium excretion which lasted for some 75 min. This decrease in sodium excretion was accompanied at first by a moderate reduction in urine flow, but ultimately resulted in diuresis. DCA had no effect on urine flow in dogs hydrated in the standard manner, or upon the retardation of diuresis effected by 0.8 milliunits of pitressin given 15 min. after the water load. The authors therefore conclude that DCA has no effect on water diuresis *per se*, or on the action of pitressin on water diuresis.

But when pitressin (0.8 milliunit/kg.) was combined with DCA in increasing doses, the natriuresis characteristic of pitressin was progressively reduced, reaching a low value of 18 per cent of the control rate established by pitressin alone when the dose of DCA was 80 microgm. The authors suggest a quantitative relation between the two agents, as suggested by Silvette and Britton. Both DCA and pitressin independently increased potassium excretion, and, when given in combination, showed almost complete summation in this respect. The authors believe that all these effects are independent of changes in the filtration rate.

Sartorius and Roberts thus find no evidence that DCA exerts a diuretic action (referable specifically to water reabsorption or antagonism to ADH). They do, however, affirm the conclusion that sodium excretion, at least within certain limits, is determined by the balance between the natriuretic effect of ADH and the sodium conservation effected by DCA (or a similar hormone in the body). In adrenal insufficiency, excessive pitressin secretion leads to sodium loss by inhibition of sodium reabsorption.*

* They note that the 'diuretic activity' of DCA was established on long urine collection periods, which are complicated by variable water intake, and that others [1494, 1668] have presented evidence that the polyuria of DCA intoxication is secondary to polydipsia; DCA leads to increased sodium reabsorption and secondarily to an increased filtration rate [1112] and/or increased water intake.

Sartorius and Roberts attribute the retention of potassium in adrenal insufficiency to the absence of a DCA-like hormone which inhibits potassium reabsorption, supplementing the similar action of ADH. The blunting of water diuresis they attribute to the unopposed action of excessive ADH secretion or to increased sensitivity of the renal tubules to this hormone.

The foregoing theory requires that pitressin possess a sustained natriuretic effect in all pertinent circumstances * in adrenal-deficient animals, and that an increased secretion of ADH be characteristic and invariable in all conditions involving failure of sodium conservation in the adrenal-deficient animal, or that the tubules be hypersensitive to this hormone.† If the premises are acceptable, the theory may be said considerably to reduce existing chaos.

Clearly, however, a final interpretation of the action of DCA and other adrenal cortical hormones on the tubular reabsorption of sodium and water must await further investigation. It may be tentatively accepted (as has so long been believed) that DCA (and a DCA-like hormone from the adrenal cortex) specifically increases sodium reabsorption in the renal (distal?) tubule; and that, in appropriate doses and under certain circumstances, ADH inhibits sodium reabsorption in the renal (distal?) tubule. But, if the data on water diuresis are correctly interpreted (ch. x), the secretion of ADH is a highly labile function, ranging from very little in habitual water consumers to almost continuous activity in men living under arid, dehydrating conditions. On the other hand, the sodium balance of the body (to repeat) is one of the most carefully guarded features of the *milieu interieur*. Consequently, to suppose that sodium balance is inversely (and precariously) related to water balance goes against the basic physiologic facts that men do not go into exsiccatory (equivalent to adrenal) failure during prolonged dehydration so long as extrarenal salt loss is

* Several reports have been cited in chapter x indicating that pitressin has no natriuretic action in normal subjects or dogs during water diuresis or in diabetes insipidus

† The difficulty of interpreting all tests for ADH, even by the use of massive quantities of concentrated urine (much less small quantities of plasma), has been noted in chapter x The postulate of hypersensitivity to ADH is, at the moment, perhaps gratuitous.

avoided, or develop edema as a result of protracted hydration. It is perhaps worthy of note that two factors may have opposite effects, without being physiologically antagonistic in the regulation of a steady state: *viz.* insulin and adrenalin, or synaptic fatigue and skeletal muscle tone.

The retention of potassium Pitts and his coworkers attribute to a specific increase in the reabsorption of this ion, unrelated to sodium reabsorption, since the time courses of the action of DCA on the two processes are different. That the retention of potassium is a renal affair is shown by the fact that neither DCA nor cortical extract influences the rising plasma level of potassium in nephrectomized dogs, i.e. these hormones are without effect upon the distribution of potassium within the body.[2240] Wirz [2249] reports that the potassium clearance is consistently reduced in adrenalectomized cats during insufficiency, but may nevertheless exceed the inulin clearance by 40 per cent or more.

The administration of cortical extract and of DCA to adrenalectomized dogs in the experiments of Roemmelt *et al.* led to an increase in renal plasma flow substantially greater than was observed during salt maintenance, with no change in filtration rate and despite the fact that the filtration rate had not been reduced before adrenal therapy.

RENAL FUNCTION IN ADDISON'S DISEASE

Margitay-Becht and Gomori [1384] were the first to attempt to assess the filtration rate in patients with Addison's disease. In 3 patients they found values for the creatinine clearance of 68, 63, and 56 cc during crisis, figures far below normal. Therapy with cortical extract increased these figures to 105, 109, and 144 cc., practically within the normal range. McCance [1290] reported a single patient not in crisis who had an inulin clearance of 50 cc.

Talbott, Pecora, Melville, and Consolazio [2043] studied 10 patients with chronic adrenal insufficiency, some of whom suffered pan-hypopituitarism. In most instances the patients were well compensated at the time of study and the renal changes, therefore, reflected the chronic effects of adrenal insufficiency rather than the disturbances of crisis. All Addisonian patients showed a low normal to very low filtration rate. DCA therapy increased the

filtration rate by an average of 32 per cent, cortical extract producing no greater improvement. Limited observations on the diodrast clearance showed proportionately less reduction in renal plasma flow, and a somewhat low filtration fraction. The filtration rate was also markedly reduced in the patients with pan-hypopituitarism, and the diodrast clearance was very low in the 2 patients studied. In the few patients examined in both groups glucose Tm was markedly decreased, diodrast Tm only slightly so.

Sanderson [1166] reported that the inulin clearance in 4 Addisonian patients during periods of insufficiency ranged from 55 to 58 per cent of normal, the diodrast clearance from 58 to 77 per cent. Tm_D had a value ranging from 61 to 92 per cent of normal, but a specific deficiency in this value cannot confidently be inferred from the data, especially in view of the reduced renal blood flow. The filtration fraction was low or low normal. Treatment with salt and DCA increased the filtration rate in only 2 subjects and the plasma flow in 1 but the filtration fraction increased in all 4. Treatment had slight positive effect on Tm_D. He suggested that the consistent rise in filtration fraction is related to the rise in blood pressure under therapy.

Waterhouse and Keutmann [2150] studied 13 Addisonian patients who were receiving either salt therapy or DCA and who were in good clinical condition at the time of examination. In 7 women the filtration rate, renal plasma flow, and Tm_{PAH} were consistently below the normal limits * Renal blood flow and filtration rate were also subnormal in all 6 men; renal plasma flow was markedly reduced in 1, but remained normal in 2 who had anemia (in anemia the blood flow but not the plasma flow is reduced [216]). Tm_{PAH} was within normal limits in all men except 2 who had hypertensive disease, which may itself reduce this function. The filtration fraction was low on salt, and subsequently increased in 2 patients who were treated with DCA; this fraction was normal or slightly elevated in all but 1 of the patients who had been maintained with DCA or cortical extract. Although the C_{PAH}/Tm_{PAH} was low normal in the patients on salt therapy, those who had been on DC

* The excretory activity of chick proximal tissue in tissue cultures is increased by whole cortical extract and by compound E, but not by compound A or amorphous fraction L-Ascorbic acid is also ineffective.[241]

therapy for long periods, or who had pituitary insufficiency, showed a relatively greater reduction of renal blood flow than of Tm_{PAH}. This finding suggests that DCA therapy operated either to maintain Tm_{PAH} or to reduce the effective renal blood flow, perhaps by an adverse action on the renal vascular tree.

From Waterhouse and Keutmann's observations, it appears that the patient with Addison's disease prior to specific therapy will show a low filtration fraction, in contradistinction to panhypopituitarism where the untreated subject may be expected to show a high filtration fraction. None of the functions studied increased consistently under treatment with DCA or cortical extract, and it may be that the treatment was inadequate or that irreversible changes had occurred in the kidneys. In this connection, the sex differences noted above are of interest. The renal blood flow and filtration rate were more markedly reduced in women than in men, and in women Tm_{PAH} was reduced whereas it was normal in 4 men without hypertensive disease. Testosterone propionate failed to restore Tm_{PAH} in women, although the authors recognize that hormonal factors made by the testes appear to maintain a sex difference in Tm_{PAH} in favor of males. However, testosterone propionate is ineffective in increasing tubular function in dogs and man, despite its renotrophic action in rodents (ch. xv).

Repeated administration of ACTH increased the filtration rate, renal plasma flow, and uric acid clearance in 2 patients with hypopituitarism and in 1 patient with lymphatic leukemia, but not in a patient with pernicious anemia.[987]

As Talbott *et al.*[2043] observe, the pathogenesis of depressed renal function in Addison's disease is functional, in the sense that no structural changes are consistently observed in the kidneys of patients who have died of advanced adrenal insufficiency. Nevertheless, the data indicate that some impairment of the vascular tree and tubules of a profound and difficultly reversible nature occurs in chronic disease and, in acute adrenal insufficiency, marked reduction of blood flow, filtration rate, and Tm_{PAH} occur, though possibly entirely because of circulatory insufficiency.

Clinical disturbances of unidentified etiology have been described, in which there is abnormal retention of sodium and chlo-

ride, presumably renal in origin,[41] but the mechanism is wholly obscure.

CUSHING'S SYNDROME

Cushing's syndrome is accompanied by hyperfunction of the adrenal. In such subjects, DCA caused an increased excretion of sodium rather than retention [1950, 1951] When 400 cc. of 5 per cent sodium chloride were given to 3 normal subjects, chloride and water excretion increased slightly during the next 80 min , while in patients with Cushing's syndrome chloride and water excretion were much more markedly increased. The effects of hypertonic saline on the filtration rate and renal plasma flow in both groups were slight and inconstant. The authors incline to the view that in Cushing's syndrome there is increased production of hormones of the 17-hydroxycorticosterone type, which are believed to accelerate the excretion of sodium.

CHAPTER XIII

Acid-base Equilibria in Plasma and Urine

EXCRETION OF ACID

One of the most carefully guarded features of the electrolyte pattern of the plasma is the H^+ ion concentration, which is maintained close to pH 7.4 by the buffering action of the salts of weak acids. Because of its great importance in the neutralization of acids other than H_2CO_3, the plasma $BHCO_3$ is frequently called the 'alkali reserve.' For the neutralization of H_2CO_3 itself the other buffers of the blood and tissues, and chiefly the BHb of the red blood cells, afford a supply of base which is commonly designated as 'total available base.'*

In the plasma, and hence in the glomerular filtrate, all the acid-base components—H_2CO_3, HPr, $H_2PO_4^-$, etc.—are necessarily in equilibrium with the same H^+ ion concentration, and it is improper to say that the latter is determined by any one buffer system. But, in quantity of production and excretion, the H_2CO_3—$BHCO_3$ system is by far the most important. H_2CO_3 is the chief acid formed in the oxidation of food; the quantity produced by a normally active man amounts to over 20 mols/day, equivalent to 2 liters of concentrated HCl or over 20 times the total available

* We may omit the hemoglobin of the red cells from the following discussion, although this constitutes the chief source of alkali for the respiratory transportation of CO_2, and is second only to $NaHCO_3$ in buffering the blood against the invasion of fixed acids, it participates in renal function only indirectly through the plasma, since the kidney cannot operate upon it directly.

EXCRETION OF ACID

base in the body, which may be taken as 1000 mEq. Because of the volatility of its anhydride, CO_2, this acid is excreted almost entirely by the lungs. Thus, in the first instance, the respiratory center is charged with the chief responsibility for regulating the H^+ ion concentration of the plasma by regulating its CO_2 tension. But, according to the mass law, $BHCO_3$* plays stoichiometrically an equal part with H_2CO_3 in determining the H^+ ion concentration, and respiration has no power to regulate the concentration of $BHCO_3$ in the plasma, which is accomplished entirely by the kidneys. So, in the final analysis, the regulation of the H^+ ion concentration of the plasma or, more broadly, of the acid-base equilibria of the body fluids, is much more of a renal than a respiratory problem

Tending to deplete the body of its $BHCO_3$, or more accurately of its available base, are such non-volatile acids (H_3PO_4, H_2SO_4, lactic, β-hydroxybutyric, etc.) as are produced by normal or abnormal metabolism The daily metabolism of 100 gm. of protein produces on the average 60 mEq of sulphate by the oxidation of the protein S, and a quantity of phosphate by the oxidation of protein P, which requires 50 mEq of base for its neutralization to pH 7 4. An additional 50 mEq. of base are required to neutralize the phosphate from 100 gm. of fat containing 10 per cent lecithin. Although most proteins bind considerable fixed base at pH 7 4, and meat contains some $NaHCO_3$, the potential acid exceeds the intake of available base by some 50 to 100 mEq/day. In severe ketosis, an additional burden of 500 mEq. or more of β-hydroxybutyric acid may be added from the incomplete oxidation of fatty acids, half of this acid requiring base for its neutralization at the maximal acidity of the urine (pH 4 5).

A normal man excretes 10 to 30 mEq. of free acid per day, and 30 to 50 mEq of acid combined with ammonia. In diabetic acidosis the free acid may increase to 70 to 150 mEq, and the acid combined with ammonia to 300 to 500 If supplied with adequate urinary buffer, the human kidney can excrete at least 480 mEq of free acid per day In nephritic acidosis the free acid drops to 2 to 20 mEq. and that combined with ammonia to 0 5 to 15 mEq/day.

* The expression $BHCO_3$ is to be preferred to $NaHCO_3$, since any cation may participate in the stoichiometric reactions described here.

2. By forming NH_3 from amide and amino acid precursors. This synthetic cation serves as a substitute for inorganic base in the neutralization of H_2SO_4, BH_2PO_4, etc., permitting the further conservation of B^+ and accounting for the excretion of 20 to 5 mEq. of acid per day, though this figure may reach 500. The relative importance of these processes in ammonium chloride acidosis is illustrated later in this chapter (fig. 72).

ACIDIFICATION OF THE URINE

The acidification of the urine is accomplished as follows: the glomerular filtrate contains approximately the same concentration of $BHCO_3$ per kg. of water as the plasma, the sole deviation being that due to the Donnan equilibrium; part of this $BHCO_3$ is normally reabsorbed as such in the proximal tubule, the remainder being passed to the distal tubule where the urine is acidified. Here H^+ ions are added by the tubule cells to the tubular urine, with two consequences: (a) the urinary buffers are converted in part (in inverse proportion to pK′) to free acids; and (b) the B^+ ions thus liberated are made available for reabsorption by the tubule cells:

(1) $$\downarrow H^+ + BHCO_3 \rightarrow H_2CO_3 \rightarrow CO_2 + B^+\uparrow$$

(2) $$\downarrow H^+ + B_2HPO_4 \rightarrow BH_2PO_4 + B^+\uparrow$$

(3) $$\downarrow H^+ + B\ \text{lactate} \rightarrow \text{lactic acid} + B^+\uparrow$$

(4) $$\downarrow H^+ + BA \rightarrow HA + B^+\uparrow$$

The CO_2 formed from $BHCO_3$ is reabsorbed as such by passive diffusion into the tubule cells and is there available to combine with reabsorbed B^+ to form $BHCO_3$, which is then returned to the plasma, the final acidified urine having a CO_2 tension equal to that of the renal venous blood. B^+ liberated from acids other than CO_2 is also reabsorbed with Cl^- to form plasma BCl.

It is to be noted that the two major buffers present in the plasma and the glomerular filtrate, $BHCO_3$ and B_2HPO_4, are themselves subject to elective reabsorption by the tubules. The acidification of the urine therefore presents the circumstance that two or more buffer systems, the acid-base equilibria of which are interde-

pendent because they are contained in the same solution, require more or less independent excretion.

THE ISOHYDRIC PRINCIPLE APPLIED TO PLASMA AND URINE

In accordance with what the physical chemist calls the isohydric principle, all buffers in a common solution are in equilibrium with the same H^+ concentration, and therefore the acid/salt ratio of any one buffer determines this ratio for all other buffers, the respective ratios being in inverse proportion to the dissociation constants of the respective acids:

$$(H^+) = \frac{(HA_1)}{(A_1^-)} k_1 = \frac{(HA_2)}{(A_2^-)} k_2 = \frac{(HA_3)}{(A_3^-)} k_3 \cdots \quad (5)$$

This equation applies independently to plasma and urine since (H^+) in these two fluids is independent

The important normal buffers common to plasma and urine are H_2CO_3—$BHCO_3$ and BH_2PO_4—B_2HPO_4 (the full list would of course include β-hydroxybutyric acid, acetoacetic acid, certain amino acids, creatinine, etc.) and any change in the ratio $(HA)/(A^-)$ for one of these buffers must be accompanied by a simultaneous change in the ratio for all others. Since all buffer ratios are dependent on (H^+), the acidification of the urine could theoretically be effected by a tubular operation on any one of the molecular species involved (i.e. on H_2CO_3, $H_2PO_4^-$, HCO_3^-), or on any two of them, or upon the H^+ ion alone. If for example H_2CO_3 and HCO_3^- were reabsorbed (singly or independently of each other, as might be the case) the ratio $(H_2PO_4^-)/(HPO_4^{=})$ would be set by the resulting value of (H^+), in accordance with the ratio $(H_2CO_3)/(HCO_3^-)$, or, if the urine were acidified by the addition of (H^+) to a specified concentration, then both $(H_2CO_3)/(HCO_3^-)$ and $(H_2PO_4^-)/(HPO_4^{=})$ would be set by this operation.

The excretion of HCO_3^- in the urine in either acidosis or alkalosis, and indeed the distribution of this ion between the plasma and any body fluid, presents a unique situation. In general, CO_2 penetrates tissues so rapidly (10 times as rapidly as O_2) that the CO_2 tension of two fluids separated by only a thin membrane (as is the case with the tubular urine and plasma) tend rapidly to reach the same value by diffusion.*

* A clear distinction must be drawn here between H_2CO_3 and CO_2. The physical properties of CO_2 are such as to endow it with great penetrating power, whereas in the light of our knowledge of the permeability of living cells to alphatic acids, it would be inferred that H_2CO_3 would penetrate very slowly, even more slowly than lactic or glycollic acid. In aqueous solutions at equilibrium, 99.9 per cent of the total CO_2 is present as dissolved CO_2 and not as H_2CO_3, and this is probably true of plasma and of tubular urine.

Apart from accidental factors which might retard the attainment of equilibrium, we may take the CO_2 tension of the plasma and urine* to be identical:

(6)

$$(CO_2)_u/(CO_2)_p = 1.0$$

Assuming that the equation

(7)

$$H_2CO_3 \rightleftharpoons CO_2 + H_2O$$

proceeds to equilibrium, we may write:

(8)

$$\frac{(CO_2)}{(H^+)(HCO_3^-)} = k$$

for both plasma and urine, where (CO_2) = the total unionized H_2CO_3 plus free CO_2.

Since k is a constant, the equilibrium concentration of any one of the three species involved is determined by the concentration of the other two species. This is true, with due consideration of thermodynamic activities, for both plasma and urine, and wholly apart from whether one or more of these species is transferred actively or passively from urine to blood, or *vice versa*. It follows that, if the U/P ratios of two of these species are given, for example $(CO_2)_u/(CO_2)_p$ and $(H^+)_u/(H^+)_p$, then the ratio of the third, $(HCO_3^-)_u/(HCO_3^-)_p$, is thereby fixed.

It follows from equations 6 and 8 that, in acidifying the urine, the tubules can operate on H^+ or HCO_3^- ions in the tubular urine, but not independently on both. If the tubules operate on any one of these species, then the ratio $(H_2PO_4^-)_u/(HPO_4^=)_u$ in the tubular urine is automatically set in consequence of equation 6. In view of the statement, to be supported shortly by evidence, that the tubules operate on H^+ ions, it follows that both the absolute value of $(HCO_3^-)_u$ and the ratio $(H_2PO_4^-)_u/(HPO_4^=)_u$ (and of all other buffers) are fixed by the final value of $(H^+)_u$

THE TUBULAR EXCRETION OF H^+ IN EXCHANGE FOR B^+ IONS

Pitts and his coworkers [1633 1636] point out that three theories as to the nature of this process have been proposed. We restate these theories with the additional qualifications imposed by the isohydric principle and the premise that $(CO_2)_u/(CO_2)_p = 1.0$.

* That CO_2 is not actively reabsorbed by the renal tubules is indicated, as Sendroy *et al* [1811] point out, by the fact that the CO_2 tension of the urine is never less than that of the arterial blood.

1. *The phosphate reabsorption theory:* A filtrate containing $HPO_4^{=}$ and $H_2PO_4^-$ in the ratio in which they exist in the plasma (4:1) is formed at the glomerulus. The $H_2PO_4^-$ is excreted, while variable amounts of $HPO_4^{=}$ are reabsorbed by the renal tubules and, reacting with plasma H_2CO_3, reconstitute plasma HCO_3^- and $H_2PO_4^-$.[1597] Here, tubular reabsorption determines the final $(H_2PO_4^-)_u/(HPO_4^{=})_u$ ratio, and, through the isohydric principle, this ratio determines the $(HCO_3^-)_u/(CO_3^{=})_u$ ratio, so that if $(CO_2)_u/(CO_2)_p = 1.0$, the absolute amount of HCO_3^- in the urine is fixed.

2. *The H_2CO_3 filtration theory.* The glomerular filtrate contains HCO_3^- and H_2CO_3 in the ratio of 20:1. This theory treats the renal tubules as impermeable to H_2CO_3 and to CO_2, and presupposes that they actively reabsorb HCO_3^-, the unreabsorbed H_2CO_3 and the amount of HCO_3^- left in the urine determine $(H^+)_u$.[1641] Here the ratio $(H_2PO_4^-)_u/(HPO_4^{=})_u$ is automatically set by $(H^+)_u$, but the absolute amount of phosphate in the urine depends on the reabsorption of $H_2PO_4^-$ and/or $HPO_4^{=}$.

3. *The ionic exchange theory.* Here it is supposed that the tubule cells reabsorb B^+ ions and replace them by H^+ ions by an ion exchange mechanism which operates independently of the associated anions in the urine; as acidification progresses, HCO_3^- is converted into H_2CO_3 and hence into CO_2, which largely escapes by diffusion across the tubules back into the blood.* [1928] The ratios $(H_2CO_3)_u/(HCO_3^-)_u$ and $(H_2PO_4^-)_u/(HPO_4^{=})_u$ are set by $(H^+)_u$, the absolute amount of phosphate is determined by elective tubular reabsorption of one or both phosphate ions; but if

* W. W. Smith [1944] has examined the mechanism of acidification in the urine in the dogfish, *Squalus acanthias*. In this animal, as in the marine fishes generally, the pH of the urine is relatively constant (5.7) and uninfluenced by the injection of large quantities of PO_4 (pH 7.4 to 7.7) or $NaHCO_3$. This fixed acidity appears to be an adaptation to the invariable presence in the urine of large quantities of Mg (absorbed by the intestinal tract from ingested sea water), which precipitates as $Mg(OH)_2$ or $MgNH_4PO_4 \cdot 3H_2O$ if the urine is alkalinized beyond pH 6.0. Both endogenous and exogenous PO_4 are excreted by the dogfish tubules and the urine invariably has a high PO_4 content. From observations based on the plasma and urine pH and PO_4 excretion after the administration of PO_4 or $NaHCO_3$, Smith concluded that the most probable mechanism of acidification is the substitution of H^+ for B^+ ions, after and independently of the tubular excretion of PO_4.

$(CO_2)_u/(CO_2)_p = 1.0$, the U/P ratio of HCO_3^- and the absolute amount of HCO_3^- excreted in the urine are fixed by the independently regulated terms, $(CO_2)_p$ and $(H^+)_u$.

Any one of these theories is plausible,* but in the first two the maximal quantity of titratable acid which can be excreted is limited by the quantity of $H_2PO_4^-$ or H_2CO_3, respectively, contained in the glomerular filtrate. In the third theory, the limit of acid excretion would be determined by the quantity of H^+ ions which the tubules could add to the tubular urine. Although the maximal H^+ ion concentration of the urine is limited to about pH 4.8, the *quantity* of H^+ ions added to the urine (i.e. the maximal quantity of titratable acid) will be conditioned by the presence in the tubular urine of one or more suitable substrate buffers with which the added H^+ ions can react, as in equations 1 to 4 Given adequate substrate buffer, the maximal quantity of titratable acid would presumably be limited only by the maximal rate of H^+ ion exchange.

Pitts and Alexander [1636] have determined the maximal rate of titratable acid excretion during acidosis in the dog, when the urine is enriched with substrate buffer in the form of phosphate or creatinine. They find that this rate is so great that it can be explained only by the third theory, i.e. the tubular exchange of H^+ ions for B^+ ions.

During moderate acidosis, the dog, if supplied with adequate neutral phosphate (pK′ = 6.8) as a substrate buffer, can excrete

* Montgomery and Pierce [1469] have shown that 0 33 M sodium phosphate solution of pH 7 5, containing phenol red, when retained within the distal tubule of the frog [illegible]

mEq. (or about 80 per cent) of the [illegible]
in 126 out of 227 mEq (or 56 per [illegible]
sorb this quantity of base from the tubular urine in less than 60 seconds, and therefore neither mechanism is beyond the range of possibility But since phosphase is very slightly reabsorbed by the frog tubule when the concentration in the plasma, and hence in the glomerular filtrate, is elevated by only a few mEq., such extensive reabsorption from 0 33 M solution appears unlikely. Therefore the only plausible explanation of the acidification of the urine in the frog is the exchange of H^+ ions for B^+ ions

from 0.198 to 0.431 mEq. of titratable acid * per min., equivalent to 285 to 620 mEq/day, this titratable acid being represented in the urine by $H_2PO_4^-$. As calculated from the rate of filtration, only 17 to 24 per cent of this acid could be accounted for by the H_2CO_3 filtration theory, and only 7 to 11 per cent by the phosphate reabsorption theory. The sum of the two glomerular acids could account for only 24 to 37 per cent of the total acid excreted. Therefore another mechanism must be involved. Since no significant quantity of anion other than substrate buffer (PO_4) is present in the urine under conditions of the experiments, the tubular excretion of a third acid can be excluded and only an ion exchange mechanism is left to account for the acidification process.

Menaker [143] has pointed out that the reabsorption of B_2CO_3 or BOH from a neutral urine would lead to acidification through the shift in equilibrium between the $CO_3^=$ and HCO_3^- ions, and notes that it is impossible on the present evidence to choose between this mechanism and the H^+ ion exchange mechanism postulated above. However, as Pitts [143] noted in advance of this criticism, the most efficient anion reabsorptive mechanism known, that for HCO_3^-, is capable of 99.99+ per cent removal to a final concentration of 10^{-7} M. The accomplishment of acidification to pH 4.5 by the reabsorption of $CO_3^=$ or OH^- would require that the efficiency of the reabsorptive mechanism be nearly 1000 times that of the HCO_3^- reabsorbing mechanism. In view of the rapidity, in the experiments of Montgomery and Pierce,[143] with which pure 0.33 M phosphate solution is acidified in the distal tubule of the frog where no $CO_3^=$ ion is available, and in view of the data from comparative physiology on the permanently acid or alkaline state of certain body fluids,[118,143] the writer, even though holding the issue *sub judice*, is inclined to favor the H^+ ion exchange mechanism.

Pitts and Alexander chose creatinine (pK' = 4.97) as an alternative substrate buffer to phosphate. When the plasma creatinine was elevated to some 200 mg. per cent, the quantity of titratable acid in the urine again reached values (0.099 to 0.146 mEq/min.) far in excess of the quantity of $H_2PO_4^-$ or H_2CO_3 contained in the glomerular filtrate, and an ion exchange mechanism is the only one that can quantitatively account for the facts. The ultimate source

* Titrated from the pH of the urine (5.89 to 6.43) either to that of the arterial blood or arbitrarily to pH 7.35

fering capacity within the possible range of urinary pH. And the more of any buffer the urine contains, the greater the titratable acidity for any value of (H^+) ion gradient (see fig. 65 for data on man).

In parallel experiments, Pitts, Lotspeich, Scheiss, and Ayer have shown that the acidification of the urine in man follows the

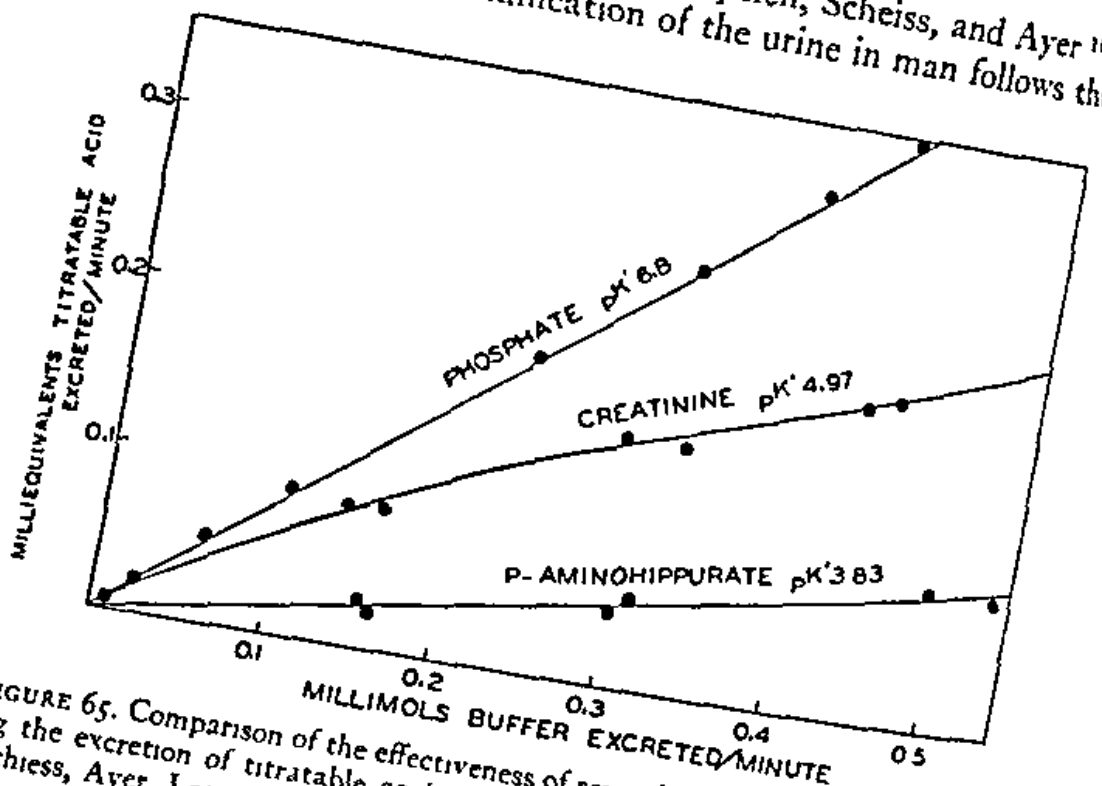

FIGURE 65. Comparison of the effectiveness of several urinary buffers in enhancing the excretion of titratable acid in man in acidosis. All data on 1 subject (Schiess, Ayer, Lotspeich, and Pitts 1951)

same pattern as in the dog. During acidosis induced by the ingestion of ammonium chloride, the excretion of titratable acid far exceeds that which enters the urine in the glomerular filtrate as H_2CO_3 or BH_2PO_4, and, as in the dog, acid must be added to the urine by an ion exchange mechanism, the tubular excretion of preformed acid being excluded by the absence of any residue of such acid in the urine.

In these experiments on themselves, Pitts and his coworkers obtained urine much more acid (pH 4.48 and 4.60) than was observed in the dog, and representing a H^+ concentration gradient between blood and urine of some 800 to 1. Because the minimal pH is lower in man than in the dog, at equivalent rates of buffer ex-

cretion man excretes more titratable acid than does the dog. In one period, one subject excreted acid at a rate of 0.333 mEq/min. (480 mEq/day)—some 3 to 4 times the highest rate ever recorded in diabetic ketosis. This was accomplished only because the plasma phosphate had been elevated to 6.52 mM/liter, thus greatly increasing the substrate buffer available to the tubules. Had the available buffer been further increased, as in the dog experiments, the rate of acid excretion would presumably have increased pro-

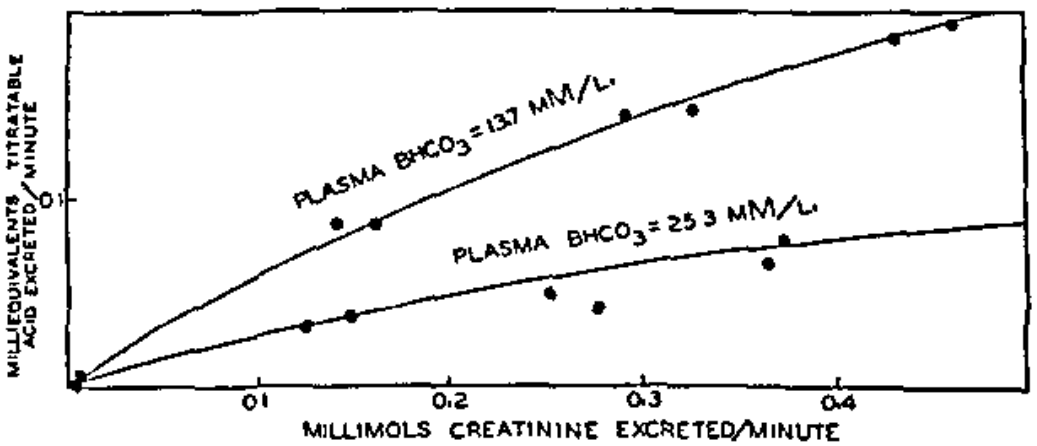

FIGURE 66 The excretion of titratable acid normally and in acidosis in the same subject at a series of comparable excretion rates of creatinine. (Schiess, Ayer, Lotspeich, and Pitts [178])

portionally. Schiess, Ayer, Lotspeich, and Pitts [178] have shown that in man, as in the dog, the pK of the buffer is a critical determinant in acid excretion, phosphate, creatinine, and PAH diminishing in effectiveness as buffers in the order named (fig. 65). For any one buffer, the greater the degree of acidosis, the greater is the conversion of that buffer from the salt to acid form, and hence the greater is the quantity of titratable acid excreted (fig. 66).

EXCRETION OF BICARBONATE

In the normal individual, the concentration of $BHCO_3$ in the extracellular fluid is maintained within the limits of 24 to 28 mEq/liter, despite wide variations in the intake of acid- and base-forming foodstuffs As with the sodium concentration of the extracellular fluid, the kidney has the sole responsibility for this regulation.

It has been seen that, during metabolic acidosis, when the individual is faced with a continuous loss of available base in combination with fixed acids, the kidneys conserve base by excreting a mildly acid urine with maximal titratable acidity effected through the normal substrate buffer, phosphate, the bicarbonate of the glomerular filtrate being practically completely reabsorbed. On the other hand, when an alkaline diet is ingested or during metabolic alkalosis, supplies of available base exceed the needs of the body and the excess base is excreted as $BHCO_3$, leading to the formation of an alkaline urine. The urine base in alkalosis always takes the form of $BHCO_3$, whether initially acquired as $BHCO_3$, BOH, or by the oxidation of the inorganic salts of organic acids. The tubular reabsorption of HCO_3 is therefore a physiological process which must be examined in its own right.

The quantitative importance of the problem is evident from the fact that approximately 190 liters of plasma, containing on the average 25 mM. of HCO_3^- per liter and making a total of 4750 mM. of HCO_3^- (or 400 gm. of $NaHCO_3$) are filtered per day. This is roughly 5 times the total available base of the body. Normally a little over 2 mM. are excreted, 99.95 per cent of the filtered HCO_3^- being reabsorbed. But, after the ingestion of $NaHCO_3$ in large amounts, excretion may increase to 1000 mM/day or more. The urine concentration may rise to 220 mM/liter, but since the urine CO_2 tension is never below and, under these conditions, is generally above that of the blood, the urine is never more alkaline than pH 8.0. Thus large quantities of base can be excreted in combination with the chief metabolic acid, CO_2, of which a large excess is always available, in a urine which is only slightly alkaline.

The variable excretion of HCO_3^- in defending the body against alkalosis is therefore complementary to the acidification of the urine in defending the body against acidosis. However, it is possible to speak of two separate processes, the 'acidification of the urine' and the 'reabsorption of bicarbonate,' only in a qualified sense: the evidence indicates that reabsorption of HCO_3^- occurs in two stages, some four-fifths of the filtered HCO_3^- being reabsorbed in the proximal tubule isohydrically, i.e. without change in the H^+ ion concentration of the tubular urine, and one-fifth in the distal tubule anisohydrically. The proximal reabsorption of

HCO_3^- is independent of the acidification process, and may be considered as one which proceeds independently of acid-base balance. In the distal tubule, however, HCO_3^- reabsorption and urine acidification are simultaneous and interdependent; it may be that they represent two consequences of a single process, the exchange of H^+ for B^+.

MAXIMAL TUBULAR REABSORPTIVE CAPACITY

Pitts and his coworkers [1637 1640] have examined the reabsorption of HCO_3^- in the dog and man by varying the plasma HCO_3^- concentration. Concentrations of HCO_3^- below normal (*c.*25 mEq/liter) were attained by acidosis induced by the oral administration of NH_4Cl, while plasma levels above normal were attained by the intravenous infusion of $NaHCO_3$.

Figure 67 shows the general relationship between $(HCO_3^-)_p$ and the quantity of HCO_3^- filtered, excreted, and reabsorbed in the dog. This figure is based upon 18 experiments in 4 dogs studied by Pitts and Lotspeich,[1640] in which the filtration rate in various experiments ranged from 46 to 101 cc. The data are expressed in mEq. of HCO_3^- per 100 cc of glomerular filtrate, first, for ease of comparison of various animals, and, second, because there is apparently a physiological relation between HCO_3^- reabsorption and filtration rate. As $(HCO_3^-)_p$ increases, the quantity filtered increases in direct proportion; essentially all the filtered HCO_3^- is reabsorbed until the load exceeds 2.5 mEq/100 cc of filtrate, when frank excretion of HCO_3^- begins. The quantity reabsorbed remains constant at this value despite further increases in $(HCO_3^-)_p$, the excess being excreted. Thus there is grossly a maximal reabsorptive capacity for HCO_3^- which is reached at a filtered load of *c.*2.5 mM/100 cc of glomerular filtrate per min.; i.e. the critical value of $(HCO_3^-)_p$ required to cause frank HCO_3^- excretion is about 25 mEq/liter (though different animals showed some variability in this figure).* The corresponding figure in three

*This value is influenced in the dog to a slight extent by water diuresis, which tends to increase the HCO_3^- excretion, and by the concentration of total body electrolytes and their specific pattern; depletion of Cl^- tends to conserve HCO_3^- and substitution of K^+ for Na^+ may alter the critical value of $(HCO_3^-)_p$ at which excretion begins.

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*This value is influenced in the dog to a slight extent by [illegible] which tends to increase the HCO_3^- excretion, and by the concentration of total body electrolytes and their specific pattern, depletion of Cl^- [illegible] serve HCO_3^- and substitution of K^+ for Na^+ may alter the critical $(HCO_3^-)_p$ at which excretion begins.

men studied by Pitts, Ayer, and Schiess [1637] is 28 mEq/liter (fig. 68).

It is to be noted that uniformity in reabsorption of $BHCO_3$ in the same animals or in different animals with widely varying

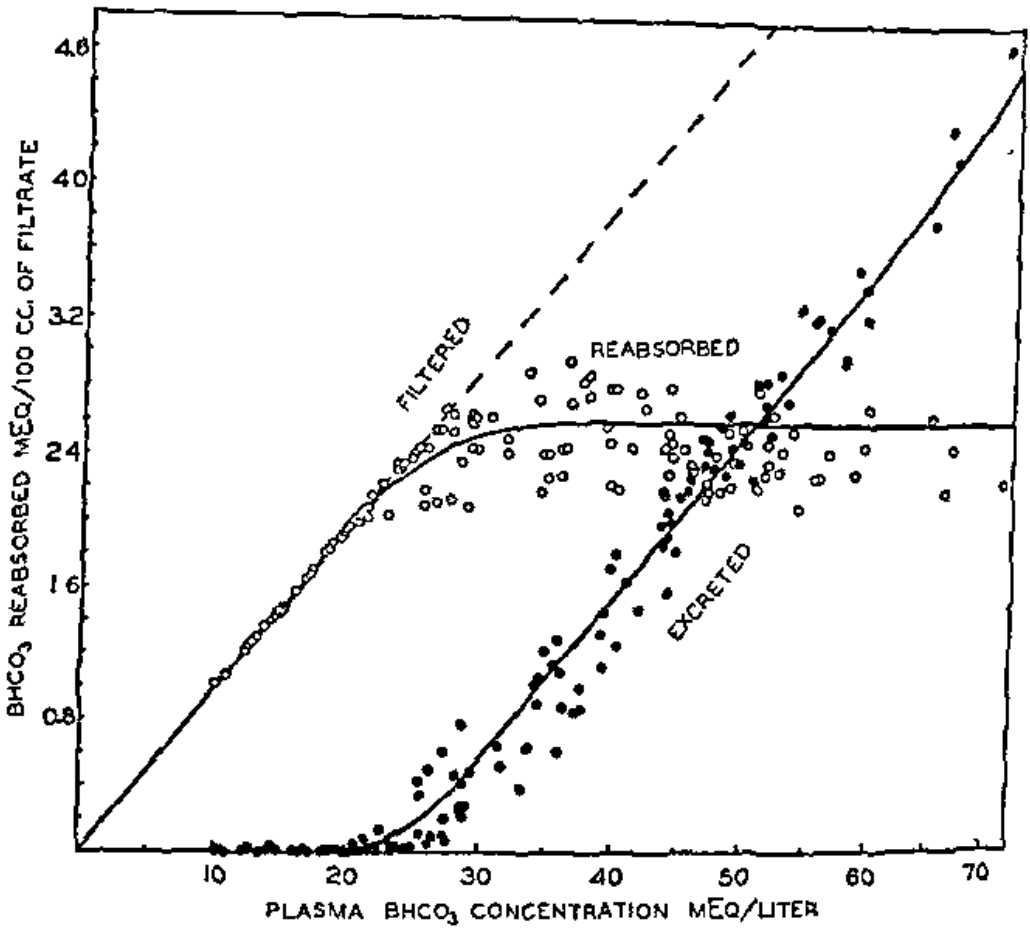

FIGURE 67. The excretion of bicarbonate in the dog as a function of plasma concentration. Note that the quantities reabsorbed and excreted are expressed in mEq/100 cc of glomerular filtrate (Pitts and Lotspeich [1640])

filtration rates is achieved only when the amount reabsorbed is expressed per 100 cc. of filtrate. This implies that (proximal) tubular reabsorptive capacity is functionally related to the filtration rate,* as is the case with sodium chloride.

* The comparison of data on any aspect of renal function in different animals per cc. of filtrate obviously tends to eliminate differences attributable to renal size. Thus, there normally exists a close correlation between the filtration rate and glucose Tm on the one hand or diodrast Tm on the other, not only between different individuals but in individual nephrons,[1939] a correlation which has its

In the frog, *Necturus*, and rat, ultimate acidification of the urine occurs in the distal tubule (ch. II). That some reabsorption of HCO_3^- occurs in the proximal tubule is plausible in view of the proximal reabsorption of sodium chloride and water. Since the pH of the urine at the end of the proximal tubule is practically identical with that of the glomerular filtrate, proximal reabsorption must be an essentially isohydric process. When the bladder urine

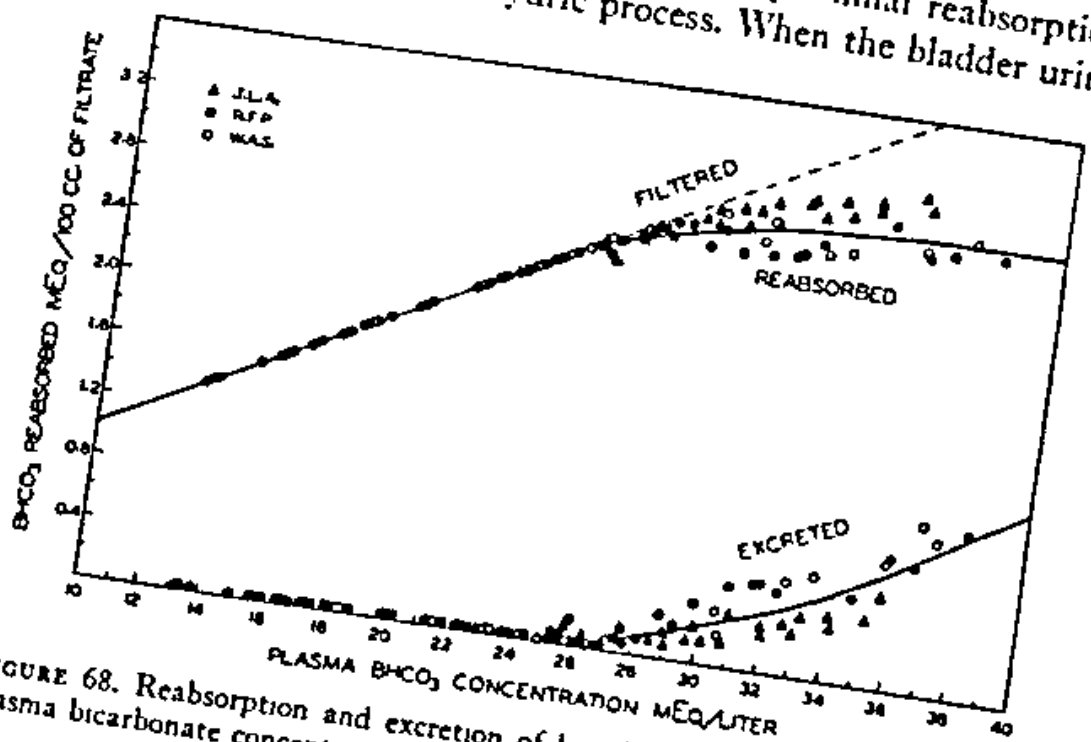

FIGURE 68. Reabsorption and excretion of bicarbonate in man in relation to plasma bicarbonate concentration (Pitts, Ayer, and Schiess [107])

is acid (i.e. in acidosis), the remainder of the HCO_3^- must be reabsorbed (or removed by acidification) distally, the process coinciding with the process of acidification.

Pitts and Lotspeich infer that proximal reabsorption accounts for roughly four-fifths, and distal reabsorption one-fifth of total reabsorption. This division is based upon the evidence previously

genesis in morphological balance. Comparisons per unit of filtrate are valid for establishing a *functional* relationship only where it can be shown that the variable under consideration increases or decreases with the filtration rate in individual animals. Pitts and Lotspeich's data seem to establish this as the case of the maximal reabsorptive capacity for HCO_3^-. In this respect, the reabsorption of HCO_3^- differs from that of glucose, vitamin C, phosphate, and sulphate, which is independent of the filtration rate.

cited that such is roughly the division of sodium and water reabsorption.

Two lines of experimental evidence in the dog support this view. Sulfanilamide reduced the capacity of the kidney to reabsorb HCO_3^-, at both normal and increased HCO_3^- loads. However, the depression of reabsorption was small in either circumstance, indicating that the greater fraction of the reabsorptive process involved a non-sulfanilamide-sensitive mechanism. Since, as stated above, sulfanilamide also depressed the distal acidification mechanism, Pitts and Lotspeich infer that the depression of HCO_3^- reabsorption effected by sulfanilamide represents distal reabsorption, and the sulfanilamide-insensitive process is therefore attributed by inference to the proximal tubule.

Secondly, when HCO_3^- is administered to an acidotic dog enriched with phosphate as a substrate buffer, the titratable acidity of the urine decreases as the quantity of filtered HCO_3^- increases, even though all the filtered HCO_3^- is reabsorbed. This can be explained by the supposition that some of the HCO_3^- reaches the distal tubule, and there competes with phosphate for H^+ and diminishes the extent to which $HPO_4^=$ is converted to $H_2PO_4^-$, thereby reducing the titratable acidity. Consequently, Pitts and Lotspeich conclude that the final reabsorption of HCO_3^- is accomplished by the same mechanism which, by the H^+ exchange, acidifies the urine. This process is independent of the filtration rate but, being small in magnitude (one-fifth of total reabsorption), it has little effect upon the picture presented by total reabsorption.

It is proximal reabsorption which is functionally related to the filtration rate. In order to explain this functional relationship, Pitts and Lotspeich conceived that the proximal reabsorption of HCO_3^- and of water could be treated as simultaneous and related processes, so that one could speak of a maximal concentration of HCO_3^- in the 'proximal reabsorbate.' They posited that this maximal concentration is 25 mEq/liter (*the normal concentration* of HCO_3^- in dog plasma). If this 'proximal reabsorbate' always represents four-fifths of the water of the glomerular filtrate, and if the concentration of HCO_3^- in this reabsorbate is limited to a value of not more than 25 mEq/liter, then the quantity of HCO_3^- so reabsorbed will of course vary roughly in proportion to the

filtration rate (fig. 69). But why the concentration of HCO_3^- in the proximal reabsorbate should be limited to 25 mEq/liter is not stated, and the postulate can be shown to be untenable * by the fact that, during osmotic diuresis induced by mannitol or urea, some 65 per cent of the water of the glomerular filtrate may be carried into the urine without significantly decreasing HCO_3^- re-

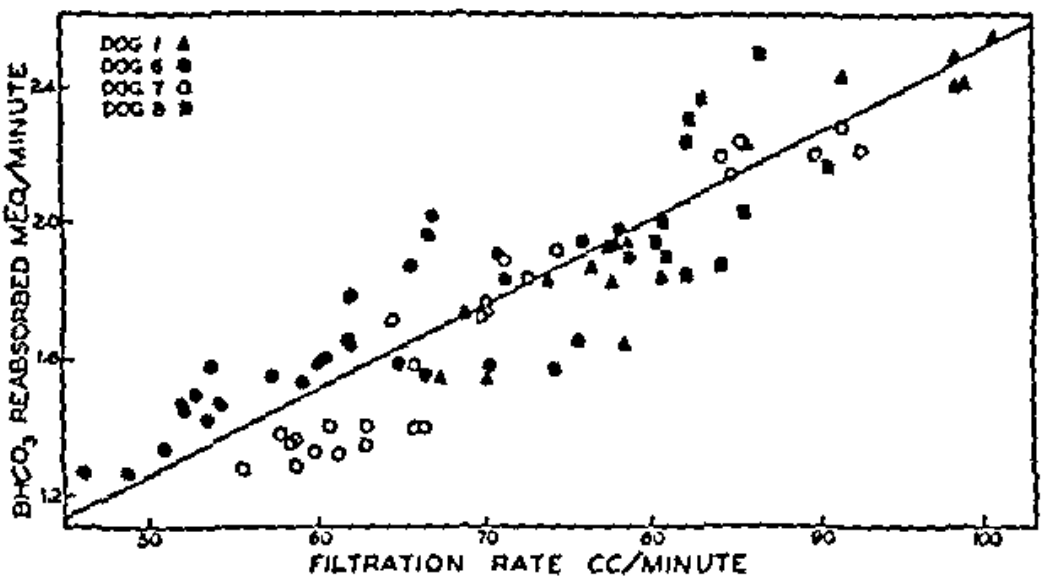

FIGURE 69 Reabsorption of bicarbonate in the dog as a function of the filtration rate All observations were made at plasma bicarbonate concentrations well above the renal threshold The filtration rate in each animal was varied by fasting and by feeding meat. (Pitts and Lotspeich [1640])

absorption.[1458 5171] HCO_3^- reabsorption continues whether water is reabsorbed or not (see fig. 55).

Pitts *et al.*[1657] note that HCO_3^- appears to be reabsorbed in the proximal tubule ahead of or more rapidly than chloride (p. 31),

* [illegible]

break down during elevation of plasma bicarbonate concentration, or no such limitation can apply The most satisfactory solution is to reject the limitation in concentration in the proximal reabsorbate which at this time seems artificial since no simultaneous HCO_3^- plus water reabsorbate can be visualized

carry weight only if it is assumed that the rate of secretion of H^+ is limited and essentially the same in acidosis and in alkalosis To the maximal rate of acid excretion reached in man (0.333 mEq/min.) (and this figure is set only by the available substrate buffer) must be added the HCO_3^- which is simultaneously neutralized, so that the true maximal rate of H^+ ion exchange must considerably exceed the supposed 0.5 mEq/min. of HCO_3^- reabsorbed during alkalosis. If the two operations represent an identical process of H^+ ion exchange, it is impossible on the data to limit that process by a maximal rate.

It is, however, a tempting hypothesis to accept that the distal reabsorption of HCO_3^- reflects not the operation of a specific mechanism but merely an incidental consequence of the secretion of H^+ ions. Against this view, however, is the fact emphasized by Pitts and his coworkers, and upon which the investigations above throw no light, that alkalosis induced by hyperventilation causes increased bicarbonate excretion without elevation of plasma HCO_3^-. Forced breathing, induced voluntarily or reflexly in consequence of anoxia, lowers the bicarbonate concentration of the blood but paradoxically leads to the formation of alkaline urine. Obviously the activity of the renal tubules in reabsorbing HCO_3^- must here be reduced by changes in the pH of the plasma or by other means. It is difficult to reconcile the continuous secretion of H^+ in the distal tubule with the alkalinization of the urine under these conditions. Until this phenomenon is assimilated into the theory, and until limitations in proximal reabsorption of HCO_3^- are further clarified, our theory of the excretion of HCO_3^- is obviously incomplete and subject to serious revision.

RELATIONS BETWEEN BICARBONATE AND CHLORIDE EXCRETION

It has previously been noted that Cl^- and HCO_3^- are, within wide limits, substituted for each other in maintaining the total base of the plasma. Thus, in alkalosis produced by protracted vomiting, plasma Cl^- may be low and HCO_3^- correspondingly high; conversely, in acidosis produced by diarrhea, plasma HCO_3^- may be low and Cl^- high

Pitts and Lotspeich [1640] find that, when NaCl is infused in such excess that frank excretion of Cl^- occurs, there is a simultaneous increase in excretion of HCO_3^-, owing to decreased tubular reabsorption, while infusion of HCO_3^- in such excess that frank excretion of this anion oc-

curs, leads to an increased excretion of Cl^- owing to decreased tubular reabsorption; while Pitts, Ayer, and Schiess [1437] in their observations on man report a close reciprocal relationship during acidosis and alkalosis: when the HCO_3^- reabsorbed increased from 1 34 to 2.79 mEq/100 cc of glomerular filtrate, the Cl^- reabsorbed decreased from 10 37 to 9.14 mEq, the sum remaining within the range of 11.71 to 12.70 mEq

However, when the body is depleted of sodium, an acid urine is excreted despite alkalosis. Failure of sodium excretion somehow arrests excretion of both Cl^- and HCO_3^-, and the pH of the urine falls toward that of a solution of free CO_2 Sodium chloride infusions restore HCO_3^- excretion by restoring the underlying disturbances, whereas the infusion of HCO_3^- does not correct these disturbances but, on the contrary, may lead to excessive alkalosis and tetanic convulsions.[2100]

In the absence of data on the filtration rate in such circumstances, one can only speculate on the interpretation, but it is possible that the decrease in filtration rate is enough not only to prevent sodium excretion, but to prevent a significant quantity of HCO_3^- from reaching the distal tubule, and, in absence of HCO_3^- distally, the urine approaches maximal acidity Interest in the point is enhanced by the circumstance that in most, if not all, oliguria (shock, post-transfusion reaction, crush syndrome, carbon tetrachloride intoxication, etc) the oliguric urine is reported to be acid by routine tests.

Wolf [2133] describes the effects of administering potassium chloride, sodium chloride, and water on the pH of the urine Water diuresis consistently causes the pH to shift from the range of 5 0 to 5 5 to the range of 6 0 to 7 0, and Eggleton [441] has shown that the intravenous administration of hypertonic sucrose or sodium sulphate solutions results in an increased acidity but decreased excretion of titratable acid, urea being without this effect in her experiments

THE CO_2 TENSION OF THE URINE

It has frequently been observed that the CO_2 tension of urine removed promptly from the bladder in such a manner as to prevent loss of CO_2 may be several times as great as that of venous blood. This fact led Sendroy, Seelig, and Van Slyke [1941] to suggest that the renal tubules are relatively impermeable to CO_2 However, in view of the experimental refutation of the 'carbonic acid theory' of urine acidification and the *a priori* improbability of any significant degree of impermeability, we may suppose that the tubular epithelium is neither more nor less permeable to CO_2 than are other cells

Occasional high CO_2 tensions in bladder urine can be explained either

as a result of admixture of acid and alkaline urine in the bladder, the result of delayed conversion of H_2CO_3 to CO_2 in the tubular urine,

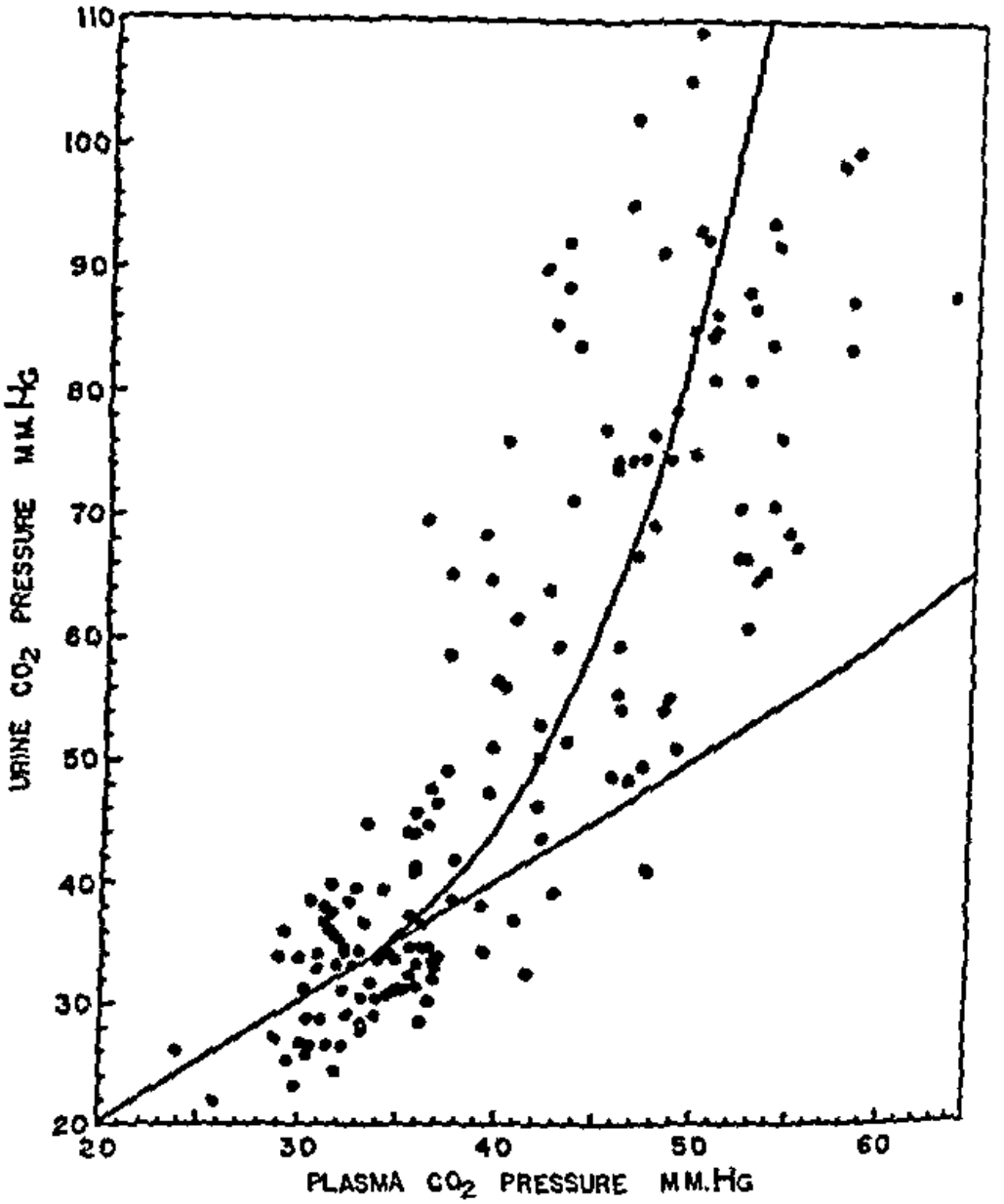

FIGURE 70. The relationship between the partial pressure of carbon dioxide in arterial plasma and in urine collected simultaneously. The diagonal straight line indicates equivalence of partial pressure. The curve is the average of all points, fitted by inspection (Pitts and Lotspeich [1940])

which is lacking in carbonic anhydrase, or the failure of CO_2 to diffuse out of the tubular urine because of the velocity of flow. The second explanation seems the most likely.

Pitts and Lotspeich [1640] report that among 160 urine samples in the dog, with pH ranging from 4.96 to 7.96, $(HCO_3^-)_a$ from 0.08 to 197 mM/liter, urine pCO_2 from 22 to 109 mm. Hg, and arterial plasma pCO_2 from 25 to 64 mm. Hg, the relationship between (HCO_3^-) and pH was a uniform one and approximated that demanded by the mass law, assuming a constant renal venous pCO_2 of 50 mm. Hg. There were, however, significant deviations, below pH 7.4 an assumed pCO_2 of 50 mm is too high, and above pH 7.6 it is too low. In acid urines, formed when plasma HCO_3^- is subnormal and the quantity of HCO_3^- delivered to the distal tubule is minimal, the urine pCO_2 is low and tends to approximate the arterial pCO_2; assuming that urine pCO_2 = renal venous pCO_2, this could mean that in acidosis the renal venous pCO_2 is essentially the same as arterial pCO_2, i.e. most of the CO_2 produced metabolically by the kidney as well as by acidification of the urine is added to the renal venous blood not as CO_2 but as HCO_3^- in association with reabsorbed B^+. However, in alkaline urines formed when the plasma HCO_3^- is above normal and the quantity of HCO_3^- delivered to the distal tubule is considerably increased, the urine pCO_2 exceeds the arterial pCO_2 by a considerable amount (fig. 70), and no doubt exceeds the renal venous pCO_2. This could mean that, in the face of the distal conversion of large quantities of HCO_3^- to H_2CO_3 and in the absence of carbonic anhydrase in the tubular urine, substantial quantities of H_2CO_3 escape reabsorption and appear in the bladder urine.

The data on man [1637] agree wholly with those on the dog. The urine pCO_2 at low levels of HCO_3^- reabsorption (acidosis) has a value of 30 to 40 mm Hg (i.e. close to that of the plasma from which it is formed), during abundant bicarbonate excretion, the value rises to as high as 136 mm Hg when pCO_2 in the plasma ranges from 32 to 42 mm. Hg.

Ryberg,[1788] reporting similar relations between the CO_2 tension and pH of the urine, confirms the conclusion that the H^+ ion exchange mechanism converts bicarbonate to CO_2 during the excretion of an alkaline urine, and that the delay in the dehydration of H_2CO_3 permits considerable quantities of this molecular species to pass into the bladder urine.

THE EXCRETION OF AMMONIA

Ammonia is a relatively toxic substance if injected directly into the venous stream, for under these circumstances it reaches the central nervous system upon which it has a strong convulsive action. Comparatively large doses may be given intra-arterially, however, because it is removed and bound by the tissues. When

taken *per os* its toxicity is equally low because it is carried by the portal circulation to the liver where it is converted to urea, this conversion being so efficient that there is no appreciable elevation of the ammonia content of the systemic blood, and it is impossible to increase ammonia excretion directly by the oral administration of ammonium salts. The one circumstance evoking increased ammonia excretion is acidosis, where the ammonium ion serves as a synthetic cation to replace sodium in the urine. The normal individual excretes 30 to 50 mEq/day of ammonia in conjunction with the excretion of sulphate, phosphate, and other fixed acids. A diabetic in severe acidosis may, however, excrete more than 10 times this amount.

In 1921, Nash and Benedict demonstrated that urinary NH_3 is formed in the kidney, and these investigators and others inferred that it is formed from urea, but Pitts [1627] showed that the difference between the urea clearance and creatinine clearance in the dog, a difference which is fairly constant at a given urine flow under all normal conditions, is unchanged as between extreme acidosis and alkalosis; and that, if the nitrogen clearance in acidosis is calculated on the sum of the urea plus ammonia, it may exceed the filtration rate by a considerable amount, whereas the clearance calculated on urea alone maintains its normal value relative to the filtration rate. Pitts concluded that the precursor of ammonia is not urea that has entered the tubular urine by way of the glomerulus. Conceivably, unfiltered urea might be removed from the postglomerular blood and be converted to ammonia by the tubules but it is just as reasonable *a priori* to suppose that the ammonia is formed from some other precursor. Pitts' observations were confirmed by Alving and Gordon,[46] who studied the extraction ratios of creatinine and urea, as well as the clearance ratios, in dogs with explanted kidneys. They found that the relative values of the extraction ratios remained unchanged as between the normal and the acidotic state; hence estimates of the renal blood flow based on the excretion rate and extraction ratio of urea alone gave identical results with estimations based on creatinine, as is the case in the normal animal, whereas such estimates based on the excretion rate of urea plus ammonia gave excessively high figures for the renal blood flow.

Van Slyke *et al.*,[207] extending the experiments of Alving and Gordon on the dogs with explanted kidneys, confirmed the conclusion that all the urea, as well as all adenosine and adenylic acid, extracted by the kidneys, is excreted as such in the urine. Moreover, inadequate α-amino nitrogen is extracted to provide nitrogen for the ammonia excreted. The amide nitrogen of glutamine, however, is removed from the blood in much greater amounts than appears in the urine, and the excess suffices to provide both the ammonia carried away from the kidney by the renal vein and 60 per cent or more of that which is excreted in the urine. The rest of the ammonia (40 per cent) can be accounted for by the disappearance of α-amino nitrogen. Administration of glutamine to a dog in acidosis markedly increases ammonia excretion, while the amount of glutamine removed from the renal blood is reduced in alkalosis A glutaminase present in kidney tubules catalyzes the degradation of glutamine to glutamic acid and ammonia.*

Lotspeich and Pitts [171] have shown that glycine, DL-alanine, L-leucine, DL-aspartic acid, and casein hydrolysate increase the rate of ammonia excretion in the acidotic dog. L-arginine, L-lysine, and L-glutamic acid are without such effect. The capacity of these amino acids to increase ammonia excretion correlates with their susceptibility to oxidative deamination *in vitro* by renal amino acid oxidases, and indicates that such amino acid oxidases are concerned in the syntheses of ammonia by the tubules. There is also a correlation between the capacity of the kidney to use an amino acid for ammonia formation and the capacity of the renal tubules to reabsorb it, possibly because oxidative deamination is involved in both processes However, this correlation does not imply that the amino acid which is reabsorbed is that which is deaminized to form urinary ammonia; the quantity of amino nitrogen reabsorbed always greatly exceeds that which is utilized in ammonia synthesis.

* According to Archibald [11] and Hamilton [111] glutamine nitrogen constitutes 18 to 25 per cent of the total free amino acid carboxyl nitrogen of plasma Its concentration is not appreciably affected by acidosis, alkalosis, or chronic renal disease The glutaminase content is reduced in chronic renal disease and P... infers that depletion of renal enzymes concerned with ammonia excretion ... basic factor in the incapacity of subjects with chronic glomerulonephritis form adequate amounts of ammonia

Ammonia excretion, like the excretion of acid, is a function of *the last two-thirds of the distal tubule* (and possibly the collecting ducts) in the amphibian kidney,[1469 2130] and it is assumed that ammonia is formed in the distal system in mammals *

Sartorius, Roemmelt, and Pitts [1771] have shown that increased ammonia excretion is demonstrable within a few minutes after the establishment of acidosis, but maximal excretion is not reached for some hours or days. These authors conceive that the stimulus to increased ammonia excretion is the same as that which leads to *acidification of the urine, namely reduction in the quantity of bicarbonate* delivered to the distal tubule, which of course issues from a reduction of the plasma bicarbonate concentration during acidosis. They speak of the distal formation of ammonia as a more or less continuing affair; when the urine is alkaline the ammonia is not captured in the urine but escapes into the blood, an interpretation which would account for the fact, demonstrated by Nash and Benedict, that the ammonia content of renal venous blood is *greater than that of the arterial blood. But, as the urine* becomes acid, the ratio of bound to free ammonia rises (the pK_a' of ammonia is 9.3) and this circumstance promotes its capture by neutralization in the tubular urine. Sartorius, Roemmelt, and Pitts [1634] find that ammonia excretion increases regularly with decreasing urine pH (fig. 71), a fact which they refer to the diffusion of free ammonia from the site of formation in the tubule cell to that of low concentration in the urine, where it exists not as free ammonia but as ammonium ion. It is obvious, however, that some factor other than plasma bicarbonate concentration (and urine pH) conditions the final rate of ammonia excretion, for this continues to increase *after plasma bicarbonate has reached its lowest and steady level* in acidosis, and the acidotic dog excretes more ammonia at the same urine pH than does the normal dog. The degree and duration of acidosis somehow increase ammonia production *in the distal* tubule. The nature of this adaptive factor is unknown.

Ryberg [1755] finds that in man ammonia excretion during acidosis reaches its maximal intensity only after some days and continues

* The kidney of a two-month-old infant who had exhibited signs of acidosis from birth showed necrosis and calcification of the distal convoluted tubules and collecting tubules The glomeruli and proximal tubules were normal.[1594]

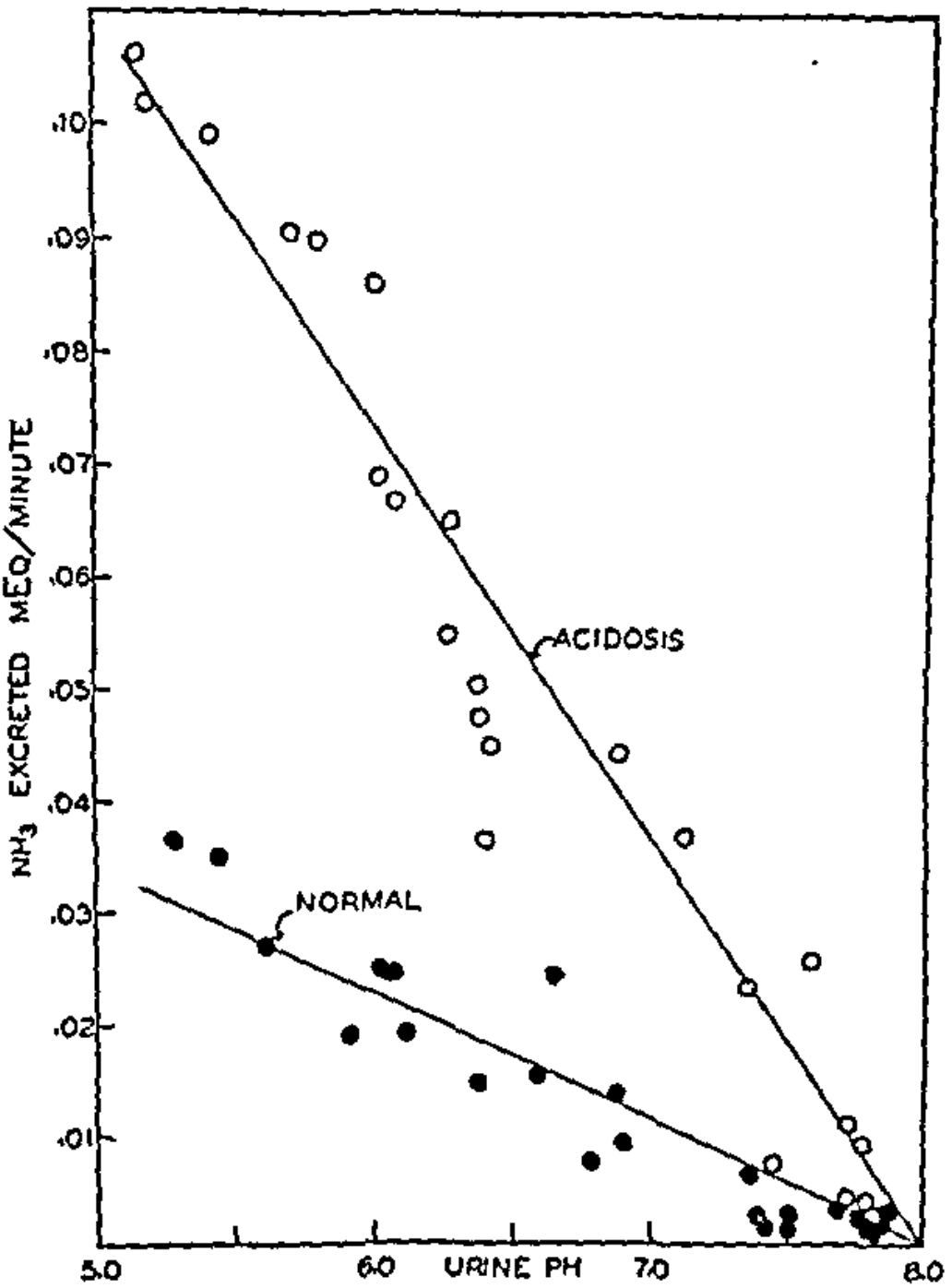

FIGURE 71 The excretion of ammonia in relation to urine pH in a normal dog and in a dog rendered acidotic for 48 hr. (Pitts [illegible])

for some time after cessation of acidosis. He reports that in dogs, however, ammonia formation reaches its full magnitude in a few hours (in contradiction to Sartorius *et al.*). The rate of production appeared to reach a maximum equivalent to 0.0022 and 0.0024 mEq/cc. of urea clearance in two male subjects and 0.0025 and 0.0024 in two dogs.*

Whereas Pitts and his coworkers think of the secretion of ammonia as simple diffusion of NH_3 from the tubule cell into the urine, Ryberg [1757] finds a positive correlation between ammonia excretion in acidosis and sodium excretion, and he infers that NH_4^+, like H^+, is secreted by exchange for Na^+. A more comprehensive examination of the variables involved is required before selection between these interpretations can be made.

PHYSIOLOGICAL RESPONSES TO ACIDOSIS

Sartorius, Roemmelt, and Pitts [1771] have followed the sequence of changes in the electrolyte pattern of the plasma in man during the development of acidosis following the ingestion of ammonium chloride (fig. 72). Immediately upon absorption, the ammonia of the ammonium chloride is converted to urea, and the liberated hydrochloric acid reacts with sodium bicarbonate to form sodium chloride, the CO_2 being excreted by the lungs. In principle, plasma bicarbonate must decrease and plasma chloride rise, mEq. for mEq., as this conversion proceeds, the plasma sodium concentration remaining unchanged. So far as the kidney is concerned, the relative quantities of sodium and water reabsorbed by the tubules remain grossly constant; the sodium in the reabsorbate must be matched by the sum of the chloride and bicarbonate reabsorbed, and, *since the chloride:bicarbonate ratio in plasma, and hence in the* glomerular filtrate, is increasing in favor of chloride as bicarbonate is reduced, this ratio also increases in the reabsorbate with the result that the plasma chloride increases as bicarbonate depletion progresses But exactly the same initial change in plasma composition would have occurred had the kidneys been removed from the picture entirely.†

However, the substitution of chloride for bicarbonate is attended ini-

* The writer has recalculated these ratios; if he understands correctly, Ryberg gives mEq NH_3 per 24 hr per urea clearance in cc/min.

† The authors emphasize the increased reabsorption of chloride as a specific renal compensation leading to elevation of the plasma chloride, but so long as the sodium:water ratio in the reabsorbate remains constant, the results can be no other than above: the maintenance of a constant plasma sodium concentration and exchange of plasma chloride for bicarbonate.

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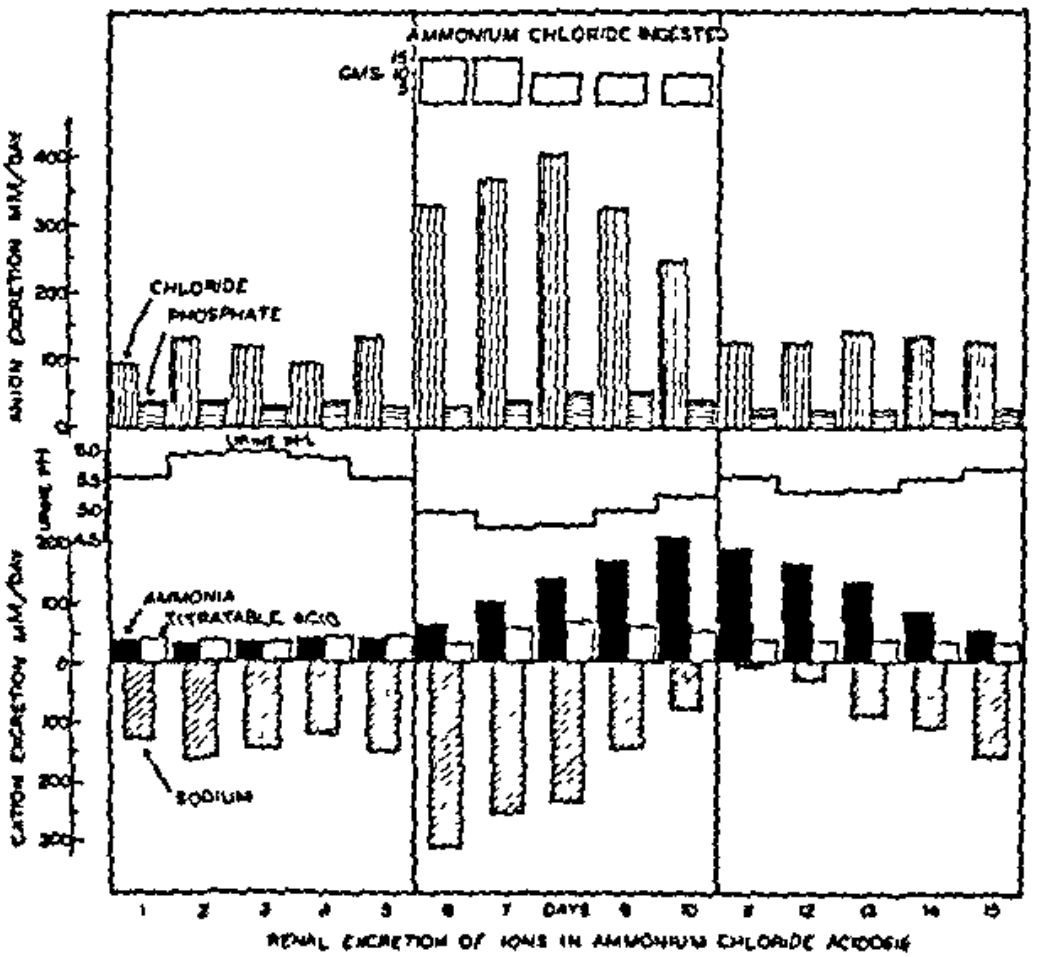

FIGURE 72 Renal excretion of ions in ammonium chloride acidosis (Pitts [144])

though this were the specific effect, but it is equally plausible to believe that it is the reabsorption of sodium that is impeded, resulting in an increased excretion of both sodium and chloride. However, this sodium carries with it nearly equivalent quantities of water, so that progressive reduction of the extracellular fluid occurs, with some simultaneous loss of the intracellular base and excretion of potassium. This latter process permits the body to draw on the large intracellular reserve of base and to curtail the reduction of extracellular volume.

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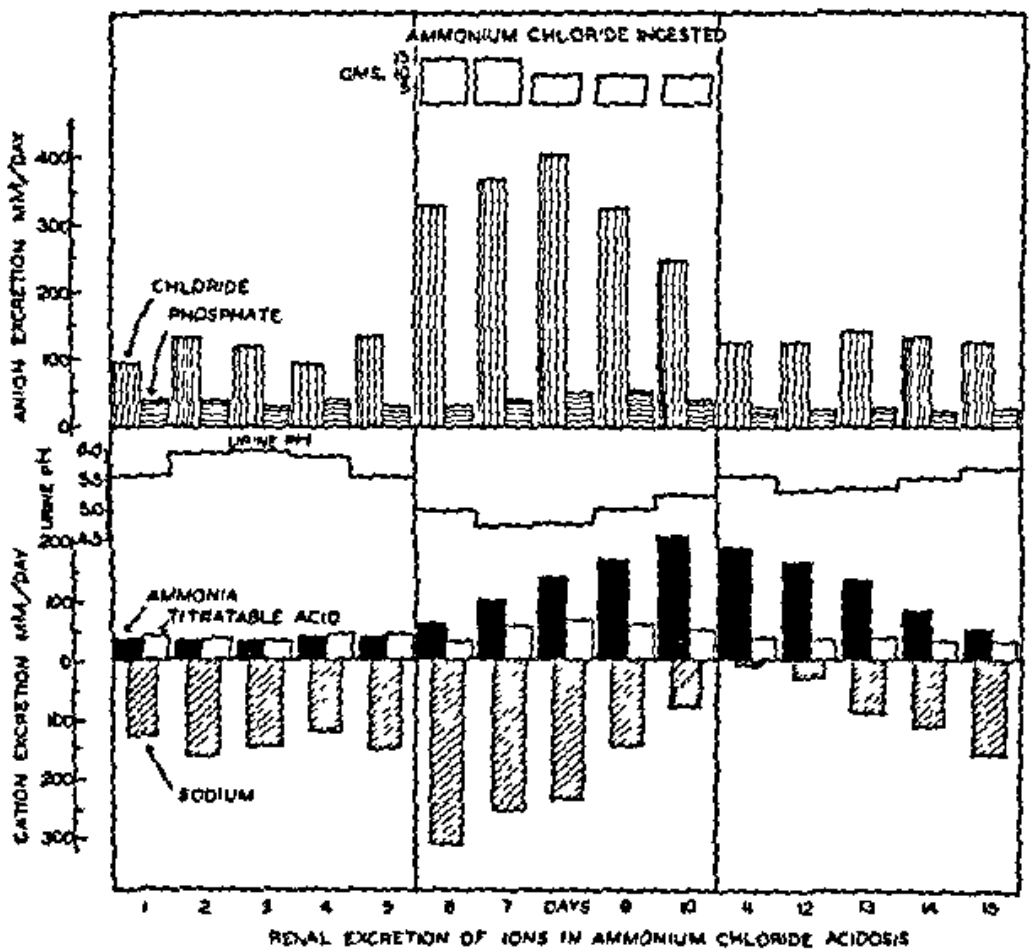

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[illegible] *of chloride as a specific* [illegible] o long as [illegible] sults can be no other than above: the maintenance of a constant plasma sodium concentration and exchange of plasma chloride for bicarbonate

pensation perhaps reflects the slow regression of ammonia formation in the distal tubule, a process which has been activated by acidosis beyond its normal level.

In the sequence of recovery from acidosis of mild degree, there are apparently no consistent changes in renal plasma flow or filtration rate, the changes in urine composition being referable entirely to tubular kinetics. In extreme acidosis, where dehydration is marked, glomerular activity may be seriously reduced and contribute to the picture by reducing the quantity of substrate buffer delivered to the distal tubule and by reducing the filtered load of sodium.

Ammonium chloride has long been used to force the excretion of sodium and water in edema, on the grounds that conversion of the ammonia to urea liberates chloride, which requires sodium for its excretion This is true only in the first few days, before ammonia excretion has reached its maximal rate. Thereafter, the ammonium ion excreted distally is sufficient to meet the requirements of chloride excretion, and sodium excretion regresses to control levels The natriuretic effect of acidosis is therefore self-limited. To judge by the data of Sartorius, Roemmelt, and Pitts, ammonium chloride acidosis promotes the excretion of more potassium in the first five days than of sodium This fact, coupled with the circumstance that the excretion of fixed base is forced only in proportion to the severity of the acidosis, may account for the waning popularity of ammonium chloride as a diuretic agent, and for the clinical experience that it is most effective if used for a few days only at intervals of a week or so

The excretion of the thiosulphate ion is obligatory, and consequently the administration of ammonium thiosulphate should lead, by the conversion of the ammonia to urea, to the obligatory excretion of sodium thiosulphate, or its derivative, sodium sulphate Experiments along this line have been carried out on dogs by Franklin, Genest, and Newman.[687] When a single dose is administered intravenously, about one-fourth is oxidized to sulphate, but, when administered as a single dose orally, half is oxidized to sulphate Since 1 thiosulphate ion on oxidation yields 2 sulphate ions, the potential base-removing power of thiosulphate is doubled by the conversion. In either case, the rapid excretion of single doses is accompanied by a large increase in sodium excretion and a slight increase in potassium excretion However, with repeated doses, acidosis develops as usual and larger amounts of ammonia are excreted, reducing the excretion of sodium and defeating the use of the salt as a sodium remover After single doses the excretion of chloride and phosphate is very low, but with repeated doses there is a low excretion of chloride

it were only continuing its normal operations. This, of course, is only a partial statement. With the induction of acidosis the composition of the urine shifts uniquely by an increase in titratable acidity and an increase in ammonia content.

Sartorius *et al.* explicitly state that the H^+ exchange mechanism of the distal tubule is limited in capacity (meaning mEq/min) and that the acidification mechanism is identical with the mechanism for the reabsorption of bicarbonate; it is implicit in their view, though not stated as such, that the H^+ exchange mechanism is operating all the time at full capacity. So long as excess bicarbonate reaches the distal tubule the H^+ exchange mechanism is overloaded, and excess bicarbonate over and above that reabsorbed by acidification is excreted in the urine As the plasma bicarbonate decreases, however, the distal load of bicarbonate falls short of the distal H^+ transfer capacity, and the urine is acidified. Titratable acid is now formed by the acidification of phosphate and other buffers in proportion to the quantity of buffer present and in accordance with the pK′ of these buffers.

Given an adequate quantity of substrate buffer, the quantity of titratable acid formed would increase in direct proportion to the reduction in distal bicarbonate load (or roughly to the reduction in total plasma bicarbonate) were it not for the excretion of ammonia. Progressive acidification of the urine leads to progressive capture of ammonium ion in the urine, so that considerable chloride (or other strong acid) is now excreted paired with this ion, and sodium is liberated for recombination with carbon dioxide to form bicarbonate. Thus, in the face of a continuing acidotic liability, increased ammonia excretion plus increased titratable acidity bring the body into a steady state where no further sacrifice of plasma bicarbonate occurs

On removal of the acidotic liability, the system operates automatically to restore the plasma bicarbonate concentration; each mol of free acid or ammonia excreted makes available a mol of base for recombination with carbon dioxide to form bicarbonate, this process continuing until the increase in plasma bicarbonate concentration leads to the excretion of a neutral urine, without either free acid or significant quantities of ammonia.

During recovery, potassium and phosphate are restored to the intracellular compartment and consequently the plasma concentration and excretion of these substances are temporarily reduced below normal Sodium reabsorption, for reasons unknown, is accelerated, and the plasma sodium concentration rises slightly above normal, accompanied by a slightly supernormal plasma bicarbonate concentration. This overcom-

Part III

and a marked increase in phosphate excretion. Continuous administration for 6 hr. causes death with a low serum sodium and a high serum potassium. Apparently dilution of the extracellular fluid by loss of sodium leads to a shift of water into the muscles and a shift of potassium from the muscles into the plasma until the concentration of this ion, superimposed on hemodilution, reaches lethal proportions.

CHAPTER XIV

The Control of the Renal Circulation and the Action of Pharmacodynamic Agents

HISTORICAL SKETCH

This chapter in renal physiology begins with Claude Bernard's observation (1859) that, when the splanchnic nerves in an anesthetized animal are sectioned, there results an increased urine flow on the operated side. Bernard had himself discovered the vasomotor nerves and had observed the vasodilator effects of sectioning the vasomotor nerves to the rabbit's ear, and he attributed this diuresis to increased renal blood flow. His conclusion is admittedly correct, but his experiment was unfortunate in two respects. His reasoning in gauging renal blood flow by urine flow was, as we can now see, unsound, during periods of hypotension or extreme renal ischemia there is a general parallelism between the two because cessation of filtration is accompanied by anuria or oliguria, but under normal conditions renal blood flow and urine flow are unrelated. Secondly, the phenomenon of 'denervation diuresis' is observable only under the abnormal conditions of his experiment, which are such as to excite vasoconstriction in the kidney. Important as was his demonstration of the renal vasoconstrictor nerves, Bernard's experiment has persisted in confusing renal physiology to the present day

An extensive literature on renal blood flow, accumulated in the period between 1859 and 1939, has been reviewed elsewhere [1929] and it will suffice if we summarize here only the more important facts emerging from these earlier studies. In 1883, Cohnheim and Roy devised the 'oncometer,' a hollow shell designed to record changes in kidney volume, and

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with it demonstrated that when the splanchnic nerves were sectioned in the anesthetized animal there occurred an increase in renal volume; conversely, the renal volume decreased on stimulation of the peripheral stump of the cut splanchnic nerves. In the main, they were probably correct in attributing the changes in kidney volume to changes in volume of the renal vascular bed, though this is not unconditionally true. Bradford, a pupil of Gaskell who was an authority on the autonomic nervous system, used the oncometer in 1889 to examine the distribution of vasoconstrictor nerves in the mammal. He showed that in the dog these nerves leave the cord in all segments from T_4 to L_2, being most abundant in the last three thoracic segments, which in the dog would be T10, T11, and T12. (For the finer distribution of vasoconstrictor nerves in the splanchnic tracts, see Gruber [879] and Mitchell.[1455])

In 1893 Landergren and Tigerstedt applied the Ludwig stromuhr to the measurement of the renal blood flow, but they inserted this device in the renal artery and thus traumatized the renal nerves. It remained for Burton-Opitz and Lucas (1908) to modify the Ludwig stromuhr and to insert it in the renal vein so that the circulation of the kidney and its nerve supply would be impaired to a minimal extent. By this more reliable method, Burton-Opitz and Lucas confirmed the function of the vasoconstrictor fibers to the kidney and added various observations on reflex excitation of these tracts. They demonstrated further that the renal innervation was unilateral, and in 1916 Burton-Opitz made the notable observation that a denervated kidney may undergo vasoconstriction in consequence of an increased secretion of adrenalin when the contralateral splanchnic nerve is stimulated.

In 1927 Rein introduced the thermostromuhr, an instrument that, with similar devices described by others,[979, 1095, 1148, 1767] represents the acme of mechanical ingenuity as applied to a difficult problem. However, a physiological disadvantage is still inherent in all stromuhr methods in that the renal vein, the renal artery, or the aorta must be dissected free and enclosed within a device of some weight; there are other minor difficulties such as the calibration of the instrument and the fact that the accumulation of fluid or scar tissue may impair the calibration. But the most uncertain feature of many thermostromuhr experiments lies in the technique of the investigator, for too frequently this involves acute experiments on anesthetized and laparotomized animals, in many instances after excessive physiological insult. Investigators naively revealed that their preparations had to be abandoned because 'no urine was formed by the operated kidney,' or because the renal blood flow was 'abnormally low,' or the renal vascular bed 'no longer responsive.'

In 1936 Mason, Blalock, and Harrison [1415] introduced a venous sound that could be inserted in the jugular vein of a dog and passed into the vena cava; by two expansible balloons carried near the end, the vena cava could be occluded above and below the renal vein while blood from the renal vein itself was being collected.

In 1931–33 H L. Sheehan and his coworkers [658,1097] first used the extraction ratio of urea and phenol red in an attempt to evaluate the renal blood flow in anesthetized animals. In 1934 Rhoads [1703] described a method of explanting one or both kidneys beneath the skin in dogs so that the renal blood flow could be measured by means of extraction ratios and clearances in the conscious animal, a technique requiring only the simultaneous puncture of the renal artery (or a systemic vein) and of the renal vein in an interval during which the urine was accurately collected This method has been slightly modified by Sheehan [1873] and Page and Corcoran,[1567] and in the hands of numerous investigators it has yielded valuable information on extraction ratios, the renal circulation, and oxygen consumption

In 1941 Cournand and Ranges [428] perfected the technique of catheterization of the right heart in man for the determination of the cardiac output by the direct Fick method Venous catheterization has subsequently been extended to the collection of hepatic and renal venous blood in man, thus making possible the measurement of hepatic and renal extraction ratios, and it may be anticipated that venous catheterization in the dog will to a great degree replace the explanted kidney.

The span of 50 years from the work of Bernard to that of Burton-Opitz and Lucas may be set apart as a pioneer period in renal physiology. In the light of present-day knowledge, certain criticisms may be leveled against the methods used by these investigators but not against the investigators for using them. Their choice of methods and the conduct of their experiments conformed with the knowledge of their time. It is to be regretted that this cannot be said of investigators in the next three decades, many of whom failed to keep their methods and their physiological approach abreast of rapidly developing knowledge.

It was in 1895 that Oliver and Shafer demonstrated the powerful vasomotor properties of extracts of the adrenal medulla, properties that we now know are attributable to the hormone epinephrine or adrenalin In 1897 Biedle demonstrated that the splanchnic fibers are secretory to the adrenal gland In 1908 Schur and Wiesel showed that when ether or chloroform is administered in anesthetic doses there is a marked increase in the secretion of adrenalin. Again, in 1912, Delbet, Herrenschmidt, and Beauvy asserted that the adrenalin content of the adrenal

medulla may be completely exhausted by chloroform anesthesia, and in the same year Elliot showed that ether, chloroform, and urethane, as well as hemorrhage itself, caused a marked increase in adrenalin secretion, even to the point of glandular exhaustion Since a denervated gland was not affected by anesthesia, it was concluded that the increased secretion of adrenalin was a result of the excitation of the sympathetic nervous system.

The fact of this sympathetic excitation has been frequently affirmed since 1921. Morphine, ether, chloroform, and urethane have all been specifically convicted. It has been shown (what every elementary student of physiology demonstrates for himself) that the so-called 'pressor' and 'depressor' reflexes are apparently fully active in the anesthetized animal. It has been shown that, during anesthesia, sensory stimulation induces not only reflex vasomotor action but also increased secretion of adrenalin. In ether anesthesia, at least, the sympathetic vasodilators may be excited simultaneously with the vasoconstrictors.

'The technique of study of the renal circulation that was in vogue for many years consisted of a series of operations which might have been specially designed to excite autonomic nervous activity. First an anesthetic was administered, then the abdomen was incised and the viscera were exposed and pushed aside; blood vessels were dissected free and ligated, and sometimes the aorta and all its lower branches, other than the renal artery, were tied. The kidney was then forcibly freed of its attachments and manipulated in order to insert a stromuhr in the renal artery or vein, or the entire organ was thrust into an oncometer and put under some pressure. Every surgeon recognizes that laparotomy complicated by even slight visceral trauma presents a circulatory hazard, and circulatory inadequacy owing to decreased venous pressure and reduced cardiac filling is imminent in all anesthetized animals wherein the flaccid skeletal muscles and the open abdomen encourage the stagnation of blood Moreover, such animals are usually either overheated or overcooled and suffer progressive hemoconcentration and oligemia. There is little *a priori* doubt that venous pressure and cardiac filling are embarrassed in an anesthetized quadruped whose legs are forcibly extended while it is tied upon its back. If under these conditions vasoconstrictor activity does not approach a maximal level, it must indeed be because of the reign of chaos in the autonomic nervous system, or because the hardy and almost indomitable receptor systems of the aortic arch, carotid sinus, and other vasosensitive zones are either fatigued or depressed below the level of response When we add to this confusion the possibility that the anesthetic, which may be concentrated

in the tubular urine, may just as well disturb the responses of the tubules or the renal circulation as those of the cerebral cortex, it may be safely inferred that the anesthetized animal is no easy place for the physiologist to find his way about Surgeons have long been aware of the physiological disturbances associated with all forms of anesthesia; physiologists, less concerned with the ultimate fate of their subjects, have too frequently remained stubbornly oblivious to them.' [1929]

To return to Bernard's original observation, when the splanchnic nerves were sectioned in the anesthetized, laparotomized animal, the renal blood flow and the urine flow generally increased on the denervated side. Whether the explanation of 'denervated hyperemia' is simple or complex, it is not surprising that the phenomenon itself failed to be confirmed in the first observations to be made painlessly on the unanesthetized and untraumatized animal. Using the explanted kidney preparation, Rhoads, Van Slyke, Hiller, and Alving [1704] found that neither local anesthesia nor surgical denervation of the kidney had any effect upon the renal blood flow Lassen and Husfeldt [1215] observed no increase in the creatinine clearance in 4 normal subjects during spinal anesthesia; where the blood pressure fell, this clearance decreased but, when the pressure was maintained by ephetonin, the clearance remained practically unaffected. Smith, Rovenstine, Goldring, Chasis, and Ranges [1940] demonstrated in normal, unoperated subjects that spinal anesthesia, up to levels (T5 or higher) considerably above those at which the efferent sympathetic pathways to the kidneys emerge from the cord, does not produce renal hyperemia as judged by the diodrast clearance, nor does it have any other consistent effect upon the renal circulation. These investigators concluded that the renal blood flow is normally determined by autonomous, intrinsic activity of the renal arterioles and is not dependent upon tonic activity in the sympathetic pathways.*

* This conclusion was extended, on the basis of negligible blood pressure changes, to the arterioles of the body generally (exclusive of the skin) but specifically only in man in the resting, basal condition and in the supine position.

tribute in some measure to the *vis a tergo* of venous return.

manipulation, such as laparotomy, and weight of abdominal retractors, hemostats, the pressure of packs and the pressure which assistants put upon the ab-

Complete surgical denervation of the kidney can be secured, according to Quinby,[1663] only by section and resuture of the artery, vein, and ureter.* Most investigators have been content, however, to divide all visible nerves entering the hilus or to cut the splanchnic nerves.

To return to the phenomenon of denervation diuresis, observations on unanesthetized animals lead to a result quite contrary to that which has been obtained over a period of 70 years in acute anesthetic experiments. In 1931 Bykow and Alexejew-Berkmann [312] explanted the ureters of a dog so that the urine flow of each kidney could be determined separately. One kidney was then denervated. After recovery from the operation, the urine flow remained almost identical on the two sides under all conditions. A similar technique involving explanted ureters was used repeatedly by Verney and his coworkers,[1135] who again found no difference in urine flow in the denervated as compared with the normal kidney. Subsequently Verney and his coworkers showed that the wide fluctuations in urine flow associated with water diuresis, with sensory stimulation, and with excitement and exercise are mediated in both the normal and denervated kidney in an entirely parallel manner by hormonal control, as shown in chapter x and figure 73. Grabfield and Swanson [832, 833] and Hiatt,[902] utilizing exteriorized ureters in the unanesthetized dog, report that there are no significant differences in urine flow or renal blood flow between the normal and denervated kidney. Chasis and Michie [796] found that unilateral denervation in patients with essential hypertension does not increase the renal blood flow or the urine flow on the operated side. Although their observations were not designed to test the point specifically, no diuresis after denervation of a single remaining kidney was observed in the dog by Rhoads *et al*,[1704] or by Smith *et al.*[1940] and other investigators who have examined renal function in man during spinal anesthesia. The fact that water intake and urine output may be temporarily increased after bilateral denervation [941] may be referable to other factors and does not refute the many observations now avail-

dominal walls, as well as the manipulation of the viscera and hemorrhage itself, [illegible] and may [illegible]

paralysis of the thoracicolumbar autonomic nervous system, the patient is deprived of nearly all defense against circulatory embarrassment. That such factors are chiefly involved is indicated by the absence of any severe circulatory changes during high spinal anesthesia in unoperated man.

* Professor Marshall relates that when Quinby wanted to denervate a dog's kidney he would remove it and pass it around among the spectators

able on unilateral denervation in the dog and man; and, in the nature of the problem, observations on anesthetized animals [1173] can no longer be considered pertinent to the question. Maluf [1176] transplanted a dog's kidney to the femoral region, exteriorizing the ureteral orifices The reabsorption of water and chloride from the glomerular filtrate (inulin or creatinine clearance) remained identical in the transplanted (dener-

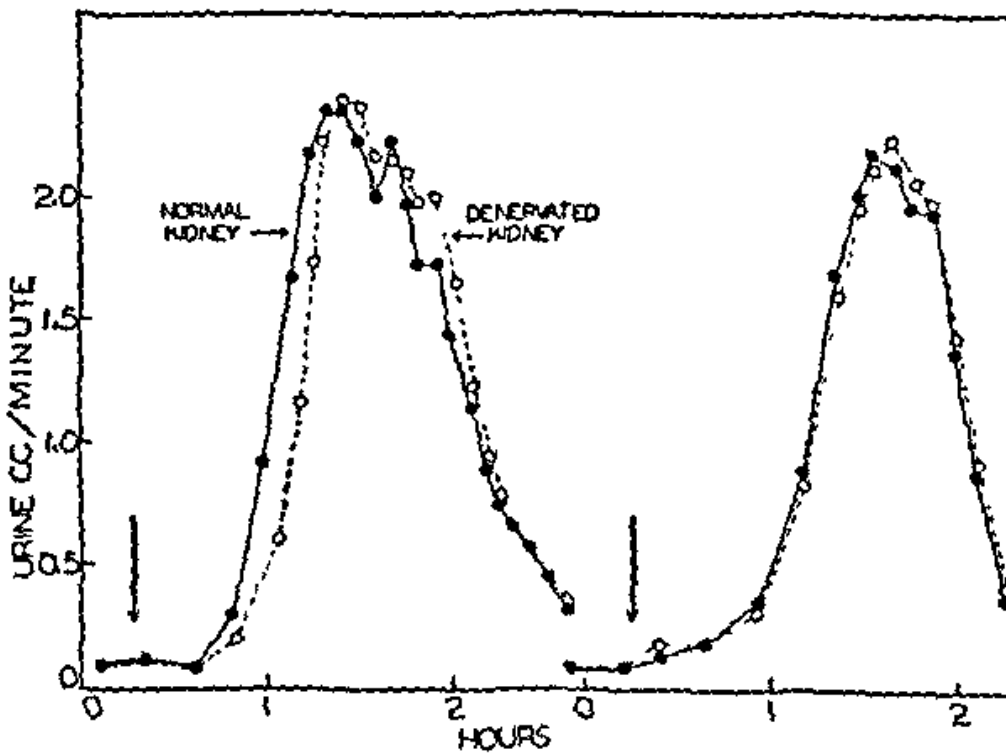


FIGURE 73. Diuretic response of the kidneys in the dog to water after section of the left splanchnic nerves. In the first test, 2 days after unilateral splanchnicectomy, 280 cc. of water were given by stomach tube; in the second test, 4 days later, 300 cc. were given. (Klisiecki, Pickford, Rothschild, and Verney [1191])

vated) and non-transplanted kidney, during both diuretic and antidiuretic conditions. The phenol red/inulin clearance ratio was also identical, indicating that transplantation had no effect on tubular excretion and no marked effect on blood flow. Moustgaard [1483] has also found that denervation does not affect the filtration rate or renal blood flow in dogs.

Like 'denervation hyperemia,' 'denervation diuresis' appears to be a release from enhanced vasoconstrictor tone engendered by anesthesia and traumatic operative procedures. The renal vasomotor pathways in man, and probably in other mammals, are normally at rest; like the sympathetic nervous system generally, they serve to meet the 'emer-

gencies' of anesthesia, hemorrhage, oligemia, traumatic excitation, fear, and shock so frequently created, among other ways, by unwary physiologists.

Despite the limitations of earlier methods, they sufficed to establish a number of important points about the renal circulation, to which we may add others that have been established subsequently.

The kidneys receive a rich supply of vasoconstrictor fibers via the thoracicolumbar sympathetics. The evidence is against the existence of vasomotor fibers of any kind in the vagus, and there is no evidence of renal vasodilator fibers in the thoracicolumbar sympathetic pathways.

Moderate doses of adrenalin and presumably mild sympathetic activity produce some degree of renal ischemia. Larger doses of adrenalin and strong sympathetic excitation produce a more marked ischemia and may render the kidney completely bloodless. No evidence exists that adrenalin in any dose produces hyperemia in the kidney (as it does in the skeletal muscle, the cardiac, pulmonary, and cerebral circulation, and in some visceral organs in some species) by vasodilation.

The renal circulation has a remarkable capacity to adjust itself quickly in the face of changing arterial pressure so that the renal blood flow tends to remain constant whether the arterial pressure rises or falls. This autonomy is not impaired by denervation, and probably accounts in great measure for the constancy of the renal blood flow during changes in blood pressure associated with spinal anesthesia in man. The renal circulation does not show reactive hyperemia (i.e. vasodilation after a period of ischemia).

Though many substances (caffeine, glucose, sodium chloride, sodium sulphate, salyrgan, histamine, theophylline, glycol, amyl nitrite, sucrose, phenol red, creatinine), when injected intravenously in relatively large quantities, have been reported to produce a momentary increase in renal blood flow, the hyperemic action of these agents is variable, fleeting, and probably nonspecific.

In unanesthetized and anesthetized dogs the kidney participates in the reflex vasoconstriction elicited by excitation of the sympathetic nervous system; the resulting renal ischemia is ac-

companied by a reduction in filtration rate and oliguria, the oliguria being in part attributable to the reduction in filtration rate, and in part to increased secretion of ADH.

Renal denervation in unanesthetized normal dogs and men does not produce renal hyperemia, the vasoconstrictor pathways being quiescent under basal conditions, nor does renal denervation have any significant effect upon the normal urine flow, upon water diuresis, or pituitary antidiuresis.

Unilateral nephrectomy increases the renal blood flow in the remaining kidney in both dog and man, the increase being of the order of 70 to 100 per cent and fully attained within a few weeks or months. This is accompanied by considerable hypertrophy of the remaining kidney.

There is no evidence that the renal nerves exert a trophic action on the kidneys There is no evidence of renal atrophy after renal denervation (observations in man extend over a period of 2 years or more).

The physiological control of the renal circulation remains almost a complete mystery. Future developments in this problem will doubtless come from isolated observations, such as are cited in the following pages, but the relative importance of these observations cannot be assessed at the present time.

CLEARANCE STUDIES ON RENAL BLOOD FLOW, ETC.

Oil of Juniper

Figure 74 has been selected as a 'control experiment' because it is, essentially, a negative one It concerns the action of a rather large dose (1 cc.) of oil of juniper in alcoholic emulsion on the renal circulation Many years ago, oil of juniper enjoyed a vogue as a diuretic, and this fact suggested that it might have some action on the filtration rate or renal plasma flow. The experiment serves chiefly to illustrate the method of examination. The subject was prepared for the measurement of renal clearances by the administration of water both the night before and early in the morning of the test in order to establish good urine flows. It is desirable to have the latter above 1 cc/min. if accurate urine collections are to be made Suitable plasma concentrations of diodrast

tion (fig. 78). Gaddum [730] believes that ephedrine acts only by potentiating the action of adrenalin, in which view, accepting the normal quiescence of the renal vasomotor pathways, it is not surprising that it is without renal action. In respect to cardiodynamic effects, ephedrine resembles adrenalin.[1675]

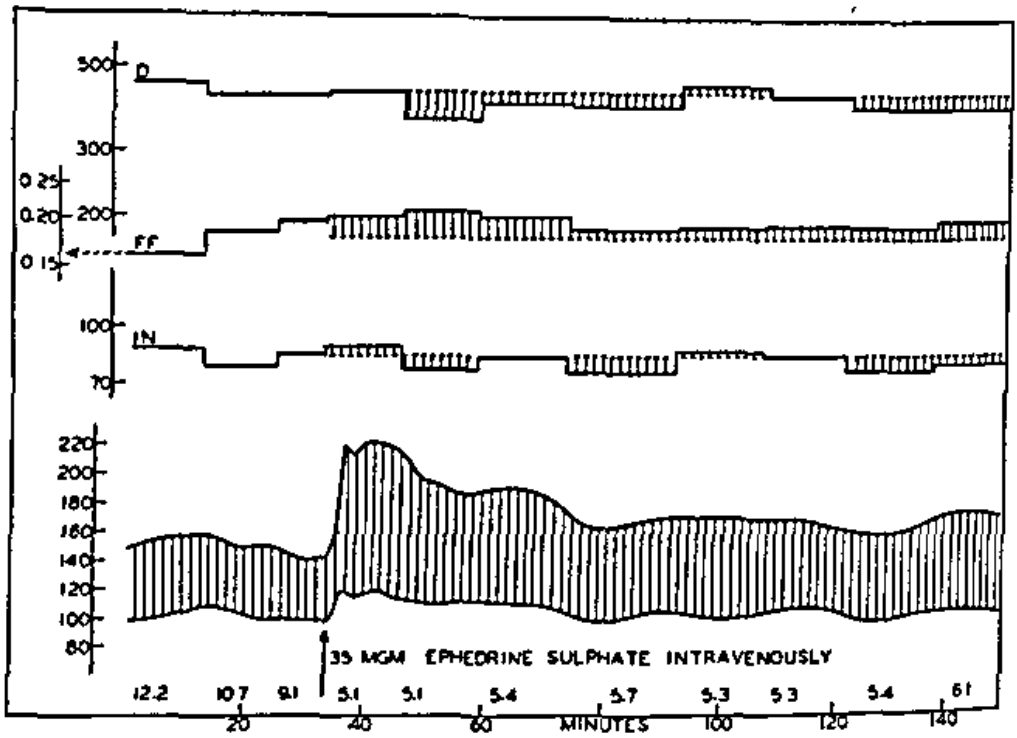


FIGURE 78. Action of ephedrine on renal plasma flow, etc, in a slightly hypertensive subject. (Smith [1331])

PAREDRINOL

Paredrinol, which appears to have a pure or predominantly vasoconstrictor action in man, mimics adrenalin in its renal action, reducing the renal plasma flow without a significant change in the rate of filtration. Cardiodynamically, it differs from adrenalin and ephedrine in that it consistently decreases cardiac output and increases peripheral resistance.[1675]

RENIN

Merrill, Williams, and Harrison [1442] found, in most of their experiments on anesthetized dogs, that single injections of renin increased the blood pressure and decreased renal blood flow; the kidney volume increased, as in the action of adrenalin. This paradoxical effect on renal blood flow and renal volume has been observed by others, who find that renin increases perfusion pressure through isolated kidneys [899]

Corcoran and Page [411 412] showed that the slow intravenous infusion of renin into unilaterally nephrectomized dogs with one explanted kidney caused a sustained reduction in the phenol red clearance, with variable effects upon the inulin clearances. Calculation of the renal plasma flow * from E_{PR} and E_{IN} showed that this decreased 35 per cent in the mean, the mean decrease in inulin clearance being only 13 per cent. This change in inulin clearance is less than is to be expected from the regression line relating spontaneous changes in renal plasma flow and inulin clearance, indicating that the filtration rate was generally somewhat increased relative to the existing plasma flow. But the 13 per cent decrease in filtration rate, opposed to an increase of 29 per cent in mean blood pressure, implies both afferent and efferent constriction, afferent predominating

E_{PR} averaged 0 485 ± 0 097 in the control periods and was not influenced significantly by renin or by the change in renal plasma flow. E_{IN} averaged 0.297 ± 0 077 in the control periods and was increased (+50 per cent) during renin infusion by the reduction in plasma flow, the clearance remaining nearly constant.

ANGIOTONIN (HYPERTENSIN)

It is generally accepted that angiotonin (or hypertensin) is the active pressor agent formed when renin-activator acts upon renin. Corcoran and Page [412] showed that, when infused into unilaterally nephrectomized dogs with one explanted kidney, angiotonin increased the arterial pressure, decreased the renal plasma flow, and increased C_{IN} The effects were similar to those observed during the infusion of renin but initially more profound and, after interruption of the infusion, more fleeting The filtration rate was generally decreased initially, indicating predominant action on the afferent arteriole, but after this transient effect the filtration rate tended to return to normal, indicating equal action on the afferent and efferent side

In man, the slow infusion of angiotonin reduces renal plasma flow without change in filtration rate, thus resembling adrenalin in its renal

Corcoran, Browning, and Page [408] have reported a subject with orthostatic hypotension who responded to a tilt of 60 degrees by syncope, hypotension, and decreased renal plasma flow. Angiotonin increased the

* The values of the mean flow separately calculated from E_{PR} and E_{IN} agreed within 1 per cent.

blood pressure and renal plasma flow. After treatment with the head-up bed, when the orthostatic hypotension had disappeared, angiotonin caused its characteristic renal vasoconstrictor effects. They accept the interpretation that, in orthostatic hypotension, the sensitivity of the arteriolar bed to normal vasoconstrictor influences is diminished

Pickering and Prinzmetal [1811] and Brandt and Grunn [245] have shown that renin injected intravenously in rabbits in doses greater than 1 unit produces a conspicuous diuresis of tubular origin, there being no increase in endogenous or exogenous creatinine clearance and generally a considerable decrease in PAH clearance. This diuresis is accompanied by a large increase in the excretion of protein, sodium, and chloride, the concentration of chloride in the urine tending to rise to or slightly above that of the plasma Smaller doses of renin have a slight antidiuretic effect.

Hypertensin acts similarly to renin in this respect; it increases urine flow and chloride excretion, the urine chloride concentration, whether high or low initially, approaching that of the plasma In the doses used, hypertensin and renin had no constant effect on the inulin clearances but always reduced the diodrast clearance. In the anesthetized rabbit, renin had no conspicuous effect on Tmo during the period of diuresis The evidence is compatible with the view that the changes in the volume and composition of the urine during diuresis produced by renin are mediated by hypertensin and are a result of reduction of the tubular reabsorption of water, sodium, and chloride.[1062] This action on the tubules has not been observed in the dog or man, and changes in the secretion of ADH are not excluded

Renin and angiotonin also produce in the rat transient proteinuria, which is attributed to increased glomerular capillary pressure.[16] This phenomenon is abolished by adrenalectomy and not restored by massive treatment with cortical extract or DCA [18]

ISUPREL

Isuprel [1-(3¹,4¹-dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride] is a compound, related to adrenalin, which has a vasodepressor action It has been suggested that pharmacologically it resembles sympathin I, once assumed to be the naturally occurring vasodepressor substance related to adrenalin Corcoran and Page [426] find that isuprel produces a moderate increase in renal blood flow when injected intravenously in dogs, with no change in the filtration rate. The effect is augmented by the sympatholytic agent, tetraethylammonium, which also (paradoxically) augments the pressor and renal action of adrenalin.

Earlier investigators had reported a variety of results after the administration of pituitary extracts or of pitressin to anesthetized and unanesthetized animals, using a thermostromuhr to follow the renal blood

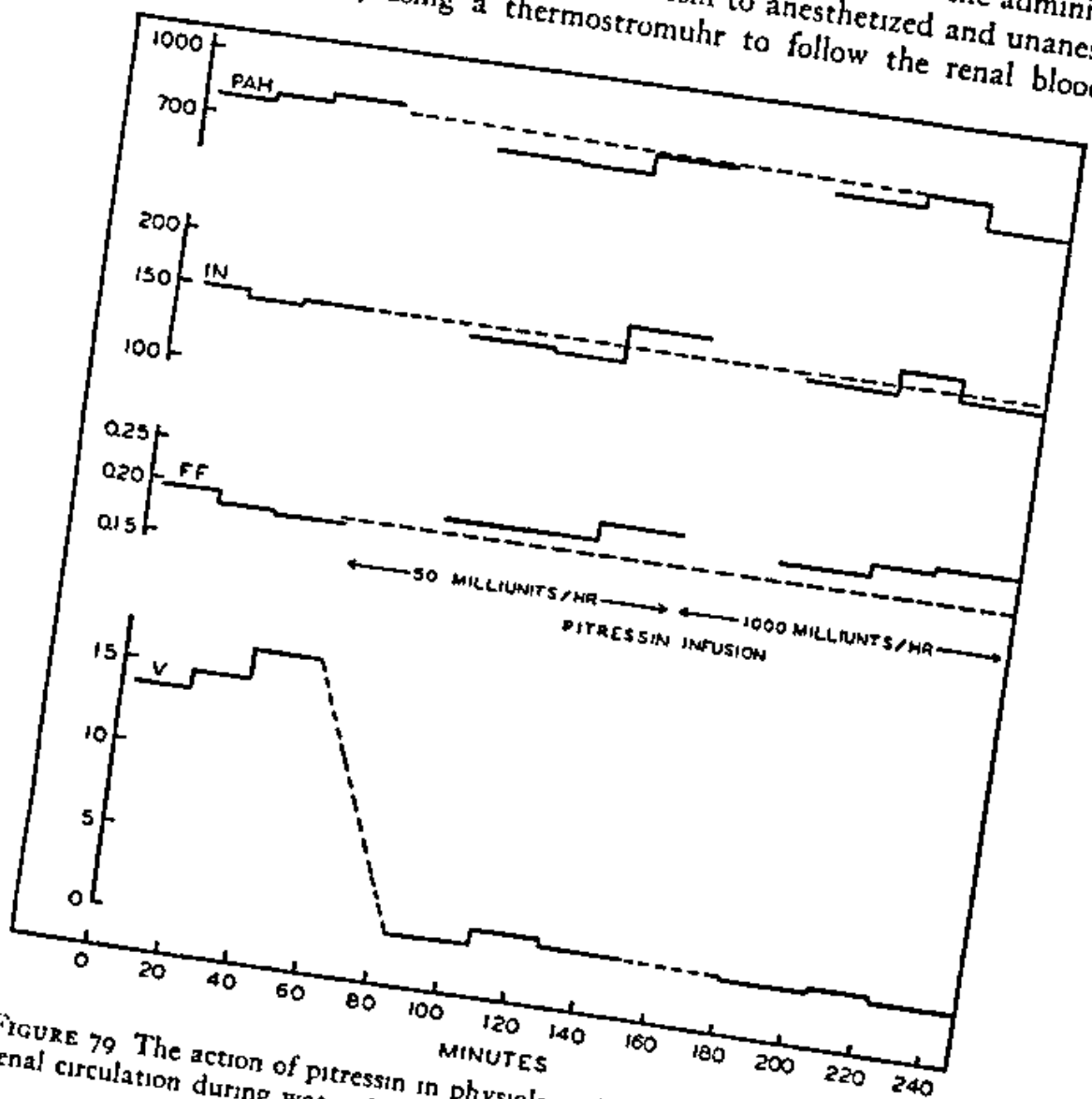


FIGURE 79 The action of pitressin in physiological doses on the urine flow and renal circulation during water diuresis in a normal subject

flow Many of the changes were very fleeting and earlier studies were complicated by the use of pharmacologic rather than physiologic doses. Corcoran and Page,[41] in observations on unilaterally nephrectomized dogs with one explanted kidney, found that the intravenous infusion of pitressin (8 to 100 milliunits/min.) caused an increase in renal plasma flow (+33 to +90 per cent), as calculated from E_{PR} and E_{IN}, in 5 out

of 11 experiments; in 6 experiments the changes were negative or slight. The inulin clearance increased in 5 experiments and showed negligible changes in the rest. E_{PR} increased in 2 and decreased (−28 to −45 per cent) in 4 experiments. The changes in renal function were so various that they do not reveal any characteristic hemodynamic pattern; the results are perhaps complicated by pitocin and by the dosage, which exceeds that required to maintain antidiuresis in the dog (5 milliunits/hr.) by 100 fold and more Retching, sometimes vomiting and defecation, usually occurred during the first half hour of the infusion, and hematemesis was observed once. From these disturbances, it may be concluded that the dosage was massive and it is of particular interest that, although there was a marked reduction in pulse rate, the pitressin had no effect on blood pressure, emphasizing the inadequacy of a pressor test in the standardization of the antidiuretic hormone.

Maxwell and Breed (pers. com.) have found that infusions in man of pitressin in physiologic doses (40 to 100 milliunits/hr.) and in larger doses (1000 to 5000 milliunits/hr.) have no significant effect on renal plasma flow or filtration rate (fig. 79). In 16 subjects there was a consistent slight downward trend in C_{PAH} during the administration of pitressin; C_{PAH} declined in 13 subjects and increased in 3. This fall was never marked, however, and averaged less than 7 per cent of control levels. The inulin clearance, E_{PAH}, and renal arterial-venous oxygen difference did not change significantly.

ATROPINE

Corcoran and Page [411] report that, during the infusion of pitressin, atropine (0 065 mg. intravenously) had no consistent effect on renal plasma flow, E_{PR}, or phenol red clearance in unilaterally nephrectomized dogs with one explanted kidney. E_{IN} and the inulin clearance increased, the latter by 9 to 23 per cent, in 5 of 7 experiments. Blood pressure increased by an average of 40 per cent over the level existing during the administration of pitressin. The experiments again emphasize the independence of the renal blood flow and systemic arterial pressure, and the absence of parasympathetic cholinergic innervation in the renal circulation.

ORTHOSTATIC HYPOTENSION

When a person assumes the upright posture, the blood tends to accumulate in the subcardial regions, particularly in the capillary and venous channels, and fluid leaves the vascular tree for the

interstitial space, causing some hemoconcentration. He normally resists venous failure by walking to and fro or shifting his weight from one foot to the other, the contractions of the leg muscles, aided by the venous valves, promoting the return of blood to the right heart If, however, he stands still, as in leaning motionless against a wall, or if he is tilted to 60 or 70 degrees on a tilt-table,

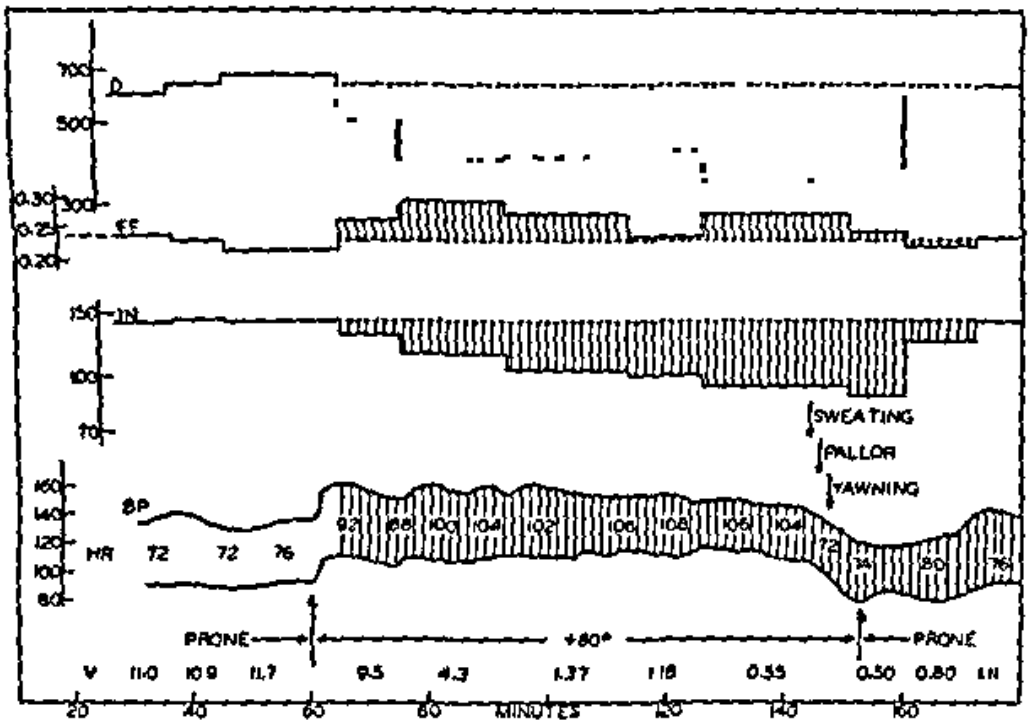


FIGURE 80 Renal ischemia induced by tilting a normal subject on a tilt-table (Smith [1925])

progressive venous stagnation leads to decreased cardiac output and vasoconstriction until the cerebral circulation is inadequate and syncope occurs. Through the sino-aortic receptors, the first lowering of mean arterial pressure elicits vasoconstriction throughout the body.

Figure 80 shows the course of events in a subject who, after 3 control periods in the recumbent position, was tilted head up to 80 degrees, remaining in this position until he fainted. As soon as he assumed the orthostatic position, the renal plasma flow decreased; in view of the fact that the mean arterial pressure did not decrease but was in fact slightly increased, this renal ischemia

must be attributed to externally imposed constriction of the renal arterioles. All subjects do not respond alike to this ordeal, but qualitatively the renal effect is invariably vasoconstriction.[1929,1931]

It will be observed that, in the subject illustrated in figure 80, syncope was accompanied by an abrupt slowing of the heart. Bradycardia or cardiac arrest is stated to be the second most common mechanism involved in fainting, the most common being abrupt vasodilatation following enhanced vasoconstrictor activity.[607]

The hepatic blood flow is also reduced during a period of quiet standing.[232]

Where the upright position is maintained for a shorter time, the changes in renal circulation are less marked but qualitatively similar to those described above.[2209] Brun, Knudsen, and Raaschou [234] have shown that oliguria persists after orthostatic syncope, despite rapid restoration of the filtration rate; they attribute the oliguria to secretion of ADH.

Deyrup [509] has shown that the filtration rate, which remains unchanged for a period of 2.5 hr. in dogs in the supine position, decreases slowly by 20 to 50 per cent when the animals are kept standing

Ni and Rehberg [1520] observed a marked drop in the exogenous creatinine clearance in the orthostatic position, and they obtained a fair inverse correlation between the creatinine clearance and the colloid osmotic pressure of the plasma, leading them to suggest that the increase in the latter was responsible for the decrease in the filtration rate. This causal relationship is, however, open to question since vasomotor changes in the kidney seem to dominate the changes in renal function. Hemoconcentration simply parallels circulatory inadequacy.

It has been reported by several investigators [1929] that in the dog the renal vascular bed does not participate in the vasomotor reflexes concerned with the maintenance of aterial pressure and mediated through the sino-aortic receptors, but the negative reports are based on anesthetized-laparotomized animals Handovsky and Samaan [908] claim that this is not true in the postoperative, unanesthetized animal, and Malméjac and Donnet [1375] report renal ischemia after section of the sino-aortic nerves in chlorolosed dogs Similarly the data of Bing, Thomas, and Waples [173] demonstrate renal vasoconstriction in dogs with sino-aortic denervation. There may be a difference between the response in dog and man because of the quadrupedal and bipedal habitus, but as the evidence stands it appears that in both species the same cardiovas-

cular stimuli evoke comparable renal vasoconstriction The decrease in the filtration rate in the face of maintained arterial pressure indicates marked afferent constriction

Gabriele [729] has examined the effects of changing the piezometric angle of the renal artery in anesthetized (nembutal) dogs When the kidney was moved cephalad and the aortic-renal artery angle reduced to 45°, the mean blood pressure and pulse pressure in the renal artery were reduced and the renal plasma flow decreased by about 36 per cent. The author suggests that a naturally high piezometric angle may be related to 'a predisposition toward hypertension,' and that elevation of the kidney during pregnancy may be related to toxemia of pregnancy, but the total evidence indicates that the renal circulation has nothing to do with the causation of either disease Movement of one or both kidneys may, however, be related to changes in renal function in the upright position as compared with the recumbent position, though the available data show changes qualitatively opposite to those to be expected from this cause alone

INCREASED ARTERIAL PRESSURE

Acutely raised intracranial pressure in anesthetized (barbital) dogs in which osmotic diuresis is maintained with glucose or sucrose causes a marked decrease in urine flow despite the accompanying great rise in systemic blood pressure In dogs in which one kidney is denervated, diminution of urine flow occurs in the normal kidney, whereas diuresis is maintained or increased in the denervated kidney The reduction of urine flow in the normally innervated kidney is probably due to renal vasoconstriction resulting from asphyxial stimulation of the vasomotor center.[1763]

NEUROGENIC HYPERTENSION

After section of the buffer nerves the renal blood flow in the unanesthetized dog either remains constant or decreases slightly, despite a marked increase in arterial pressure The overall renal resistance is increased by 20 to 80 per cent, whereas the peripheral resistance shows a much smaller change To what extent this represents autonomous adjustment within the renal circulation cannot as yet be determined [173]

Acute elevation of the blood pressure by 43 per cent, induced by clamping the carotid arteries in unanesthetized rabbits in which the kidneys are denervated and the adrenal glands demedullated, is accompanied by an average increase in filtration rate of only 8 per cent and in renal plasma flow of 5 per cent In some instances the renal plasma flow decreased during hypertension Renal autonomy is preserved without me-

diation of neural reflex action or secretory activity of the adrenal medulla in this species,[680] as in the dog [1929] and man.

FRIGHT

In the emergency theory of the function of the sympathetic nervous system, so well developed by Cannon, fright is placed high in the list of effective stimuli, exceeding even hemorrhage

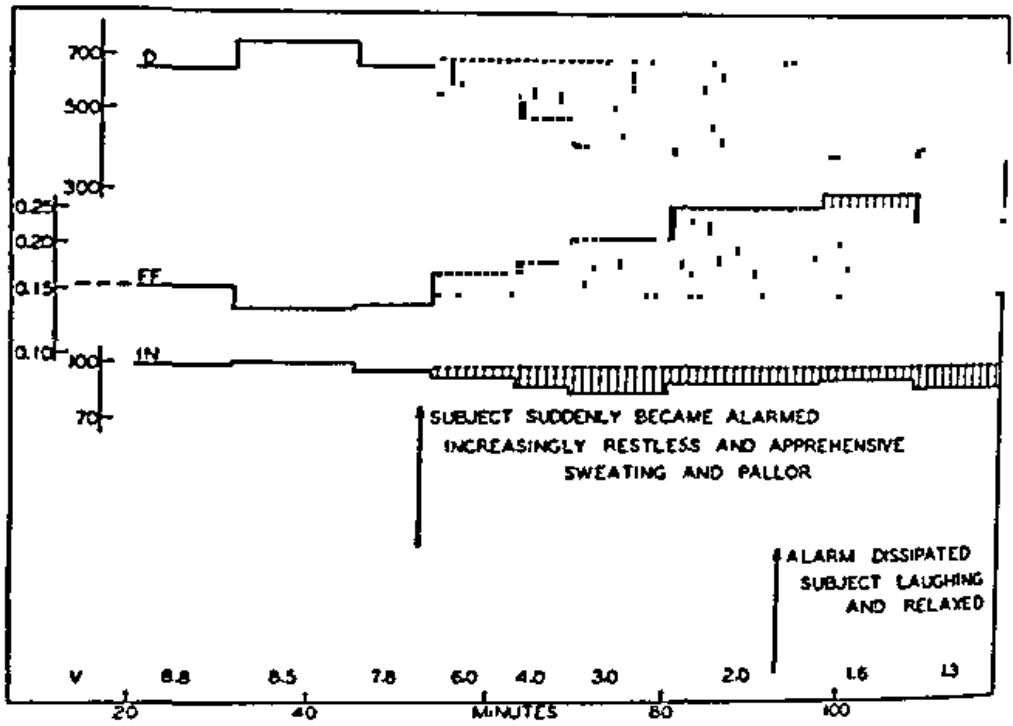


FIGURE 81. Psychogenic renal vasoconstriction during alarm. (Smith [1944])

and anger in its potency. During the series of clearance determinations illustrated in figure 81, the subject suddenly became alarmed through misunderstanding about the significance of the clearance procedure. He became increasingly restless, apprehensive, and remonstrative, and sweating and pallor indicated marked sympathetic excitation. He was so perturbed that it was impossible to make blood pressure measurements, but one can be confident that the mean blood pressure did not fall. When, after 40 min., his alarm was abruptly dispelled, his apprehension was replaced by relaxation, laughter, and the best of humor. The renal vasoconstriction that occurred at the peak of his alarm was as profound as that which is seen after the administration of large doses of

adrenalin and indeed persisted through the last observation The response is typical of adrenalin and it is, of course, impossible to exclude the action of this hormone, but in view of their well-established function it would be equally arbitrary to exclude the participation of the renal vasoconstrictor nerves. (A second study of this type is illustrated elsewhere.[1929])

PAIN

Using a headpiece with adjustable thumbscrews to elicit controlled and reproducible pain in man, Wolf[2262] has shown that pain which is tolerable for considerable periods induces a marked decrease in both renal plasma flow and filtration rate. The plasma flow was sometimes reduced to less than one-third of the control, the filtration rate to one-half. Having the subject immerse a hand in cold water to the limit of endurance was less effective, though the clearances decreased in 2 out of 3 instances after the hand was removed The reduction in the filtration rate indicates dominant afferent action, as in the case of orthostatic syncope.*

PSYCHONEUROTIC CONFLICT

A decrease of 20 per cent or more in renal plasma flow may occur in subjects with early essential hypertension when the discussion turns to

*Continuing a quotation started on p 414

'We do not suppose that every alarm and apprehension has its concomitant of increased renal vasoconstrictor tone the autonomic nervous system is too complex for easy generalization I present these observations chiefly that I may return to an earlier point if emotional disturbance, even of an extreme nature, can so markedly influence the renal circulation in man, what must we say of procedures in laboratory animals which entail profound and almost maximal sympathetic excitation by alarm and fright, by the administration of anesthetic, by excitation of sensory nerves, by surgical incisions, by the handling of the viscera, by circulatory inadequacy, by the manipulation of the kidney itself I would enter no special plea for the uncontrolled use of the clearance method in renal physiology until it has been more rigorously tested, and other methods are greatly needed to reinforce and supplement it. What I would plead is that the history of renal physiology has been in too large measure a history of traumatic procedures which have in the end only misled investigation, and that far more is to be gained by spending several years in perfecting a non-traumatic, truly physiological method than one year in applying a traumatic one Perhaps it is not too much to suggest that, so far as *immediate* experimental procedures are concerned, any observation that is too traumatic to be safely, reasonably and ethically carried out upon man is too traumatic, as far as physiological validity is concerned, to be carried out upon an experimental animal.' 1929

topics of traumatic significance in the life situation. The filtration rate remains unchanged. An increase in renal plasma flow occurred in one subject when feelings of security were induced with the aid of sodium amytal. A change in renal hemodynamics is not invariable under such circumstances, however. Under presumably similar excitation, the renal response is abolished by sympathectomy.[2263] The significance of this response, so far as the genesis of essential hypertension is concerned, is in doubt, however, because significant changes, both positive and negative, were obtained by unpleasant psychiatric interviews in 4 out of 11 experiments on 7 young males, 5 out of 8 experiments on 8 older males, and 4 out of 8 experiments on 6 females, all of whom were normotensive.[336]

COLD PRESSOR TEST

Talso, Crosley, and Clarke[2044] report that, when normal subjects immersed one foot in ice water at 1° C. for 15 min., the filtration rate and renal plasma flow were decreased by 14 to 21 per cent, respectively, this decrease occurring either during the application of the cold stimulus or within some 30 min. thereafter. The decrease in urea clearance, chloride excretion, and urine flow reported by others[1541] may be related to this decrease in filtration rate. The decrease in urine flow is not abolished by inhalation anesthesia and may involve an increased secretion of ADH elicited by pain.[1542] White and Rolf[2209] report one experiment in which one hand and about a third of the forearm were immersed in ice water at 0° C until the pain became intense; the hand was then withdrawn for a minute and the cycle repeated. Only slight reduction in clearances was observed, and no change occurred when the hand was immersed in water at 15° C.

HISTAMINE

Histamine reduces both the creatinine and urea clearances, but there is a simultaneous reduction in mean arterial pressure, and consequently the renal effects are difficult to interpret.[177] In normotensive and hypertensive subjects, histamine in subcutaneous doses sufficient to evoke a moderate general reaction caused slight reduction in the renal plasma flow, with no significant changes in the filtration rate, the filtration fraction increasing.[1698]

EXERCISE

Covian and Rehberg[441] showed that exercise in man has an antidiuretic effect and, if the exercise is severe, it is accompanied by a decrease in the urea and creatinine clearances and sometimes by albuminuria.

Barclay, Cooke, Kenney, and Nutt [62] examined the effects of a one-quarter mile run at full speed in 10 normal subjects. On the average, exercise reduced the renal plasma flow to 70 per cent and the filtration rate to 55.4 per cent of the control values (single injection method). The filtration fraction fell from an average value of 0.158 to 0 126. All subjects were in a state of water diuresis Exercise appears to annul the antidiuretic action of pitressin, relatively more water being returned and the duration of diuresis being prolonged.[85]

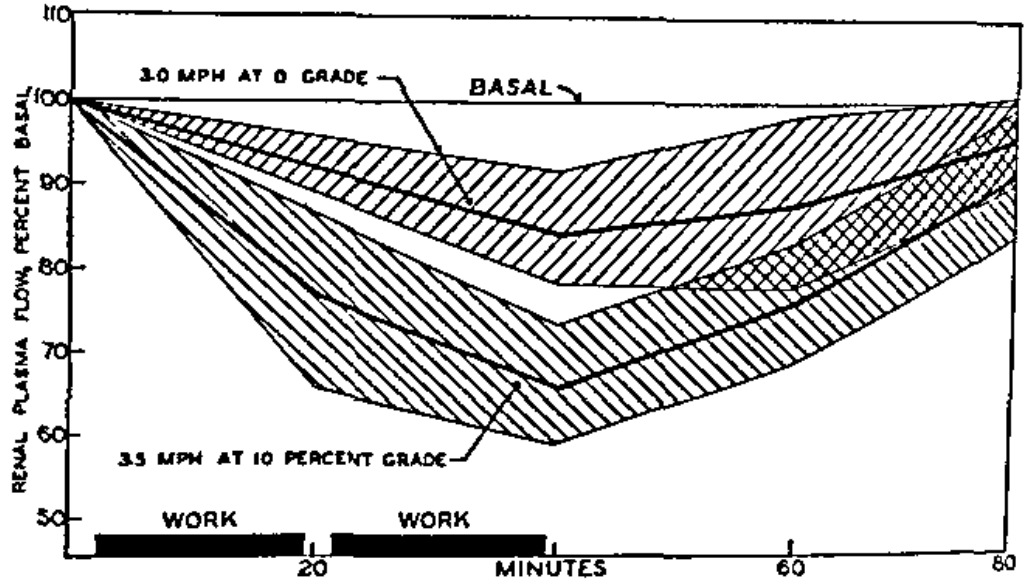
Merrill and Cargill [1410] examined the effects of stepping up and down 2 steps, each 12 5 in high, approximately 40 times, or of exercising the legs by means of a two-pedal pulley and weight device. The exercise appears to have been moderately taxing to the individual. In most cases exercise was accompanied by moderate to marked reduction in renal plasma flow and filtration rate, but in none did the filtration rate fall as low as 70 cc/min , the value that the authors consider critical for the excessive retention of sodium The authors conclude that the renal blood flow is reduced when the circulation is overtaxed by moderate exercise, a phenomenon that would be exaggerated in cardiac disease.

White and Rolf [2203] (single-injection method) examined the effects of running exercise While light exercise led to only slight reduction in renal plasma flow and filtration rate, moderate to severe exercise reduced these values to half or less of the resting levels and at least doubled renal vascular resistance, while brief maximum exercise reduced them to 20 per cent or less and increased renal resistance at least five-fold A longer period of maximal exercise at a lower rate was less effective, reducing clearances to about one-third of the resting values. The more intense the exercise, the greater the effect, and under extreme conditions White and Rolf predict that almost a liter of blood per min. may be made available for the circulation of active regions Recovery of clearances may be incomplete 60 min after cessation of exercise.

Protein did not appear in the urine formed during even the severest exercise, but, after severe exercise, was present in the first one or two postexercise samples The authors interpret this fact as indicating that exercise induces generalized vasoconstriction and that only at maximal work levels do any large number of glomeruli drop out of function and suffer ischemia to the extent that they begin to leak protein.

Reductions in renal plasma flow during short periods of exercise are reported by Aas and Blegen [2] Kattus, Sinclair-Smith, Genest, and Newman [1093] report that standing quietly but not motionless and walking on a treadmill at 3 m p.h have no effect on the filtration rate and only a moderate or no antidiuretic effect

Radigan and Robinson [1667] have compared the effects of exercise (3 m.p.h. up a 5 per cent grade on a treadmill) in cool (21° C.) and hot (50° C.) environments. In the cool environment, the resting filtration rate averaged 108 cc., and exercise did not influence it. The resting renal plasma flow averaged 695 cc., and exercise decreased it by 42 per cent. In the hot environment, the resting filtration rate was 84 cc. and exercise decreased it to 70 cc. The resting renal plasma flow in the hot en-



Keys [352])

vironment was 426 cc., and this decreased by 36 per cent during exercise

Exercise superimposed on water or alcohol diuresis decreases the pH and increases the excretion of titratable acid and of ammonia.[580] The renal ischemia associated with exercise in man is not hemodynamically typical of the action of adrenalin.[80]

Exercise also reduces the hepatic blood flow.[232]

Chapman, Henschel, Minckler, Forsgren, and Keys [352] examined men exercising on a motor-driven treadmill at energy outputs corresponding to 419, 612, and 1070 cc. of oxygen per min. per sq. m. The highest level sufficed to tax normal active males only moderately, but caused considerable discomfort in subjects accustomed to little or no strenuous exertion. During the first 16 min of exercise, the renal plasma flow decreased by an average of 6, 17, and 25 per cent of the resting control value at the three rates of exercise. Continued walking for another 16 min. yielded average reductions of 15, 27, and 37 per cent of the resting

control values. The renal plasma flow had not returned to basal levels after 40 min of recovery (fig 82). The authors note that, at the lightest rate of exercise, about 150 cc/min. of blood are diverted from the kidney for circulation elsewhere For the heaviest work load, the corresponding figure is about 330 cc, a not inconsiderable amount. Similarly, Chapman, Henschel, and Forsgren [281] found that during moderate exercise of relatively long duration the renal plasma flow decreased in 4 young men by 9 to 23 per cent, during the second 16 min period it decreased by 15 to 37 per cent and during the third 16 min. period by 19 to 34 per cent During the second and third hours of exercise, there was little further change In 2 men examined, the renal plasma flow had returned to within 10 per cent of the control value 1 hr. after cessation of exercise

HYPOXIA AND SIMULATED ALTITUDE

Most investigators report that anoxic hypoxia in unanesthetized animals and man causes transiently a moderate to marked diuresis with generally increased chloride excretion [60, 1212 1447 1891, 2030 2031] In anesthetized animals, on the contrary, anoxic hypoxia usually leads to oliguria or anuria [1374, 1794 1892 2080 2081 2082 2090] Stickney, Northup, and Van Liere [2009] conclude that mild hypoxia in anesthetized dogs generally produces polyuria, while severe hypoxia produces oliguria, but the incidence of either appears to be affected by the type of anesthetic agent used Since hypoxia may affect the tubular epithelium, the renal circulation, the secretion of adrenalin and antidiuretic hormone, and possibly the secretions of the adrenal cortex, these changes in urine flow as well as changes in the composition of the urine are uninterpretable without further information

McCance [1288] reports a subject who suffered syncope from apnoic anoxemia following voluntary ventilation During the ensuing oliguria, the rate of excretion of creatinine and sulphate were reduced to three-quarters and two-thirds, respectively, of their initial values, indicating a marked reduction in the filtration rate Urea excretion was reduced even more, probably because of the oliguria Ammonia formation and the capacity to form a concentrated urine were not affected

Caldwell, Rolf, and White [221] repeatedly subjected an army pilot and an untrained subject to 9 3 to 13 0 per cent oxygen for periods up to 19 min., with no effects on filtration rate, renal plasma flow, renal vascular resistance, or plasma glucose levels

Exposure of 5 normal male adults to simulated altitudes of 10,000 to 18,000 feet for 4 to 6 hr daily, 6 days a week, caused no change in renal plasma flow, filtration rate, or urine flow over periods of 4 to 6 weeks

Tm_D, however, increased within 3 weeks at altitude, and this increase persisted for weeks or months after discontinuance of exposure The increase ranged from 10 to 35 per cent. The intermittent exposure to low oxygen tensions had no immediate detrimental effect on the kidney.

Acute exposure of dogs to simulated altitudes of 18,000 and 24,000 feet had no consistent effects on the filtration rate. In observations starting 5 min. after reaching altitude, the renal plasma flow increased in all dogs at 18,000, and was further increased in 1 dog at 24,000 feet, but decreased below the ground level values in the others. In 7 observations, Tm_{PAH} was unchanged, but in 3 observations this value increased by 88, 135, and 222 per cent [1314] Tm_G was significantly decreased in 2 of 3 animals at 18,000 feet [1107]

Reduction of the arterial oxygen tension to 50 mm Hg in 9 subjects, 7 of whom were normal and 2 emphysematous, produced only slight changes in filtration rate (−5.2 to +22 8, average +6 per cent) or renal plasma flow (−1.3 to +29 4, average +13 per cent).

The most pronounced effect was on the excretion of sodium, which increased from 162 to 256 μmEq/min , and chloride, which increased from 161 to 245 μmEq/min. The effects on urine flow, pH, and the excretion of potassium, phosphorus, and ammonia were negligible. The authors note that anoxic hypoxia probably does not contribute to the reduction in renal plasma flow or the retention of sodium and water observed in congestive heart failure.[125]

Aas and Blegen [2] observed a slight increase in renal plasma flow in 2 normal subjects breathing 9 5 per cent oxygen, the filtration rate decreasing slightly. Equivocal results were obtained in 2 patients in congestive heart failure

Renal vasoconstriction, as judged by paling, occurs in anesthetized (nembutal) laparotomized rabbits when the trachea is occluded, the renal blood flow being restored when air is allowed to enter the lungs These vasomotor effects are reduced or prevented by renal denervation.[688]

PRESSURE RESPIRATION

When respiration is carried out for 30 min. periods against pressures of 10 to 40 mm Hg above ambient pressure, the urea clearance and urine volume undergo progressive reduction, apparently reflecting a reduction in filtration rate [546]

ABDOMINAL COMPRESSION

Bradley and Bradley [235] studied the effects on the renal circulation of increasing the intra-abdominal pressure by the application of a pneu-

matic abdominal pressure girdle Measurements of the venous pressure in the inferior vena cava and renal vein by venous catheterization revealed that a compressional pressure of 80 mm Hg raised intra-abdominal venous pressure to about 20 mm. Hg, as compared to 2.9 to 7.4 mm Hg normally. The PAH clearance and filtration rate were invariably reduced by increased intra-abdominal pressure, on the average by −24.4 and −27.5 per cent, respectively The filtration fraction showed no change The authors believed that the elevation of renal venous pressure was probably sufficient to account for the reduction in renal plasma flow, but in view of other studies on renal venous pressure this remains doubtful. E_{PAH} was not changed during compression, showing that there was no arteriovenous shunting

Tm_D was reduced significantly by compression in 5 subjects, in about the same proportion as the filtration rate and renal plasma flow, so that the ratios C_{IN}/Tm_D and C_D/Tm_D remained about constant Tm_G fell in 3 out of 5 subjects studied, also in proportion to the filtration rate, so that the ratio C_{IN}/Tm_G also remained constant. The authors believe, since the diodrast clearance, the inulin clearance, Tm_D, and Tm_G were equally reduced, that the rise in venous pressure is accompanied by a rise in pressure in the renal pelvis, which blocks urine outflow from those (longest) nephrons in which the terminal pressures are lowest. As a result, all excretion in these nephrons ceases and all functions (C_{IN}, C_D, Tm_D, and Tm_G) are decreased proportionally Renal hyperemia did not occur after release from compressional ischemia

It is noteworthy that compressional ischemia was accompanied by an increased reabsorption of water, even in one subject with diabetes insipidus, implying that some change in renal hemodynamics is modifying tubular activity This matter is further discussed in chapter XXII.

French, Moland, and Booker [698] report that in dogs an increase to 10 mm Hg or less in intra-abdominal pressure has no effect on the filtration rate At pressures of 20 to 30 mm this function is decreased, and it falls to low levels at 40 to 50 mm The phenol red and creatinine clearances tend to return to normal in chronic experiments if the pressure is not increased too rapidly, indicating compensation, but remain reduced at the higher pressures

HOT ENVIRONMENTAL TEMPERATURE

Byfield, Telser, and Keeton [309] examined the effects of environment, as between a comfortable atmosphere (83 5° F , 2 per cent humidity), a hot dry atmosphere (99 5° F , 19 per cent humidity), and a hot wet atmosphere (99 5° F , 55 per cent humidity) on peripheral blood flow and

renal function. The higher temperature increased peripheral blood flow about fourfold but was without effect upon the filtration rate in 20 subjects. Two normal subjects and 3 with essential hypertension (in all of whom the filtration rate was above 110 cc.) showed only small changes in the renal plasma flow in the hot room; but in 2 subjects with essential hypertension and 1 with chronic glomerulonephritis, in whom the diodrast clearance was reduced (129 to 580 cc.), this clearance dropped by *16 to 42 per cent. Two other nephritic subjects with low diodrast clearances* (76 and 119) showed no change. It appears that hot environmental conditions do not increase renal plasma flow and, if shunting of blood to the periphery is marked, may substantially decrease it. The marked decrease in both filtration rate and renal plasma flow in a hot environment reported by Radigan and Robinson [1667] has been discussed under exercise. In 6 trials, 4 subjects showed no change in T_{mD}, but in 1 normal and 1 hypertensive subject this function increased by 48 and 33 per cent, respectively This *observation recalls the abrupt increases* in T_{mD} recorded above in decompression and, on confirmation, would be of considerable interest relative to tubular metabolism.

DIATHERMY AND FEVER

Conventional diathermy was reported by Grant and Medes [846] to increase the filtration rate in dogs, but Nicholes, Boynton, and Herrin [1521] obtained only slight increases by this method, and Page [1564] observed no significant change in the urea clearance during fever therapy in normal subjects or patients with renal disease. Farr and Moen [626] observed only negligible changes in the urea clearance of rheumatic fever patients heated by carbon filament lamps. When hyperthermia was induced in dogs by electromagnetic induction, the *filtration rate decreased by* 12 to 79 per cent. Section of the splanchnic nerves and removal of the lumbar sympathetic ganglia nearly or completely abolished this decrease [1521]

Electromagnetic induction of heat in the region of the kidney also caused a slight decrease in the urea and creatinine clearances in patients with essential hypertension, acute rheumatic fever, and renal disease.[190]

ANESTHESIA

Pentobarbital sodium anesthesia (30 mg/kg. intraperitoneally) produced no consistent change in the inulin and diodrast clearances or in T_{mD} in dogs.[418] *This anesthetic does not depress the diodrast extraction ratio,*[418,429] from which it may be concluded that the renal plasma flow is not changed during anesthesia (from 129 ± 4.8 to 146.7 ± 21.1 mm. Hg); and the unchanged diodrast clearance and filtration fraction im-

ply autonomous renal vasoconstriction in the face of elevated blood pressure.

In 3 of 37 dogs, renal failure occurred during anesthesia; the diodrast and inulin clearances were extremely low and in 1 instance were observed to fall abruptly with only a slight increase in filtration fraction (0 23 to 0.27), while the mean arterial pressure was maintained at 116 mm. Hg or above The cause of renal failure was undetermined, but the authors suggest renal arteriolar constriction, since others have observed that thiobarbiturate given intravenously may increase blood pressure and simultaneously decrease kidney volume.

Repeated anesthetization of dogs with cyclopropane, ether, and chloroform over a period of 8 months does not affect the maximal urea clearance Ninety-one control determinations on 5 animals averaged 34 9 ± 6.1 cc (σ/m = 0 176), and 83 determinations after 19 periods of anesthesia with the 3 agents averaged 35.2 ± 5.9 (σ/m = 0.166) cc/min. per sq. m [1557]

Craig, Visscher, and Houck [447] have shown that light ether and cyclopropane anesthesia (stage III, plane 1) in dogs produces no significant alteration in PAH or creatinine clearances, but in deep anesthesia (stage III, plane 3), uncomplicated by surgical operation, depression of renal function occurs; the PAH and creatinine clearances were reduced to 53 ± 8 9 and 48 ± 7 7 per cent of the values observed during light anesthesia, *despite maintenance of arterial pressure. The filtration fraction* fell only very slightly (to 91 ± 3 2 per cent) These clearances returned substantially to normal when the animal was allowed to recover from stage III, plane 3, to stage III, plane 1 The reduction in creatinine and PAH clearances in deep anesthesia were attributed to neurogenic constriction of the afferent arterioles Reduction in glucose Tm at load/T_G ratios above 1 25 indicates that glomerular activity was reduced much more in some nephrons than in others Repeated anesthesia did not alter glucose Tm when measured without anesthesia. Deep anesthesia decreased urine flow to 41 ± 3 6 per cent of the value observed in stage III, plane 1 The decrease in filtration rate could well account for this oliguria, especially since mannitol or glucose was infused to maintain osmotic diuresis, but increased secretion of antidiuretic hormone cannot be excluded

Coller, Rees, Campbell, Iob, and Moyer [398] state that inulin and diodrast clearances in man are not affected by ether anesthesia, provided the anesthesia is well controlled and significant blood volume reduction does not occur Inulin clearances in 4 patients studied under cyclopropane anesthesia were depressed; in 2 patients the diodrast clearance in-

creased and in 2 it decreased. Ether and cyclopropane appear to have no effect on ammonia production.

Burnett, Bloomberg, Shortz, Compton, and Beecher[298] report that in 8 patients during ether anesthesia maintained in stage III, plane 2, the mannitol clearance was reduced by an average of 21, the PAH clearance by 39, and the urine flow by 51 per cent. The filtration fraction was increased by an average of 25 per cent. In 7 patients receiving cyclopropane, these changes were −31, −52, −47, and +35 per cent. While qualitatively the effects of ether and cyclopropane on renal function are similar, quantitatively cyclopropane was believed to be more active in reducing renal function.

The administration of ether to rabbits invariably reduced the filtration rate, renal plasma flow, glucose Tm, and urine flow, without significant changes in systemic blood pressure. These effects were transient and passed off during anesthesia, indicating that they are neurogenic responses to the administration of an irritant anesthetic agent. The rabbit is apparently more sensitive in this respect than the dog or man However, the intravenous administration of sodium pentobarbital can produce deep anesthesia in the rabbit without disturbance of renal function.[678]

If the decreased urine flow and clearances associated with deep anesthesia are attributable to neurogenic vasoconstriction, as Craig *et al.* point out, an explanation is provided for the diuresis and renal hyperemia, which, in the older literature, were attributed to renal denervation In the 30 studies cited by Smith,[1929] beginning with those of Claude Bernard in 1859, the anesthesia must have been fairly deep, probably deep enough to depress the renal blood flow and filtration rate Under these conditions, denervation might be expected to block vasomotor activity and to permit the renal blood flow and filtration rate to increase

In addition to the studies on spinal anesthesia discussed in the early part of this chapter, other studies on subjects with essential hypertension are cited in chapter XXIII.

RENAL VASODILATATION

Pyrexial Hyperemia

Attention has been called to the fact that inulin—as indeed almost any organic or inorganic material—may become contaminated by bacteria, molds or yeast, the proteins of which, on parenteral administration, prove pyrogenic, i.e. they induce chills,

fever, headache, nausea, lumbar and other pains in the familiar manner of typhoid vaccine. The reaction is most severe when pyrogenic material is given intravenously. Early in investigations utilizing inulin, it was found that this substance may be contaminated with pyrogen to the extent that, where 150 gm. of non-pyrogenic inulin could be given intravenously to man without

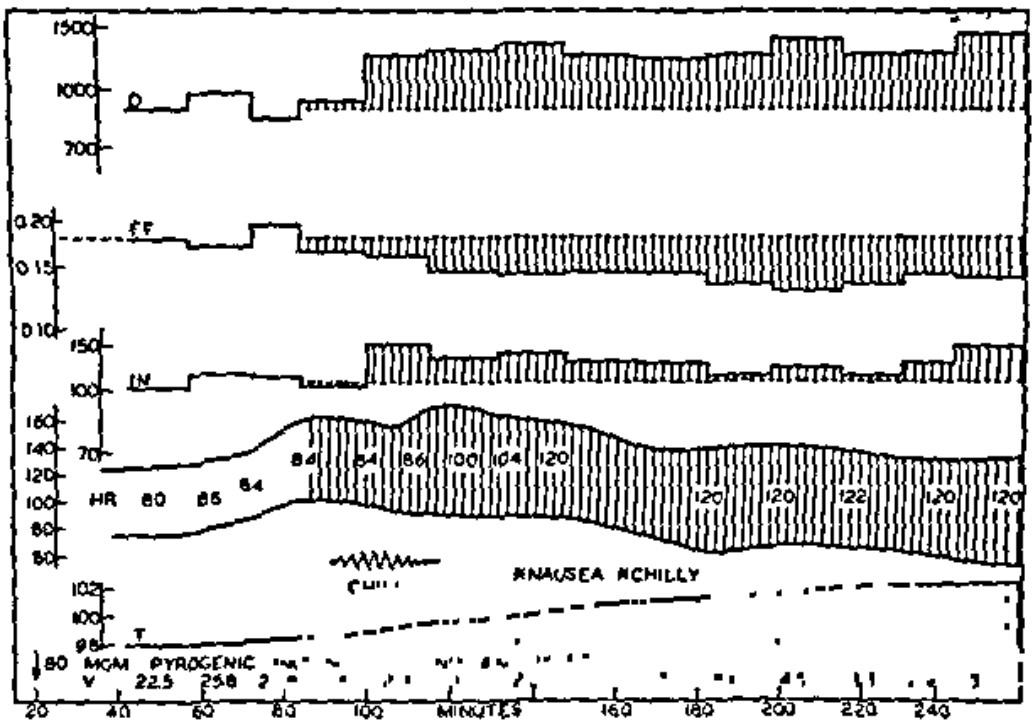


FIGURE 83. Renal hyperemia induced by pyrogen in a normal subject with no premedication Note the chills, nausea, increase in blood pressure and heart rate, and the rise in rectal temperature, T

This test was made 1 week after the observation in figure 84 in order to circumvent the possibility that the reaction might be diminished by antibody formation. (Smith [1929])

any disturbance whatever, 50 to 150 mg. of pyrogenic (*toxic*) inulin would produce a severe pyrexial reaction. It was also an early discovery that among the sequelae of this reaction is a remarkable increase in renal blood flow. Triple typhoid vaccine and other pyrogens have this same action, and both pyrogenic inulin and triple typhoid vaccine have been used to produce sustained renal hyperemia in animals and man, this being an effective method of attaining this end.[237, 356, 358, 798, 993, 1929]

Figure 83 shows the effects of 80 mg. of pyrogenic inulin ad-

ministered intravenously to a normal subject without premedication. Characteristically, a latent period of 70 to 90 min. intervenes after the injection of the pyrogen before any physiological disturbance is evident; this latent period extends over the first 3 urine collection periods in figure 83, and these may be taken as control values. Typically, about an hour after injection the blood pressure begins to rise, and the subject complains of chilliness (peripheral vasoconstriction). Soon a more or less severe chill occurs, and with the chill the body temperature begins to rise and continues to rise for 3 to 4 hr. regardless of whether there are more chills or not. At the peak of the reaction there may be additional chills, nausea, headache, back pain, and other symptoms of febrile reaction. At about the time of the chill, the renal plasma flow begins to increase; this increase is frequently but not invariably preceded by a short phase of renal ischemia. Renal hyperemia usually persists for 4 hr. or more. In general, the hyperemia will range from 30 to 60 per cent above the control value, though increases of 100 per cent have been observed—the relative increase, of course, depends in great measure upon the control level. It is perhaps more exact to say that at the peak of hyperemia the renal whole blood flow will reach 2000 to 2500 cc/min., the largest figure on record being 3000 cc. (The average normal figure in men is 1166 cc/min.) The fact that the increase in blood flow is accompanied by a reciprocal change in filtration fraction (the filtration rate remaining constant) shows that both afferent and efferent arterioles are dilated. (Other studies on pyrexial hyperemia are illustrated elsewhere.[237, 1931])

This phenomenon of renal hyperemia is naturally of great interest and an early effort was made to control the fever and other adverse reactions by various means. It was found that the administration of a suitable dose of the antipyretic, aminopyrine, produces in this complex response a remarkable dissociation. Figure 84 shows observations on the same subject as in figure 83, after the same dose of pyrogen but now *premedicated* with aminopyrine (10 grains every 4 hr. during the preceding 16 hr.). This experiment was carried out before the one shown in figure 83, in order to circumvent the possible development of tolerance to the pyrogen. Under aminopyridine medication, the rise in blood pres-

sure, the chill, the nausea, all aches and pains, as well as the rise in body temperature, are abolished; one would not know that the subject had received pyrogen, yet the renal hyperemia still appears and, as far as can be judged, is not diminished either in magnitude or duration.

Pyrexial hyperemia is not dependent upon the renal nerves;

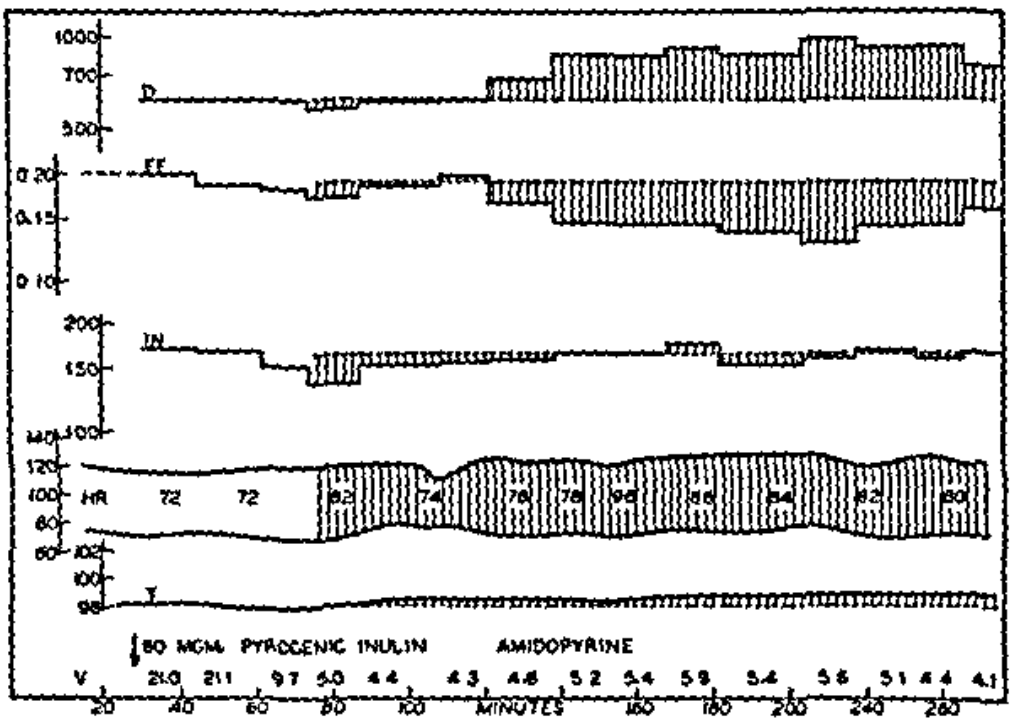


FIGURE 84 Renal hyperemia induced by pyrogen in the same subject as is shown in figure 83, but after premedication with amidopyrine (10 grains every 4 hr. during the preceding 18 hr.) Note the absence of all febrile disturbances, despite the persistence of the renal hyperemia (Smith [illegible])

Goldring *et al.*[793] found that a fair degree of hyperemia was induced by pyrogen in 3 sympathectomized hypertensive subjects, in one of whom the kidneys were examined separately before and after unilateral sympathectomy, while Hiatt [993] has shown that pyrexial hyperemia in the dog is essentially unmodified by renal denervation (fig 85). It appears, therefore, that the dilatation of the renal arterioles is effected either by a local action of the pyrogen (or some derivative) on these arterioles or by the secretion, perhaps elsewhere in the body, of a vasodilatory agent which is transmitted to the kidneys by the blood. The first is the more likely interpretation.

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pertension [798] and to observe the effects of the repeated induction of renal hyperemia on blood pressure in hypertensive subjects.[356]

Maxwell, Morales, and Crowder (pers. com.) have shown that E_{PAH} is not reduced during hyperemia.

The hepatic blood flow is also increased during the pyrexial reaction, *in one subject from 2 to 4.0 liters/min.*,[232] *hypatic hyperemia*, like renal hyperemia, being uninfluenced by premedication with aminopyrine [233]

ADENYLIC ACID, ADENOSINE, AND ADENOSINE TRIPHOSPHATE

Adenylic acid derivatives are known to be powerful vasodilators and, since they are natural tissue metabolites, their action on the kidneys is of some interest Houck, Bing, Craig, and Visscher [1041] have examined the effects of the continuous intravenous infusion of yeast (3-adenylic) and muscle (5-adenylic) acid in dogs In adequate doses, these substances produce a marked fall in blood pressure, accompanied by reduction in filtration rate ranging from 10 to 100 per cent depending upon the degree of blood pressure reduction Where the filtration rate is not too greatly reduced (0 to 35 per cent), the renal plasma flow remains constant or increases above the control value At lower pressures, renal plasma flow decreases In all cases the filtration fraction decreases Immediately after the infusion is stopped, the blood pressure and filtration rate return to or near the preinfusion level, and the renal plasma flow reaches hyperemic levels ranging from 111 to 240 per cent of the control, the hyperemia lasting for as long as 100 min The filtration fraction remains reduced Qualitatively similar results were obtained with yeast adenosine and sodium adenosine triphosphate The hemodynamic relations indicate an equal effect on the afferent and efferent arterioles.

CINCHONA ALKALOIDS

The fact that large doses of some of the cinchona alkaloids cause peripheral dilatation and a marked reduction in blood pressure led Hiatt and Suhrie [996] to examine their effects on the renal circulation in dogs In 14 out of 19 experiments, quinidine, cinchonidine, cinchonine, and quinine caused an increase in the PAH clearance of 30 to 50 per cent, the increase beginning within 30 min and lasting for several hours, according to the sojourn of the drug in the blood. The filtration rate also increased, but to a lesser extent It is presumed that these compounds act directly on the renal arterioles An increase of PAH clearance of 50 per cent or more can be maintained over a period of several days in normal

Bradley, Chasis, Goldring, and Smith [237] have shown that during the afebrile reaction (in premedicated normal subjects) the cardiac output generally increases, usually as a result of an increase in both the pulse rate and the stroke volume, while total peripheral resistance is decreased. Generally, these reciprocal changes are *such that the arterial pressure is well maintained* but, in some individuals, especially hypertensive subjects, the increase in cardiac

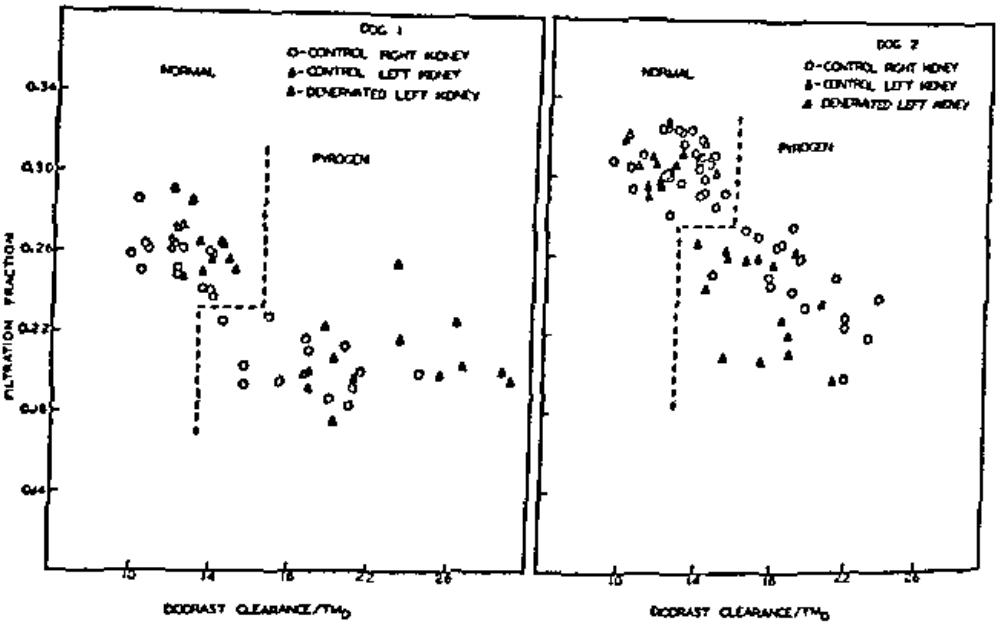

FIGURE 85. The filtration fraction in relation to the renal plasma flow per unit Tm_D in the intact and denervated kidneys of 2 dogs under normal conditions and during pyrexial hyperemia Each datum represents a clearance period (Hiatt [891])

output is inadequate to offset the decrease in resistance and arterial pressure is reduced, even to shock levels where it is necessary to keep the patient in a head-down position in order to maintain the cerebral circulation. At the peak of the reaction, most subjects show *circulatory inadequacy, if placed in the upright position,* owing to imbalance between cardiac output and peripheral resistance. In the recumbent position the renal fraction (per cent of cardiac output going to the kidneys) is increased, implying greater vasodilatation in the renal vascular bed than in the rest of the circulatory system.

Pyrexial hyperemia has been used to examine glomerular dynamics in normal persons [1934] and in subjects with essential hy-

circulatory picture closely resembles the early stages of shock prior t vasomotor collapse

Figure 87 shows observations made during the continuous intravenou infusion of sodium nitrite, a technique that proves more amenable tc control than inhalation of amyl nitrite. It will be observed that the stronger infusion in the latter part of the test reduced the blood pressure but caused no severe circulatory disturbance. When, however, at

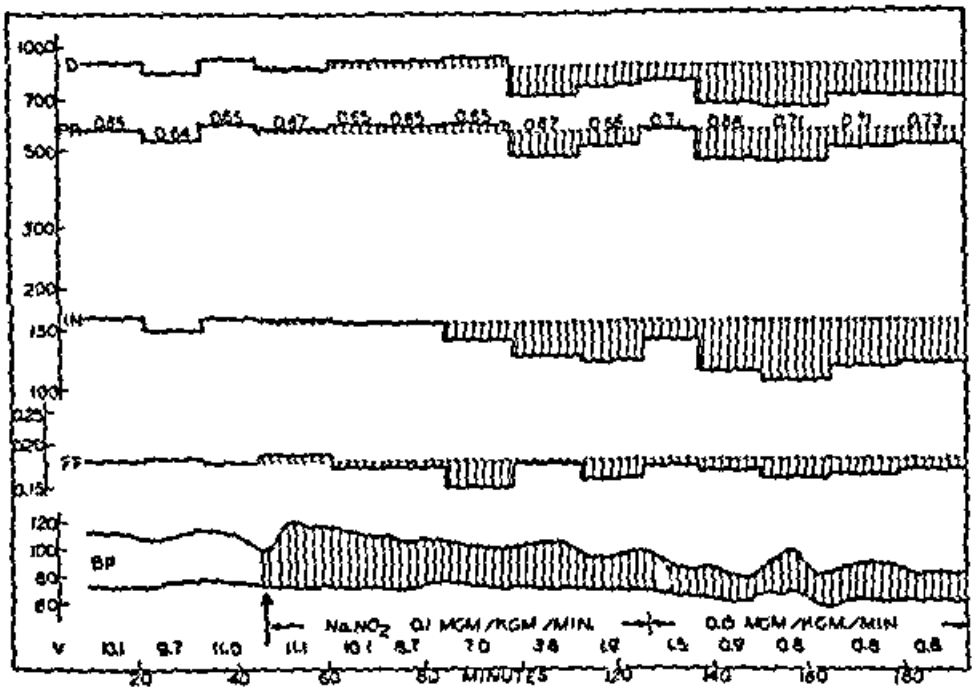

FIGURE 87. The effects of the constant intravenous infusion of sodium nitrite in a normal subject (Chasis, Ranges, Goldring, and Smith [344])

the conclusion of the last period the subject was raised in bed to 45 degrees, the blood pressure fell to 66/44 mm Hg and he complained of vertigo, demonstrating circulatory inadequacy

As the nitrite began to reduce the blood pressure, the renal plasma flow and filtration rate decreased, the latter to a slightly greater extent. In the last few periods there was marked oliguria perhaps related to the reduced filtration rate, although increased secretion of ADH cannot be excluded The renal response here is unlike that induced by adrenalin and presumably sympathetic excitation, in that the filtration rate decreased in a manner parallel with the renal plasma flow. This may be attributable in part to reduction in mean arterial pressure, but it is possible that the renal response involves dominant afferent constriction.

filtration fraction invariably decreasing Toxic manifestations are said to be relatively unimportant Blood pressure showed a definite reduction only in some hypertensive patients. The effects on renal hemodynamics are similar to those produced by pyrogen.

TETRAETHYLAMMONIUM

This quaternary ammonium compound has a marked sympatholytic action. Aas and Blegen [1] report that it reduces renal function in normal subjects The filtration rate decreased by 4 to 62 per cent (average −26.6), the renal plasma flow by 11 to 65 per cent (average −30.2) in 8 subjects receiving 100 mg/min of the drug by intravenous infusion The diastolic pressure was reduced in only 2 subjects, and the reduction in renal function appears to involve renal vasoconstriction, but perhaps of an autonomous nature. The drug also produced an acute reduction in urine flow, with some proteinuria. It is of interest that Page and Taylor [1568] have adduced evidence that this compound augments the vasoconstrictor action of adrenalin and other pressor drugs, as well as the depressor effects of isuprel, which pharmacologically resembles sympathin I.[426] Aas and Blegen caution restraint in using tetraethylammonium in conditions where renal vasular spasm may be present. There is no warrant to believe that, even if wholly effective as a sympatholytic agent, this compound would be effective in restoring renal function in anuria (ch. XXIV). Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick [1256] report that the PAH clearance was not decreased during the hypotensive phase which follows its administration, although the filtration rate fell in a manner parallel with the blood pressure. From these and other observations on dogs, they infer that the compound produces some renal vasodilatation, but it must not be overlooked that the renal circulation autonomously tends to maintain itself in the face of reduced blood pressure, however produced, and a specific action on the kidney is not certainly indicated by these reports

SODIUM NITRITE

It has long been accepted, though on little evidence, that nitrites in general and sodium nitrite in particular lower the systemic blood pressure by dilating the arterioles However, Wilkins, Haynes, and Weiss [2220] have adduced strong if indirect evidence that sodium nitrite acts predominantly by dilating the venous system and reducing venous pressure; there follows a reduction of cardiac output and hence in arterial pressure, and the latter, acting through the carotid sinus-aortic arch receptors, induces vasoconstriction of the arteriolar bed The resulting

was followed in 15 to 20 min. by maximal diuresis, the average urine flow at the peak being 10.9 cc/min. above the control level.

In summary, the foregoing studies show that, while the renal circulation has considerable lability, the afferent and efferent arterioles have remarkable autonomy, or at least apparent autonomy, of action. However, most of the circumstances so far described as eliciting changes in renal function are rather extreme in nature, such as those that excite marked sympathetic activity and vasoconstriction elsewhere in the body. Clearly, whatever other regulation is imposed on the renal vascular bed, the renal circulation is subordinate to the emergency function of the sympathetic nervous system.

As opposed to this subordination, it may be reiterated that an outstanding feature of the renal circulation is the subtle capacity of the renal vascular bed so to adjust itself that the renal circulation tends to be restored in the face of prolonged increases or decreases in arterial pressure. The evidence indicates that this readjustment reflects autonomous activity which is independent of the vasomotor nerves, though that it is independent of extrarenal humoral agents cannot be stated One senses that this autonomous regulation actually acts in opposition to, or as a check upon, externally imposed vasomotor excitation, yielding only under extreme provocation, and that somewhere within the complexities of the renal circulation is a more subtle stimulus (or group of stimuli) which, because it is integral to the mechanism of autonomous control, can produce more immediate and profound changes in filtration rate and renal blood flow than are produced by most extrarenal factors. If we approach the problem of the control of the renal circulation with the *a priori* notion that this control consists of a balance of forces between opposing stimuli reaching the kidney from the outside, we are certainly destined to be disappointed. Despite certain limitations, the renal circulation performs a nicely quantitative job without the aid of the sympathetic nervous system, the adrenal medulla, the adrenal cortex (if adequate sodium is available), the neurohypophysis, or most of the other endocrine glands, and in doing so must make some remarkable readjustments of its own activitie

creased by 111 per cent. In a second, E_{PAH} averaged 0.925 before, and 0.89 when the renal plasma flow had increased by 53 per cent

It seems probable to the writer that the interpretation of Michie, Barker, and their coworkers, that large rapid doses of albumin open arterial-venous anastomoses, is the correct one. The problem is, however, a complicated one and will be discussed at greater length in chapter xxv.

Goodyer, Peterson, and Relman [812] report that the intravenous administration of 75 gm. of human salt-poor albumin into normal subjects during water and mannitol diuresis, which served to increase the plasma volume by 20 per cent as judged by hemoglobin and hematocrit, led to a reduction in urine flow, to a slight decrease in mannitol clearance (single injection method) (−11 per cent), to a decrease in sodium (−46 per cent) and chloride (−62 per cent) excretion, and an increase in potassium excretion (+40 per cent).

Venous pressure fell 15 to 60 mm. of saline in 2 subjects and rose 35 to 100 mm. in a third. A similar reduction in sodium excretion (from 3 0 gm. to 1.8 to 2.2 gm/day) occurred in a subject receiving 75 gm of albumin per day for 4 days, with no increase in urine volume. When albumin was stopped, sodium excretion returned to control levels. No albumin was excreted in the urine.

These negative results with respect to filtration rate and the decrease in sodium excretion contrast sharply with the increase in filtration rate and in salt and water excretion following the administration of albumin to patients in the nephrotic syndrome, where albumin infusion generally causes a large increase in filtration rate and sodium excretion (ch xxvi)

PLASMA

Lauson, Bradley, and Cournand [1217] did not observe any remarkable increase in renal function following transfusion of blood or plasma in patients in shock beyond what might be related to the improvement in the circulation. In most cases the renal blood flow remained at subnormal levels.

When large quantities (900 to 1955 cc.) of reconstituted plasma were given fairly rapidly to convalescent subjects who for the most part had normal renal function, Wilson and Harrison [2213] found a marked increase in the creatinine and PAH clearances, the filtration fraction invariably decreasing. (E_{PAH} was not determined.) The maximal increase occurred about 25 min. after infusion and

CHAPTER XV

Trophic and Other Factors Related to Renal Function

ANTERIOR PITUITARY

Numerous lines of evidence have long indicated that among the various trophic hormones elaborated by the anterior pituitary gland, one or more has a powerful renotrophic action The kidneys of hypophysectomized rats weigh less than those of normal animals,[1363] and hypophysectomy prevents compensatory hypertrophy in uninephrectomized dogs [2202, 2247] and mice [1363] Anterior lobe extract causes renal hypertrophy in castrate male mice, this effect being greatly enhanced by the simultaneous administration of thyroxin, although the latter has only a moderate effect alone [1828] and such extracts inhibit the renal atrophy in rats which follows unilateral ligation of the ureter [1836] The thyroid, gonads, and adrenals are not necessary for renal hypertrophy in rats, although hypertrophy may, for some unknown reason, be prevented by dietary factors.[670 932 934] Fontaine [670] inferred that renal regression in hypophysectomized rats is almost entirely the result of the decrease in endogenous protein catabolism, but this may be questioned since the renotrophic effects of anterior pituitary extracts are apparently not related to protein metabolism

White, Heinbecker, and Rolf [2198 2203] have shown that functionally the dog kidney is very sensitive to the trophic action of the anterior pituitary gland. Denervation (or puncture) of the neurohypophysis in the dog results only in transient disturbances of renal function. The diodrast and inulin or creatinine clearances are slightly (10 to 15 per cent) increased after the operation, to fall slightly (20 to 25 per cent) below

Complementary to this speculative, almost intuitive, view is the fact that in some respects the kidney is charged with almost the sole responsibility for the regulation of the composition of the internal environment with respect to salt and water; and that, in carrying out this task, a nice balance must be maintained between glomerular and tubular function. The requirements of glomerular-tubular balance extend to the individual nephron, and thus one is tempted to the further speculation that what we observe in the mass action of the kidneys is but a statistical mean of many essentially autonomous units. There is evidence that here is at least one avenue (it need not be the only one) of approach along which we can search for the *vis a tergo* of renal regulation. The problem cannot be explored profitably except against a background of knowledge of electrolyte excretion, and further speculation can profitably be postponed to later chapters.

White and his coworkers early inferred that the thyroid and adrenal cortex were not directly involved in the trophic action of the anterior pituitary, and they attributed the change in renal blood flow and filtration rate to renal vascular changes and the reduction in Tm_D to a reduction in the quantity of some hypothetical transport substance in the tubule cells involved in diodrast excretion. Reduction in quantity of this transport substance would not necessarily reduce the extraction ratio at low plasma levels, but would reduce the maximal excretory capacity under load [2199, 2200, 2202, 2203] The cardiac output in the dog is permanently reduced after hypophysectomy, to about the same degree as are the oxygen consumption and the renal blood flow.[2204]

Comparable depression of renal function as measured by Tm_{PAH} has been subsequently reported by White, Heinbecker, and Rolf.[2205] They affirm that this depression is not due to adrenal cortical regression, since adrenal replacement therapy adequate to maintain renal function in adrenalectomized dogs has no protective effect after hypophysectomy, and ACTH has no effect on renal function of hypophysectomized dogs ascribable to adrenocortical stimulation. Since the thyrotrophic and gonadotrophic hormones have been excluded, the essential loss in hypophysectomy is ascribed to some anterior lobe factor which acts directly on the kidneys.

More recently these investigators [2206] report that the renotrophic action is attributable to the growth hormone, which, administered daily for 9 to 12 days to normal dogs, doubles the PAH clearance and almost doubles the inulin clearance and Tm_{PAH}, while it raises the depressed values of hypophysectomized dogs to or above the normal levels In view of the negative results obtained with the adrenotrophic and gonadotrophic hormones, and the slight effect of the thyrotrophic hormone, they attribute the principal effect to the growth hormone itself, or some substance not yet separated from it The growth hormone, however, has but slight effect on renal function in adrenalectomized dogs maintained on DCA pellets, implying that its action, though not mediated through ACTH, requires normal cortical activity.

De Bodo, Earle, Schwartz, Farber, and Pellegrino (pers. com) confirm the reduction in filtration rate and renal plasma flow in hypophysectomized dogs, and find that Tm_G is also reduced Such animals respond to salt deprivation (intake 2 mEq/day for 3 weeks) in a normal manner in that urinary excretion of sodium and chloride are reduced to negligible values and the serum sodium shows only a minor decrease. Their tolerance to the acute intravenous administration of potassium is normal and excretion increases promptly to a level equalling or exceed-

normal at 4 to 6 weeks, with return to normal by 6 months Tm_D may fall by 20 to 30 per cent within a few days of operation, but returns to normal within a few weeks and remains there permanently. White and his colleagues attribute these transitory disturbances of renal function to reversible damage to the pars distalis at operation.

Total (and simple) hypophysectomy,* however, resulted in a marked decrease in the inulin (or creatinine) and diodrast clearances, the former from an average of 104 cc per sq. m to 52.2 cc. by the fifth postoperative day, the latter from 237 cc. to 155 cc. E_D remained unchanged, being in the range of 0.71 to 0.85 before, and 0 70 after operation. Tm_D was also decreased, the loss in tubular function being even more striking than the reduction in circulation. Complete hypophysectomy reduced Tm_D from an average value of 21 mg. of iodine to 5.5 mg. 5 days later. There was no tendency to return to normal in 380 days In 5 completely hypophysectomized dogs, the inulin clearance was reduced from an average of 104 cc. per sq. m. to 54.2 cc. on the fifth postoperative day; before and after simple hypophysectomy these figures were 80 and 54 cc.

Blood volume, as measured by T-1824 and calculated on the actual body weight, decreased by not more than 5 to 10 per cent during the first 6 weeks after operation; since the reduction in renal plasma flow and filtration rate occur much earlier, they were apparently not referable to decreased blood volume. There was no evidence of glomerular intermittence, as judged by White's[2192] injection method Blood pressure (auscultatory) did not increase, but frequently both systolic and diastolic pressures decreased by 10 to 15 per cent 4 to 6 months after operation. Anterior pituitary extract markedly increased Tm_D in normal and 'puncture' dogs, and restored this function to or toward normal in hypophysectomized dogs, in which it is markedly reduced prior to treatment. It increased the diodrast and inulin clearances in all 4 groups.[946,2198] Comparable reductions in filtration rate and urea clearance in hypophysectomized dogs, but not in diabetes insipidus dogs, are reported by Pickford and Ritchie.[1616]

The urea clearance is increased in normal and diabetes insipidus cats receiving anterior lobe therapy.[625]

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stance was generally less effective They suggest that the action of thyroxin on Tm_D and Tm_G is effected by making more energy available through acceleration of phosphorylation, since thyroxin is known to accelerate the intestinal absorption of substances undergoing active absorption by a mechanism generally considered to involve phosphorylation However, possible effects of thyroxin upon the anterior pituitary are not excluded. Thyroxin does not increase the rate of tubular reabsorption of galactose [692]

Moustgaard [1835] reports that, although thyroidectomy resulted within 4 days in a 15 to 20 per cent decrease in renal plasma flow and filtration rate, it did not diminish the capacity of the dog kidney to respond with an increase in both functions on a high protein diet.

Thyroxin is known to cause an increase in renal weight in rats,[1149 1329, 1830 2029] but no data are available on the relative changes in different parts of the nephron Thyroidectomy does not prevent or reduce compensatory renal hypertrophy in the rat.[1365] The Addis urea excretion ratio varies with the BMR in patients with hypo- and hyperthyroidism, the correlation being better in the latter group.[1335]

ANDROGENIC HORMONES

Testosterone

Korenchevsky and his associates [1160] have shown that gonadectomy reduces the kidney weight in male rats but not in females, that androsterone and esters of testosterone produce hypertrophy of the kidney in both normal and gonadectomized female rats and in castrated males, and in large doses estrogens produce cyst-like degenerative changes in the juxtamedullary layer of the cortex. These renotrophic effects have been demonstrated in mice [1141, 1144, 1808, 1828] and the dog,[187, 2167] and confirmed in rats [1278] A number of such renotrophic steroids are now known; in a few (ex 17-methyl-androstanediol-3α, 17α) the renotrophic action appears to predominate over the androgenic action [1141, 1142] Testosterone increases the hypertrophy of the remaining kidney after unilateral nephrectomy,[1328] decreases renal atrophy after unilateral ureteral ligation,[1934] and affords some protection against mercuric chloride poisoning [1829] and the 'nephrosclerotic' action of DCA in rats.[1837] Unlike the renotrophic action of anterior lobe extract, the renotrophic action of androgens is not potentiated by thyroxin.[1328]

The renal hypertrophy induced by androgens is chiefly localized in the tubules In mice, the flat epithelium lining the parietal layer of Bowman's capsule undergoes marked thickening to the extent of be-

ing the filtered load. The excretion of water administered *per os* is, however, markedly delayed, only some 5 to 15 per cent of a dose of 40 cc/kg. being returned in 3 hr., whereas normally the return is 100 per cent.[491]

Oliver [1550] has pointed out that in compensatory renal hypertrophy in the rat the volume of some proximal tubules may increase fivefold, although the total kidney tissue increases only twofold. This trophic effect on the proximal tubule would appear to be related to the changes in Tm_D and Tm_{PAH} reported above.

The data available on man [96] are insufficient to indicate any consistent change in acromegaly.

THYROID

Thyroid in nontoxic doses causes enlargement of the adult rat kidney with hypertrophy of the tubule cells, while toxic doses cause atrophic changes [1149] The oral administration of thyroid increases the filtration rate in normal and diabetes insipidus dogs,[910, 914, 1624] and it increases Tm_D [946] and Tm_G [914] in normal dogs, and Heinbecker, Rolf, and White [946] have shown that it effects some restoration of Tm_D in dogs in which this function has decreased in consequence of simple or total hypophysectomy. Thyroid is, however, less effective in this respect than anterior lobe extract. It had only a slight positive effect in 'puncture' dogs, i.e. with a hypothalamic lesion causing diabetes insipidus and obesity. The diodrast clearance was not affected by thyroid treatment in the normal and 'puncture' dogs but increased substantially in hypophysectomized dogs, in which it was markedly reduced before thyroid treatment. The effects on the inulin clearance were positive but less striking

Thyroidectomy produces some decrease in the diodrast clearance and Tm_D, with little or no effect on the inulin clearance; the effects are far less than those of hypophysectomy, and the depressed renal function after hypophysectomy cannot be attributed to loss of the thyrotrophic hormone. Thyroid administration to thyroidectomized dogs raises the diodrast clearance and Tm_D, with slight effects on the inulin clearance As noted above, anterior lobe extract, which causes large increases in these clearances and Tm_D in normal and hypophysectomized dogs, produces small and inconsistent increases in thyroidectomized dogs, as in adrenalectomized dogs.[2204]

Eiler, Althausen, and Stockholm [591] have shown that thyroxin in massive doses (20 mg/day) increased the creatinine clearance in 3 dogs by 21, 42, and 45 per cent, Tm_G by 40, 29, and 56 per cent, and, in 2 of the 3 dogs tested, Tm_D by 115 and 48 per cent. The feeding of thyroid sub-

stance was generally less effective. They suggest that the action of thyroxin on Tm_D and Tm_G is effected by making more energy available through acceleration of phosphorylation, since thyroxin is known to accelerate the intestinal absorption of substances undergoing active absorption by a mechanism generally considered to involve phosphorylation However, possible effects of thyroxin upon the anterior pituitary are not excluded. Thyroxin does not increase the rate of tubular reabsorption of galactose [592]

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ANDROGENIC HORMONES

Testosterone

Korenchevsky and his associates [1150] have shown that gonadectomy reduces the kidney weight in male rats but not in females, that androsterone and esters of testosterone produce hypertrophy of the kidney in both normal and gonadectomized female rats and in castrated males, and in large doses estrogens produce cyst-like degenerative changes in the juxtamedullary layer of the cortex These renotrophic effects have been demonstrated in mice [1141, 1144, 1803, 1828] and the dog,[187, 2187] and confirmed in rats [1278] A number of such renotrophic steroids are now known; in a few (ex 17-methyl-androstanediol-3α, 17α) the renotrophic action appears to predominate over the androgenic action [1141, 1142] Testosterone increases the hypertrophy of the remaining kidney after unilateral nephrectomy,[1378] decreases renal atrophy after unilateral ureteral ligation,[1524] and affords some protection against mercuric chloride poisoning [1829] and the 'nephrosclerotic' action of DCA in rats.[1857] Unlike the renotrophic action of anterior lobe extract, the renotrophic action of androgens is not potentiated by thyroxin.[1828]

The renal hypertrophy induced by androgens is chiefly localized in the tubules. In mice, the flat epithelium lining the parietal layer of Bowman's capsule undergoes marked thickening to the extent of be-

coming cuboidal, and acquires brush border.[415,1823] Such cuboidal cells are present in small numbers in untreated mice, particularly during pregnancy.[445] Testosterone has no effect on the juxtaglomerular tissue.[197]

Castration does not produce any change in kidney weight in guinea pigs [1053,1144] and male Syrian hamsters,[1143] and in neither species do androgens cause significant renal hypertrophy.

Lattimer [1216] pointed out that the kidney in rats, cats, and humans tends to be slightly larger in males than in females, the sex ratio increasing to 1.5 in old cats.[889] He presents new data which give a kidney weight/body weight ratio in adult men (20 to 40 years of age) of 6.68 ± 0.17, and 5.99 ± 0.16 gm/kg in adult women. In male infants (80 per cent below 1 year of age) the male ratio was 10.2 ± 0.40 and the female ratio 9.99 ± 0.34 gm/kg He suggests that the male sex hormone increases the renal weight. He obtained evidence of renal hypertrophy in dogs treated with 10 mg/day of testosterone propionate for 32 days, and these observations led him to test this compound in man However, he obtained only insignificant changes in filtration rate and Tm_D in 2 normal men, 2 with essential hypertension, and 3 with only 1 kidney, treated with 25 mg of testosterone propionate intramuscularly daily for 14 days

In dogs again, Welsh, Rosenthal, Duncan, and Taylor [2167] found that testosterone propionate in doses of 100 mg daily produced a rapid rise in Tm_D, sometimes to the extent of a 100 per cent increase. This increased tubular function was reversible, but the time required for function to return to normal varied greatly. The creatinine and diodrast clearances were unaffected, as was the blood pressure But, in man, Taylor and his coworkers [1138] and Dean *et al* [481] found that 90 to 300 mg daily of testosterone propionate for periods of 8 to 29 days did not significantly alter the filtration rate, renal plasma flow, Tm_{PAH}, or Tm_G, 4 normal men and 5 patients with impaired renal function being tested In at least 2 subjects, the dose (300 mg/day) was comparable to that which had proved effective in dogs. A second androgen, pregnenolone, in doses of 100 gm daily for 30 days failed to influence the filtration rate, renal plasma flow, Tm_{PAH} or Tm_G in the 2 subjects tested.

The presumed efficacy of testosterone in the treatment of renal disease [1580] is problematic in view of these negative results Henderson, Seneca, Abd El Messih, and Weinberg,[976] however, report that the mortality in a cholera epidemic was substantially reduced by the administration of 25 to 50 mg. of testosterone propionate daily as a supplement to the established therapy. The authors attribute the beneficial effect in part to relief of oliguria and uremia. They note that albuminu-

ria decreased after therapy This interesting report presents several difficulties in interpretation, as do all problems involving the treatment of oliguria when recovery can occur spontaneously, but further studies will be awaited with interest.

ESTROGENIC HORMONES

Selkurt, Talbot, and Houck [1877] observed no significant changes in filtration rate in dogs receiving alpha estradiol benzoate, and the administration of this compound in doses of 4 to 6 mg/day in 4 normal women produced no consistent change in filtration rate, renal plasma flow, Tm_{PAH}, or Tm_G, although vitamin C Tm was reduced [451] as noted in the dog by Selkurt *et al* (ch. v)

Bilateral orchiectomy in 2 women had no effect on the filtration rate, renal plasma flow, Tm_{PAH}, or Tm_G,[431] and similar negative results with respect to the filtration rate and Tm_D are recorded in the dog.[2204]

Progesterone increases the urine output of both normal and hypophysectomized rats, the effect being most marked in terms of absolute diuresis in the latter, in which the urine flow may amount to 50 per cent of the body weight per day Resistance to water intoxication is increased in these animals [1832]

It is of some interest that Boettiger and Boettiger [201] report that estrogens are excreted by the tubules of the aglomerular fish, *Opsanus tau* Conjugation may be necessary before excretion is possible. If tubular excretion occurs in mammals, the assumption that blood and urine levels always run parallel may be questioned.

ADRENAL CORTEX

The action of adrenal cortical extracts and of DCA have been discussed in chapter XII

TROPHIC ACTION OF VITAMINS *

Vitamin A

Starting from the observations that, 5 to 7 hr after the ingestion of butter, the postabsorptive urea clearance in dogs may be increased by 45 per cent, Herrin and Nicholes [983] examined the non-saponifiable fraction of butter and cod liver oil and concluded that vitamin A was chiefly responsible for the functional change. Vitamin D was without effect.

* The term trophic is used here to designate the slowly developing increase in function which persists for some time after the exciting agent is withdrawn, in contradistinction to the rapid and transient functional changes associated with high protein diet, etc.

Supplementing a diet presumably containing sufficient vitamin A with 50,000 units daily in the form of halibut liver oil resulted in a 41 to 94 per cent increase in urea clearance, the earliest increase occurring within a week, the maximum after 96 days. In 1 dog, the clearance remained elevated for 44 days after the supplement was withdrawn. A dosage of 20,000 to 30,000 units daily reduced the variability in response and shortened the period required for maximal response. The larger dosage may have induced toxic effects. The urea clearance cannot be kept permanently elevated by the continued administration of vitamin A, the maximal observed duration of the effect being 87 days. The changes in urea clearance are paralleled by changes in inulin clearance, the urea/inulin clearance ratio averaging 0.537 during avitaminosis and 0.514 where the clearances were maximal as a result of vitamin A therapy.

Vitamin A deficiency decreased the urea clearance, which rose again to supernormal values near terminus. The depressed clearance rose in 11 to 50 days after the administration of 15,000 to 30,000 units of vitamin A (halibut liver oil or crystalline carotene) daily, the difference between low and high vitamin diets in most cases being of the order of 75 per cent. In rats, vitamin A deficiency caused a 23 to 77 per cent decrease in the urea clearance, without pathological changes in the urine or kidneys. Administration of carotene increased the urea clearance by 30 to 170 per cent over the level reached during vitamin deficiency.[940]

In man, daily supplementation of the diet by 50,000 to 75,000 units of vitamin A (halibut liver oil or concentrate) produced no change in urea clearance in 2 subjects; in 4 subjects the clearance increased 11 to 15 per cent, and in 7 subjects the increase ranged from 24 to 91 per cent. This variability in response was not evident in dogs or rats. It is suggested that the individual with the greater amount of subcutaneous fat, who gains or loses weight easily, is the type who is most likely to respond with an increase in urea clearance In man, as in other animals, the elevated clearances begin to decline after a prolonged period of vitamin administration.[984]

Bing[171] found that doses of 5000 and 50,000 units per day of vitamin A in corn oil had no effect on the filtration rate, renal plasma flow, or Tm_D in dogs However, the daily administration of 200,000 units caused an increase in Tm_D or Tm_{PAH} in 3 out of 4 animals, the increase ranging from 50 to 100 per cent of the control value. Increased tubular function became apparent within 3 to 5 weeks. Only a slight increase was observed in Tm_D in a fourth animal. The filtration rate and renal plasma flow increased slightly in 3 out of 4 dogs, the filtration fraction remaining constant The effect of vitamin A differs, therefore, from that of

pyrogen or yeast adenylic acid, where the filtration fraction falls during renal hyperemia. Bing suggests that the increased renal plasma flow and filtration rate may represent a circulatory adjustment to the increased tubular function (an increase in renal weight not having been demonstrated).

Taylor, Corcoran, Schrader, Young, and Page [2033] studied the effects of vitamin A on man in relation to reported benefit in the therapy of essential hypertension. Of 2 normal subjects, 1 showed a 15 per cent increase in renal plasma flow; neither showed an increase in filtration rate, and the only one examined showed no increase in Tm_D. Of 10 subjects with hypertension, the renal plasma flow increased in 8, the range being from 0 to 110 per cent; the filtration rate increased in 6 (range 0 to 110 per cent), and Tm_D increased in 4 out of 7 subjects examined (range 0 to 95 per cent). In 3 subjects, the maximal increase in Tm_D was observed after treatment had been discontinued for 28, 21, and 30 days. There were no consistent changes in cardiac output (ballistocardiograph) The increase in Tm_D, the authors point out, may reflect an increase in the concentration of carrier substance in the tubule cells or an increase in cell mass, and, contrary to Bing, they suggest that the increased tubular function may be the result of prolonged hyperemia rather than a trophic action

Dicker and Heller [515] report that, in adult male rats on a basal diet containing 125 units of vitamin A per day, a supplementary daily dose of 250 units produces an increase in filtration rate, renal plasma flow, and Tm_D Free fluid occurred in the abdominal cavity in 9 out of 22 animals, a phenomenon never observed in control rats receiving the same water load.

Corcoran and Page [422] found that crude vitamin A concentrates, when given to rats in dosage of 2000 units per day intramuscularly, increased Tm_{PAH} by 100 per cent Crystalline vitamin A (2 mg/day) and neovitamin A (2000 units/day) were inactive. They conclude that the trophic action is not attributable to vitamin A, but to some other factor in commercial concentrates.

Vitamin B

There is some evidence that the capacity of the tubules to reabsorb glucose may be decreased in dogs suffering from deficiency of vitamin B [442]

Vitamins D and E

Herrin and Nicholes [933] found that the prolonged administration of vitamin D (irradiated ergosterol) and vitamin E (wheat germ oil) to dogs

was without effect on the urea clearance. A diet high in vitamin D decreased this clearance by 42 per cent and produced a urine which was dull reddish-brown in color and contained red and white cells and albumin, but no casts.

DIET

Jolliffe and Smith [1078,1079] first reported that the urea clearance in dogs in the postabsorptive state (i.e. 18 hr. after the last meal) is considerably increased on a high protein (meat) diet as compared with a cracker meal (low protein) diet. The changes in the urea clearance are attributable to proportional changes in the filtration rate, as indicated by the creatinine or inulin clearances.[1865 1866,2099] Though generally reproducible, the effects of a high protein diet in animals fed only once a day are far from quantitative, but all studies of renal function in dogs must be interpreted with due consideration of the maintenance diet.

The filtration rate may be increased nearly 100 per cent, 4 to 5 hr after a meal of raw beef, and it tends to persist at an elevated level for some hours so that the effect is cumulative. The maximal change, as between postabsorptive observations on a low protein diet and postprandial observations on a high protein diet, may be 3½-fold

The effect of meat protein can be duplicated qualitatively by casein, by the administration of thyroxin and phlorizin, both of which increase endogenous protein metabolism, and by the intravenous administration of glycine,* [66 1630,1632] or the oral administration of glycine, glycylglycine, alanine, glycolic, and pyruvic acids, but not by glucose † [1624] Herrin *et al.*,[985] confirming the effects of protein, casein, and amino and hydroxy acids on the postprandial urea clearance, found that a similar effect was produced by lactic, acetic, and propionic acids, but not by gluconic acid. Benzoic acid depressed the clearance when the basal values were low, but markedly elevated it when the clearance was at an average level. Butter and the non-saponifiable matter of butter, when added to a meal of starch and lard, increased the average clearance by 45 to 57 per cent.‡

* In these experiments Pitts infused saline at a rate of 5 to 7 cc/min., which may have contributed to the renal hyperemia since saline is known to have this effect (ch. xi)

Glycine in amounts sufficient to raise the plasma concentration to 60 mg/100 cc is toxic and produces a decrease in renal blood flow and filtration rate, and an increase in the filtration fraction

† M. Friedman [701] reports that the oral administration of glycine does not increase the filtration rate or renal blood flow in the white rat.

‡ Vitamin A increases renal function in dogs, but the effect is rather more trophic than functional (*vide infra*).

Alpert and Thomas [43] showed that the urea, inulin, and diodrast clearances increase together, the inulin and urea clearances rather more than the diodrast clearance Normal, renal hypertensive, and neurogenic hypertensive dogs responded in a similar manner. Van Slyke, Rhoads, Hiller, and Alving,[2099] and Pitts [1632] showed that the increased filtration rate is accompanied by an increase in renal blood flow.

The most complete study of the effects of protein on renal function in the dog is that of Moustgaard,[1453] who has shown that, after a high protein meal, the inulin and hippuran clearance reach their maximal values at 3 to 6 hr, and return to normal by 24 hr. The effect on renal function is perceptible with 30 gm/kg of protein and reaches its maximum at 60 gm/kg when observed 4 hr after feeding The maximal increase in Moustgaard's experiments amounted to 80 and 70 per cent, respectively, in the inulin and hippuran clearances If protein is administered at intervals of 10 to 12 hr, these clearances do not return to low protein diet postabsorptive values, and the cumulative effect is such that postabsorptively they level off at about the maximal value reached 4 hr. after feeding, this maximum being reached on the third day. On return to low protein feeding, the clearances drop to initial values within 4 to 5 days

Moustgaard found that the intravenous administration of casein hydrolysate (5 cc/min of 8 per cent solution for 25 min) produces its maximal increase in the inulin and hippuran clearances (50 to 60 per cent) in about 100 min, the clearances do not return to normal in 8 hr. despite the almost immediate reduction of the blood amino acid to pre-injection levels after the cessation of the infusion Moustgaard did not get increased renal function with the intravenous administration of lactic and pyruvic acids Increased protein intake had no demonstrable effect on glucose Tm, confirming the evidence from other sources that all the glomeruli in the dog are active However, the plasma glucose concentration at which saturation of the tubules occurred decreased as the filtration rate increased, as is to be expected

It is particularly noteworthy that Moustgaard observed no difference between the enervated and denervated dog kidney in this response to protein His studies on the effects of unilateral nephrectomy are recorded later in this chapter

The effects of protein feeding on renal function in man are in general less marked than in the dog Large variations in protein intake have been found to have almost no influence on the postabsorptive urea clearance in adults,[403, 801] although children appear to be more susceptible [673] The critical circumstance in man seems to be a very low protein diet;

Longley and Miller [1268] found that in normal adults the maximal urea clearance increases when the dietary protein is increased from 0.3 to 2.4 gm/kg per day, but no further increase occurs at higher protein intakes The administration of urea had no effect like that of protein These authors found that the urea and inulin clearances increased proportionally, the clearance ratio remaining unchanged. However, Nielson and Bang [1529, 1530] report that on a low protein diet the urea clearance decreased 33 per cent while the inulin clearance decreased only 7 per cent, the diodrast clearance by 2 per cent. The observations on the two diets were made at essentially the same inulin U/P ratios, and the reason for the drop in the urea/inulin clearance ratio is obscure *

As compared with a light breakfast, a large protein meal (beef steak) had no effect on the renal plasma flow in 1 subject reported by White and Rolf,[2209] though it increased the filtration rate slightly. A high protein intake (220 gm/day) for a week raised the PAH clearance 18 per cent and the inulin clearance 31 per cent. Pullman, Alving, and Landowne [1662] kept 10 young adults on diets containing 0.3 to 0.4, 1.0 to 1.1, and 2.3 to 3.0 gm/day per kg of body weight, for successive 2 week periods. Eight subjects showed an increase in filtration rate, averaging 21.9 per cent on the high as compared with the medium protein diet. Seven showed a higher renal plasma flow, the average increase being 20.0 per cent. On the low protein diet, some subjects showed lower renal function as compared with the medium protein diet, but the differences were not significant. These authors also note that on a low protein diet the urea clearance decreases more than the filtration rate

On a low protein, low salt diet, subjects with essential hypertension show a slow decrement in filtration rate and renal plasma flow, these functions decreasing to about 65 and 80 per cent, respectively, of their control values, but the effect is clearly referable to the low salt intake, since both functions return to control levels on addition of salt to the diet.[355]

Moustgaard [1483] reports that, in the fasting dog, both the hippuran and inulin clearances begin to increase after the fifth day of the fast and by the twelfth day have risen some 10 to 20 per cent. Whether renal function is modified in man in consequence of prolonged undernutrition cannot be decided from the available evidence [1461]

The difference between man and dog in respect to the effects of dietary protein on the renal circulation is one of the most marked differ-

* This decrease may be related to increased proximal reabsorption of sodium and water. The urea/inulin clearance ratio has never been examined in man at various levels of glomerular activity.

ences in renal function between these two species.* It is paralleled by the equally great difference in the response of the glomerular circulation to the administration of saline (ch xi).

Dicker, Heller, and Hewer [619] find that in rats a protein deficient diet (carrots or turnips) maintained for about 36 days increases the filtration rate and renal plasma flow On the carrot diet, T_{mD} did not change significantly, but on the turnip diet it decreased from 0.132 mg iodine to 0 089/100 gm In contrast to normal animals, the filtration rate on the low protein diets was significantly correlated with urine flow. The low protein diets reduced the average maximal specific gravity from 1 070 to 1 041, and were accompanied by renal lesions.

Dicker [613] has further examined the effects of protein on the filtration rate in rats, with special reference to the relation of filtration rate to urine flow He finds that, in both young and adult rats, with a plasma protein concentration below 6 8 gm/100 cc the filtration rate increases with urine flow In adult rats fed on a diet containing at least 18 per cent casein and having a plasma protein concentration above 6 8 gm/100 cc, the filtration rate is independent of urine flow. Higher concentrations of protein in the plasma are accompanied by higher mean rates of filtration; rats fed an 18 per cent casein diet and having an average plasma protein of 6 83 ± 0 02 gm/100 cc. had a mean filtration rate of 0 43 ± 0 009 cc/min per 100 gm. body weight, while rats fed a 25 per cent casein diet and having an average plasma protein of 7 33 ± 0 026 gm/100 cc had a mean filtration rate of 0 76 ± 0 335 cc/min. per 100 gm body weight In both groups, the correlation between filtration rate and urine flow is slightly negative, whereas on diets of lower protein content in both young and adult rats the correlation is positive, the regression coefficient increasing as the protein content diminishes †

RENAL HYPERTROPHY ON A HIGH PROTEIN DIET

Addis, MacKay, and MacKay [20] first demonstrated that, when rats are placed for the first third of their life, beginning at 30 days after birth, on a high (70 per cent) protein (casein) diet, the kidneys undergo hypertrophy with no pathological change and no abnormalities in the urine. Enrichment of the diet with sodium chloride, calcium chloride (which

* Attention may be called to the fact that in the seal the phenomenon of diuresis is related to the assimilation of food, the urine flow increasing from oliguric levels to substantial values after a protein meal Here diuresis is attributable in large part to an increase in glomerular filtration (ch. xvii)

† It should be noted that the urine flow recorded here represents the spontaneous water intake and not water diuresis

is acidotic), or sodium bicarbonate has no effect on kidney weight.[21,1341] Hypertrophy does not result if the high protein diet is instituted after the animals have attained an age of 346 to 400 days.[1342] Urea, in quantities equivalent to that excreted on the high protein diet, has a slight hypertrophic effect, but it is less than that of protein,[1344] whereas no enlargement is observed in rats receiving repeated intraperitoneal injections of urea solutions [102] or saline [2010] Osborne, Mendel, Parke, and Winternitz [1558] found that lactalbumin was effective, and inorganic salts ineffective, in producing hypertrophy Evidence was obtained by these investigators that, after hypertrophy had been induced, some regression in kidney weight occurred if the animals were returned to a low protein diet.

The relation between protein intake and renal weight is a linear one An increase in a given percentage in the protein intake causes a larger relative and actual increase in renal weight in young rats because the protein intake per unit of body surface area for a given diet is much higher in young rats, while renal weight is essentially constant per unit surface area at all ages.[1328, 1331, 1332, 1337, 1339]

MacKay and Cockrill [1327, 1329] suggested that kidney weight is dependent on maintenance metabolism, and is almost directly proportional to endogenous protein metabolism on diets devoid of protein, but Wilson [2231] found that gelatin produces a greater increase in kidney weight than does casein or liver; glycine, glutamic acid, and gluten each produces an increase roughly proportional to the additional nitrogen consumed. Wilson believed that hypertrophy was associated with some stage in the intermediary metabolism of protein, probably deamination by the kidney. Feeding thyroid [1329] and phosphate [1341] also lead to renal enlargement.

A high protein diet leads to hypertrophy of the adult dog kidney when explanted under the skin. Such a kidney also shows increased size after a meat meal, and during saline diuresis.[39] Presumably hypertrophy occurs *in situ*, but it has not been demonstrated.

The increase in renal function brought about in the dog by a high protein diet is both too rapidly attained and too rapidly lost on a low protein diet to be attributed to hypertrophy, but must be conceived as primarily a functional effect.

Whether a high protein diet causes renal hypertrophy in man is unknown. Functionally the human kidney responds to dietary protein in a different manner than does the kidney of the dog and rat.

which follows partial nephrectomy.[849]

Baxter and Cotzias [102] obtained renal enlargement in young rats by the repeated intraperitoneal injection, over a period of 9 days to 2 weeks, of gelatin, human albumin, bovine globulin, and rat [illegible] hypertrophy effected by gelatin [illegible] hydro[illegible]

least with globulin. Only [illegible] cytologic changes, which consisted of enlargement and vacuolization of the cells of the tubules, the proximal segment being more markedly involved than the distal segment. Otherwise there was no evidence of renal injury and, except in one isolated group receiving gelatin, there was no formation of casts or dilatation of the tubules. The renal enlargement was readily reversible and the kidneys regressed to normal weight within 3 or 4 days after the injections were terminated The moisture and nitrogen content were not significantly changed, so that the increase in weight was apparently due to addition [illegible] and water in nearly the ratio [illegible]

In animals injected with [illegible] bumin in the urine by serol[illegible] suggested that only a part, probably less than one-half of the urinary protein increase, was human albumin The remainder [illegible] protein that accompanied [illegible] globulin The authors believe that the renal enlargement may have been caused in part by the injected protein molecules *per se*, perhaps by effects on the tubules of increased filtration of protein, rather than entirely by products of protein degradation

Since the intraperitoneal injection of casein hydrolysate does not produce renal enlargement, whereas casein administered in the diet does, it appears that the enlargement observed by Baxter and Cotzias is not related to protein metabolism, as in the case of a high protein diet generally

The authors conclude that prolonged continuous proteinuria under the conditions of their experiments, and of the degree obtained by them, does not lead to a persistent increase in glomerular permeability or to any form of chronic or progressive renal injury In the anomalous instances where tubular injury did occur (gelatin), the renal lesions resembled those seen in nephrotic kidneys The similarity between these lesions and those frequently seen in disease raises again the question whether some of the changes in the renal tubules frequently associated with intense proteinuria are secondary alterations resulting from exces-

sive amounts of protein passing through the glomerular membranes (ch. XXVI).

The proximal tubules in patients dying shortly after the administration of gelatin solutions as a plasma substitute show granular, finely vacuolated swelling similar to the hydropic changes which have been reported after large doses of sucrose These changes appear to be specifically related to the gelatin; they appear within half an hour after the intravenous administration of this substance and disappear within 120 hr. Pectin produces similar changes with pathologic implication.[1648,1907] The parenteral administration of all foreign proteins, no matter how apparently inert, is not without danger of renal injury, especially if renal function is impaired, as it is apt to be under the circumstances where such proteins are likely to be used.

COMPENSATORY HYPERTROPHY

It has long been known that atrophy of one kidney associated with unilateral renal disease is accompanied by hypertrophy of the contralateral organ. This hypertrophy can be accomplished experimentally by removal of one kidney (uninephrectomy) or by uninephrectomy plus removal of some fraction of the remaining kidney or various fractions of both kidneys (subtotal nephrectomy). Uninephrectomy in man, in the absence of disease on the contralateral side, is compatible with a normal life span.[1010,1168]

The increase in renal mass is attributable to hypertrophy and hyperplasia of the tubules, with swelling but no increase in number of glomeruli [86,1066,1471] Uninephrectomy during adult life in the white rat does not prevent the decrease in the total number of glomeruli that accompanies senescence [1474]

When experimental animals are maintained on a standard diet of moderate protein content, the remaining kidney after uninephrectomy usually increases to about 75 per cent of the initial weight of the two organs.[19] Addis' [14] data indicate that in the rat the increase in tissue, as judged by protein content, amounts to 50 per cent of the quantity of tissue lost, regardless of the latter figure. The hypertrophic process is independent of the nerve supply,[1377] and Morpurgo [1476] states that double nephrectomy in one of a pair of parabiotic rats caused hypertrophy of both kidneys in the other. No data are given, however.

Rollason [1740] concludes that hypertrophy following uninephrectomy begins in rats immediately after recovery from the shock of operation, maximal hypertrophy being reached within 20 days. Both cortex and medulla increase in size, the latter to a lesser extent. The tubules be-

come enlarged within 24 hr as a result of cellular hypertrophy, and on the second day increased mitosis reveals significant hyperplasia in all parts of the tubule other than the thin segment The glomeruli become enlarged in this species and in rabbits,[1769] primarily because of an increase in the size of the cells of the capsule and capillary tuft. Contrary to older views, he finds no evidence of an initial transient period of pseudohypertrophy (edema) Rollason believed that increased mitotic activity in the tubules is almost entirely restricted to the second day after operation, but Sulkin [2013] states that the peak of mitotic activity occurs between 72 and 240 hr after operation

Hypertrophy is greater in young than in old animals [1084,1332 1740] It is accelerated by a high protein diet and the ultimate increase in mass of renal tissue is greater.[14,1325 1326 1918] Whole meat, extracted meat, whole liver, and extracted liver are about equally efficacious in promoting hypertrophy.[247 248] In rats fed a standard diet (18 per cent casein), the remaining kidney statistically increases in weight by about 24 per cent within the first 3 weeks after uninephrectomy From the 21st to the 120th day there is a further steady increase at a slower rate, to the maximal increase of 48 per cent On a high protein diet (85 per cent casein) this hypertrophy is greatly accelerated and accentuated, the increase at the end of 3 weeks being about 60 per cent, a maximal increase of some 120 per cent being reached in 4 months These figures are relative to standard diet kidney weights and therefore include the sum of hypertrophy due to the increased protein intake plus the compensatory hypertrophy. The degree of hypertrophy is roughly proportional to the protein content of the diet Pathological changes are reported to be associated with the accentuated hypertrophy effected by a high protein diet [1457 1918]

In subtotally nephrectomized rats raised on a moderate to high protein diet, the hypertrophy is most marked in the proximal tubule, this segment increasing in volume 5- to 10-fold, although the total kidney mass increases to only somewhat more than one-half that of the normal bilateral figure [14,1550]

Bollman and Mann [204] believe that hypertrophy of the remaining kidney after nephrectomy is increased by the accumulation of urinary products in the blood following transplantation of the ureter so that the urine drains into the duodenum, but no control data are given.

Hinman [1010] states that, after partial nephrectomy on one side, both the untouched kidney and the fragment undergo hypertrophy, the increment being in proportion to their mass.

Compensatory hypertrophy does not occur after total hypophysec-

tomy, the anterior pituitary gland being necessary (*vide supra*) Thyroidectomy retards the growth of the kidneys, but it does not prevent compensatory hypertrophy of one kidney after uninephrectomy.[398 1131, 1363 2247, 2289] Castration is also without effect.[1326] Testosterone propionate accelerates compensatory hypertrophy in uninephrectomized rats and dogs.[1218, 1328]

Maluf[1377] reports that nephro-omentopexy reduces rather than increases function in the operated kidney, and it fails to prevent atrophy after subsequent division of the renal artery. After this operation, function in the contralateral kidney increases rapidly, maximal function being attained in about 2 months.

Water diuresis in rats from which one and one-half kidneys have been removed is at first greatly diminished but, within 4 weeks after operation, diuresis (as per cent of body weight per hour) recovers to about two-thirds of the control values. Forced water diuresis does not modify the normal weight of the kidney, the extent of hypertrophy, or the water content.

Using the venous sound method, Levy and Blalock[1231] found that uninephrectomy in dogs was followed by a slowly progressive increase in renal blood flow, somewhat more rapid in the first month, and reaching approximately the combined flow of the two kidneys at the end of 3 months.

Although earlier data on the urea clearance[23, 1092, 1703] are somewhat ambiguous with respect to increase in function, it is clear from these and other measurements that the ultimate increase in function is proportional to the increase in weight. The urea clearance ultimately increases after uninephrectomy to above 80 per cent of the two-kidney value in the rabbit[23] and dog[1092, 1703]

In one uninephrectomized rabbit, W. W. Smith[1947] obtained a filtration rate of 65 cc/min. and a diodrast clearance of 232 cc/100 gm. kidney weight, figures to be compared with her average normal values of 66.6 and 250. The single kidney weighed 15.3 gm. as compared with a mean weight of two kidneys in 5 other animals of similar size of 18 6 gm Thus, both function and size were about 80 per cent of normal

Moustgaard[1433] has shown that, 16 to 18 hr after uninephrectomy, renal function is at a level of 20 to 40 per cent of the original bilateral function, as judged by the inulin and hippuran clearances. During the next few days, function increases again to the preoperative value, after which it decreases a second time until after 2 to 4 weeks it reaches a steady level of 65 to 75 per cent of the preoperative value.

In the first phase of postoperative recovery, feeding protein does not

cause the typical increase in filtration rate and renal plasma flow, these functions already being maximal; but, as function decreases thereafter, protein again causes increased function, the maximal level attained after protein feeding increasing until some 3 weeks after nephrectomy when it levels off at about 65 to 70 per cent of the preoperative maximal postprandial capacity of the two kidneys. Tests carried out 11 to 16 months after uninephrectomy showed that both basal and maximal function had increased slightly, to a level of 72 to 82 per cent and 78 to 85 per cent, respectively, of the preoperative values.

Braun-Menendez and Chiodi [248] report that uninephrectomy in the rat reduces the inulin clearance and Tm_D during the first 20 days to 60 to 70 per cent of normal, these functions increasing to 80 per cent of normal after 3 months Watschinger and Werner,[2181] however, report that after uninephrectomy the inulin clearance is reduced to half its normal value (from 0 58 to 0 28 cc/100 gm body weight) and remains(?) low (0.23 cc) up to the fiftieth day The diodrast clearance by the fourth day was restored nearly to normal (normal 1.89, operated 1.75 cc/100 gm), as was Tm_D (normal 0 117, operated 0 123) Thus, the filtration fraction decreased from 0 30 to 0 16 and the C_{IN}/Tm_D ratio from 4 8 to 2 3 T_G (measured at plasma glucose concentrations of 267 to 326 mg/100 cc) decreased from 1 05 to 0 76 mg/100 gm , but at the reduced filtration rate Tm_G was probably not reached These changes in diodrast clearance and Tm_D appear to have been completed by the fourth day after operation, but one may wonder if the number of observations is sufficient to establish this point It is of particular interest that the average inulin U/P ratio in spontaneous urines decreased from 13 4 to 8 35, the urine volume in the normal and operated animals showing no significant difference

Weiss and Chasis [2169] examined a patient with unilateral chronic atrophic pyelonephritis of the left kidney before and after removal of that organ The right kidney was already slightly hypertrophic, as a result, no doubt, of atrophy of the pyelonephritic left kidney; functional data in the right kidney before nephrectomy were $C_M = 84$ and $C_D = 386$ cc , $Tm_D = 45.4$ mg. of iodine, $C_D/Tm_D = 8.5$, $C_M/Tm_D = 1.85$, $C_M/C_D = 0.218$ The left kidney had very little function· $C_M = 1$ and $C_D = 56$ cc., $Tm_D = 3.0$ mg of iodine, $C_D/Tm_D = 18.7$, $C_M/Tm_D = 5.67$, $C_M/C_D = 0.304$ Two and a half months after removal of the left kidney, the renal plasma flow had increased in the right kidney, the function of which was now almost equivalent to two normal kidneys, $C_M = 96$ and $C_D = 593$ cc , $Tm_D = 48.4$, $C_D/Tm_D = 12.3$, $C_M/Tm_D = 1.98$, $C_M/C_D = 0.162$

Welsh, Wellen, Taylor, and Rosenthal [2169] report functional studies on 2 women in whom one kidney was removed, in one instance for persistent bleeding and in the other for adenocarcinoma No observations were made before uninephrectomy, and in the absence of control data the only change confidently indicated is a slow rise in Tm_D from 23 to 34 mg. of iodine within a year after removal of the functioning kidney in the first patient, with a corresponding decrease in the C_{IN}/Tm_D ratio.

Friedman, Selzer, Kreutzmann, and Sampson [712] examined 5 patients with essential hypertension and unilateral renal disease. The total diodrast clearance was reduced in 4 out of 5 of these patients, and in 3 examined by ureteral catheterization it was lower in the affected kidney than in the normal one. The total inulin clearance was subnormal in 2 and normal in 3 patients. The removal of the diseased kidney was accompanied by an increase in renal blood flow and filtration rate in all 5 patients, indicating that the remaining kidney had increased considerably in function.

Indications of increased filtration rate and Tm_D are reported by Lattimer [1218] in dogs with solitary kidneys treated with testosterone propionate. Two men who were treated during the period of compensatory hypertrophy (9 to 23 days postoperatively) after uninephrectomy showed some increase in filtration rate (11 and 28 per cent), and 1 showed a 39 per cent increase in Tm_D, the second only a 3 8 per cent increase in this function. Another postnephrectomy patient, in whom treatment was started on the twentieth postoperative day, showed a 7 per cent increase in filtration rate and a 22 per cent increase in Tm_D. These changes, of course, may have only reflected the process of hypertrophy.

Hogeman [1024] reviews the literature and gives data on 19 persons, 14 of whom had undergone nephrectomy 14 days to 23 years before study, and 5 had only one functioning kidney as judged by urography. The average inulin clearance was 77 cc., diodrast clearance 290 cc., filtration fraction 0.274, and renal plasma flow 520 cc. The data on inulin clearance alone indicate a significantly greater function in those operated on before rather than after the age of 30 years. These figures indicate a more moderate increase in function than do other data, but the statistical basis of comparison in subjects of widely different ages and with the potentiality of renal disease renders the comparison uncertain.

HEMIHYPERTROPHY

In a patient reported by Moore [1472] with hemihypertrophy (relative enlargement of the right kidney, right adrenal, right testicle, right lobe

of the thyroid, right cerebral hemisphere, and right half of the spinal cord), the right kidney weighed 195 gm. and contained 17,563 glomeruli/gm , the left weighed 150 gm. and contained 15,824 glomeruli/gm. The estimated total number of glomeruli in the right kidney was 906,251, in the left, 846,109 The enlargement of the right kidney had no significant effect upon the total number of glomeruli in the two kidneys

OXYGEN CONSUMPTION

Van Slyke, Rhoads, Hiller, and Alving [2093] reported the first simultaneous determinations of oxygen and urea extraction by the kidney in normal, unanesthetized dogs, using the explanted kidney technique of Rhoads,[1702] by which blood from the renal vein could be obtained by needle puncture through the skin The renal blood flow was calculated from the urea extraction ratio and clearance These authors review the extensive literature on the oxygen consumption of the dog's kidney as determined in anesthetized, operated animals.

The average renal blood flow in 11 experiments on 8 dogs with both kidneys explanted averaged 4 0 cc/min per gm of kidney (range 1 9 – 7 4). In 13 experiments on 8 dogs from which one kidney had been removed at least one week previously, this figure was 6 7 cc/min per gm of kidney (range 2.5 to 10 7). The oxygen consumption in the two-kidney dogs averaged 0 08 cc/min per gm of kidney (range 0.03 to 0.1); in the uninephrectomized dogs this figure was 0.15 cc (0.04 to 0.4). Thus removal of one kidney caused the blood flow to increase by 70 per cent in the remaining kidney, while the oxygen consumption was nearly doubled when examined within a week or so after nephrectomy In neither group of animals did diuresis correlate with renal blood flow or oxygen consumption, nor were these values affected by administration of urea

The oxygen consumption correlated positively with renal blood flow, and in general as the latter decreased the oxygen arterial-venous difference tended to remain constant at 2 5 cc/100 cc of blood The authors note that the renal venous blood in the dog is usually more than 70 per cent oxygenated, indicating that the kidney is kept under higher oxygen tension than are most other organs

Using the figures cited in chapter XVII and assuming a hematocrit of 45, the clearance method indicates a renal blood flow of 3.7 cc/min. per gm of kidney, a figure which compares satisfactorily with the figure reported by Van Slyke *et al.*

In the studies above, the urea clearance roughly paralleled the renal blood flow, E_u remaining generally independent of blood flow E_u was

demonstrated to be independent of plasma concentration. This relationship also obtains when the renal blood flow is increased by a high protein diet.[2099]

The relative constancy of the oxygen arterial-venous difference (or alternatively of the extraction ratio), with consequent proportionality between oxygen consumption and renal blood flow, obtains in the dog during the renal ischemia attending shock until the blood flow falls below 1 cc/min. per gm.[531]

Mason, Blalock, and Harrison,[1416] using the venous sound method, obtained an average renal blood flow of 21.1 cc/min per kg body weight (range 16 0 to 29 8), a figure to be compared with 19 3 cc obtained by Van Slyke *et al.*[2098] After uninephrectomy, the renal blood flow in the remaining kidney increased by about 70 per cent, the oxygen consumption increasing proportionally and the oxygen arterial-venous difference remaining essentially constant.[1231] The average oxygen consumption in two-kidney dogs was 21.2 cc/min. per kg. of body weight (50 cc/min. per kidney).

In dogs rendered hypertensive by constriction of the renal arteries, the oxygen consumption parallels the renal blood flow, the oxygen arterial-venous difference remaining practically unchanged. Levy, Light, and Blalock [1232] estimate that in their control data the renal blood flow averaged 3.5 cc/min per gm of kidney; after application of the arterial clamps this figure was 2.7 cc. Levy *et al.*[1233] report that partial ureteral occlusion reduced the renal blood flow by an average of 41 per cent, without an increase in oxygen arterial-venous difference

Kramer and Winton [1158] studied the changes in oxygen consumption associated with acute changes in renal blood flow and other variables in the perfused dog kidney. In this preparation, as in the intact animal, the oxygen consumption paralleled the blood flow, and was only transiently modified by urea diuresis.

Weiss, Parker, and Robb [2160] obtained rénal venous blood by venopuncture in 3 normal subjects, and found an oxygen arterial-venous difference of 1 3 to 3 cc/100 cc. In a patient in the malignant phase of essential hypertension (nephrosclerosis), the oxygen arterial-venous difference was zero.

Warren, Brannon, and Merrill [2144] report a renal oxygen arterial-venous difference of 2.3 cc/100 cc (1 9 to 2 6) in 8 normal subjects examined by renal vein catheterization. The simultaneous systemic oxygen arterial-venous difference was 4.4 cc/100 cc. (3 7 to 6.1).

Cargill and Hickam,[329] in 10 normal subjects, found an average oxygen arterial-venous difference of 1.42 ± 0.25 cc/100 cc (range 1 09 to

1.87); the total renal blood flow averaged 1155 ± 229 cc/min. (ra
835 to 1456), and the oxygen consumption averaged 16.0 ± 2.9 cc/m
(range 12 to 20.8), or about 0 05 cc/min per gm. of kidney by estimat
weight. They note that the normal renal oxygen arterial-venous diffe
ence of 1.42 cc/100 cc is notably small in comparison with accepte
figures for mixed venous blood (4 cc/100 cc or more) and smaller tha
the recorded figures in the dog. The oxygen requirements of the kidney
which are relatively high per gm of tissue, are met by the large rena
blood flow

Clark and Barker [333] find that water diuresis, mannitol diuresis, and saturation of the tubules with PAH have no effect on renal oxygen consumption in normal subjects Their normal average value, based on estimated kidney weights, is 6 1 ± 2 27 cc/100 gm kidney weight. Bucht, Werkö, and Josephson [239] also find that saturation of the tubules with PAH does not increase the oxygen consumption. Their data on renal oxygen consumption range from 7 to 13 2 cc/min, the oxygen arterial-venous difference from 0 85 to 1 90 cc/100 cc of blood

In 6 patients, studied by Cargill and Hickam, with essential hypertension in whom the filtration rate was above 100 cc, the oxygen arterial-venous difference averaged 1.30 cc/100 cc (range 0 82 to 1.51), the total renal blood flow 1008 cc (range 701 to 1237), the renal oxygen consumption averaged 13 2 cc/min (range 7 7 to 22 4). In 5 subjects with renal damage from hypertensive disease (nephrosclerosis) and filtration rates below 100 cc, these figures were 1 77 cc/100 cc, 487 cc and 8 1 cc As destruction of renal parenchyma proceeds, renal blood flow and oxygen consumption decrease without any marked increase in oxygen utilization.

In 6 patients with chronic nephritis or pyelonephritis, in whom the filtration rates ranged from 56 to 19 cc, these figures were 1 68 ± 0 20 cc/100 cc (1 30 to 1 90), 353 ± 176 cc (168 to 638), and 6 1 ± 3 3 cc (2 7 to 11 7) Here again, blood flow and oxygen consumption decrease in a parallel manner with no increase in oxygen utilization.

In marked contrast to the groups above, in 9 patients with acute or subacute glomerulonephritis who showed low (corrected) filtration fractions (mean 0 11 ± 0 03, range 0 08 to 0 16), the renal oxygen consumption was reduced to the average of 7 3 ± 2.5 cc/min (range 0 9 to 13 6) The oxygen arterial-venous difference averaged 0 71 ± 0 45 cc/100 cc (range 0 09 to 1 07), despite the fact that the renal blood flow remained normal or nearly so (average 1062 ± 179 cc., range 816 to 1362) This circumstance reflects either inability of the renal parenchyma to get oxygen out of the blood or a decreased metabolic demand.

Cargill and Hickam lean to the latter explanation and note that, considering all subjects examined by them, normal, hypertensive, nephrosclerotic, chronic and acutely nephritic, the renal oxygen consumption correlates with the filtration rate, implying that the load of material delivered to the renal tubules (for reabsorption) is the primary determinant of tubular metabolic activity. In this connection they quote Bradley and Halperin's [240] demonstration that oxygen consumption decreases with decreased filtration rate (and renal blood flow) during the ischemia induced by abdominal compression, and note that these authors suggested the possibility that renal oxygen consumption depends upon the relative proportion of tubular tissue actively functioning in the formation of urine from the glomerular filtrate. There are, as Cargill and Hickam recognize, alternative explanations, and this interesting idea must await substantiation No data are available to indicate to what extent oxygen consumption might correlate with active tubular tissue, as measured by Tm_{PAH} or Tm_G.

During abdominal compression, the renal blood flow, filtration rate, and Tm_D and Tm_G are substantially reduced in man,[240] apparently because the simultaneous elevation of renal venous pressure and intrapelvic pressure act respectively to decrease blood flow and arrest urine excretion from nephrons which have relatively low terminal intraluminal pressures Thus a large proportion of the renal parenchyma drops out of function. Under these conditions, the renal oxygen consumption drops from the control range of 6 to 14.2 cc/min. (average 10 3) to 1.2 to 9.3 cc/min (average 5.1) The oxygen arterial-venous difference is not significantly changed, so that oxygen consumption goes down roughly in proportion to the blood flow.

The intravenous injection of large doses of concentrated human plasma albumin is known to produce a transient but marked increase in renal blood flow (ch. XIV). Barker, Clark, Crosley, and Cummins [87] find that this hyperemia is accompanied by a decrease in renal arterial-venous oxygen difference, so that the renal oxygen consumption remains unchanged. In this instance, a simultaneous decrease in E_{PAH} indicates that arterial-venous shunts are opened, which permit direct transit to additional blood over and above that normally perfusing the renal parenchyma; in this interpretation, a decrease in oxygen arterial-venous difference and renal oxygen consumption would be expected. The temporal relations between oxygen consumption and E_{PAH} are roughly such as to support this view. These investigators confirm that in a variety of circumstances the oxygen consumption varies *directly with the* renal blood flow, though the proportionality is not exact.

GLOMERULAR-TUBULAR BALANCE

Since the individual tubule is fixed in size and, judging from the kidne as a whole, limited both in its reabsorptive and excretory capacities, is a fair assumption that the quantity of filtrate delivered internally and the quantity of blood delivered externally per unit time are some how conditioned relative to this fact Moreover, in so far as the peri tubular blood in the mammals is derived from the postglomerular ar terioles, tubular perfusion is dependent on continuing glomerular cir culation The problem of glomerular-tubular balance therefore contains many important issues, ranging from the quantity of filtrate delivered to each nephron in relation to the reabsorptive capacity of the nephron for specific substances (sodium, water, glucose, vitamin C, etc), or the quantity of perfusate to each portion of the tubule in relation to its ex cretory capacity, to the questions of glomerular intermittency and the basic regulation of the renal circulation as a whole.

The supposition that the glomeruli in the mammalian kidney are inter mittently active has been expressed repeatedly, with no supportive evi dence. The idea stems from the observation of Richards and Schmidt [1715] in 1924 that only in some of the glomeruli of the frog, or in some of the capillaries in individual glomeruli, is the circulation active at any one moment, an observation which has been confirmed in other cold-blooded animals. In these cold-blooded forms the glomerular circulation can be increased by water diuresis and various drugs, notably caffeine, and de creased by splanchnic stimulation [28 156 162 897 1709 2156] In the frog,[674] the alligator (Shannon, unpubl obs), and the marine teleost fishes [888] the rate of glomerular filtration is more or less proportional to the rate of urine formation, the inulin U/P ratio varying through only a narrow range In the chicken,[1624 1885] however, and in most mammals studied this is not true (dog,[1860] cat,[2249] rat,[813 814] sheep,[1931] and man [363]) White [2192] concluded from injection experiments in the dog and rabbit that, where all the glomeruli are not injected, the unequal distribution is attributable primarily to differences in the patency of the larger, preglomerular ves sels, rather than to inactivity of individual glomeruli, and that under normal conditions all the glomerular vessels are open

A priori it could be argued that the well-developed renal-portal cir culation to the tubules, which characterizes the kidney in the fishes, Amphibia, reptiles, and birds, would, by sustaining tubular perfusion, favor intermittent glomerular activity, whereas the complete absence f such a renal-portal circulation in the mammals would militate against ntermittent activity The first part of the argument may be true, but

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the second part is not certain; in the marine seal, an animal entirely dependent upon its metabolic water for urine formation, both glomerular filtration and renal blood flow decrease during diving and increase markedly after the ingestion of food; these responses are, however, clearly adapted to an aquatic and salt-water life.[231, 995]

If one accepts the observations of Kaplan and Smith,[1096] Dicker and Heller,[514] Wilkinson and McCance,[2221] and Forster,[678] in the rabbit, glomerular activity increases or decreases with hydration or dehydration; if one accepts the observations of W. W. Smith,[1946, 1947] Brod and Sirota,[265] and Wills and Main,[2227] this relationship is a methodological artifact. Apart from the rabbit, the evidence is against glomerular intermittency in the mammals.

Smith, Goldring, Chasis, Ranges, and Bradley[1931, 1939] *developed the* glucose titration curve as a method of examining the variability of the *ratio* c_{in}/tm *in the human kidney, where* c_{in} *is the filtration rate in an* individual glomerulus and tm is the maximal glucose reabsorptive capacity in the attached nephron. As premises they accepted (a) that every tubule reabsorbs all the glucose presented to it by its glomerulus until the load is exactly equal to its maximal reabsorptive capacity; when the load exceeds this capacity, the excess glucose is excreted in the urine; (b) the status of individual nephrons remains unchanged during the period required for the completion of titration. Premise (a) excludes significant splay in the titration curve of an individual nephron. The method has not been developed further, in part because it seems unwise to extend either premise too far in respect to the diseased kidney, and glucose for technical reasons is not a suitable substance for this purpose. But the conclusions drawn by these investigators from their titration studies on normal subjects appear to be warranted. The data (see fig. 18) show that no appreciable number of nephrons have a glomerular activity (defined as c_{in}/tm) below 0.60 or above 1.5 times the mean glomerular activity (C_{IN}/Tm_G) for the entire kidneys; glomerular activity is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the nephrons fall within ±40 per cent of the mean. There is no large number of nephrons (i.e. the fraction is no greater than 5 per cent) in which glomerular activity is less than 60 per cent of the mean. Hence the notion of 'glomerular reserve' posited on the assumption of glomerular intermittency is untenable.

The conclusion reached by the glucose titration method is confirmed by the fact that Tm_G is not significantly modified by adrenalin, caffeine, or pyrexial hyperemia, all of which profoundly modify the renal blood

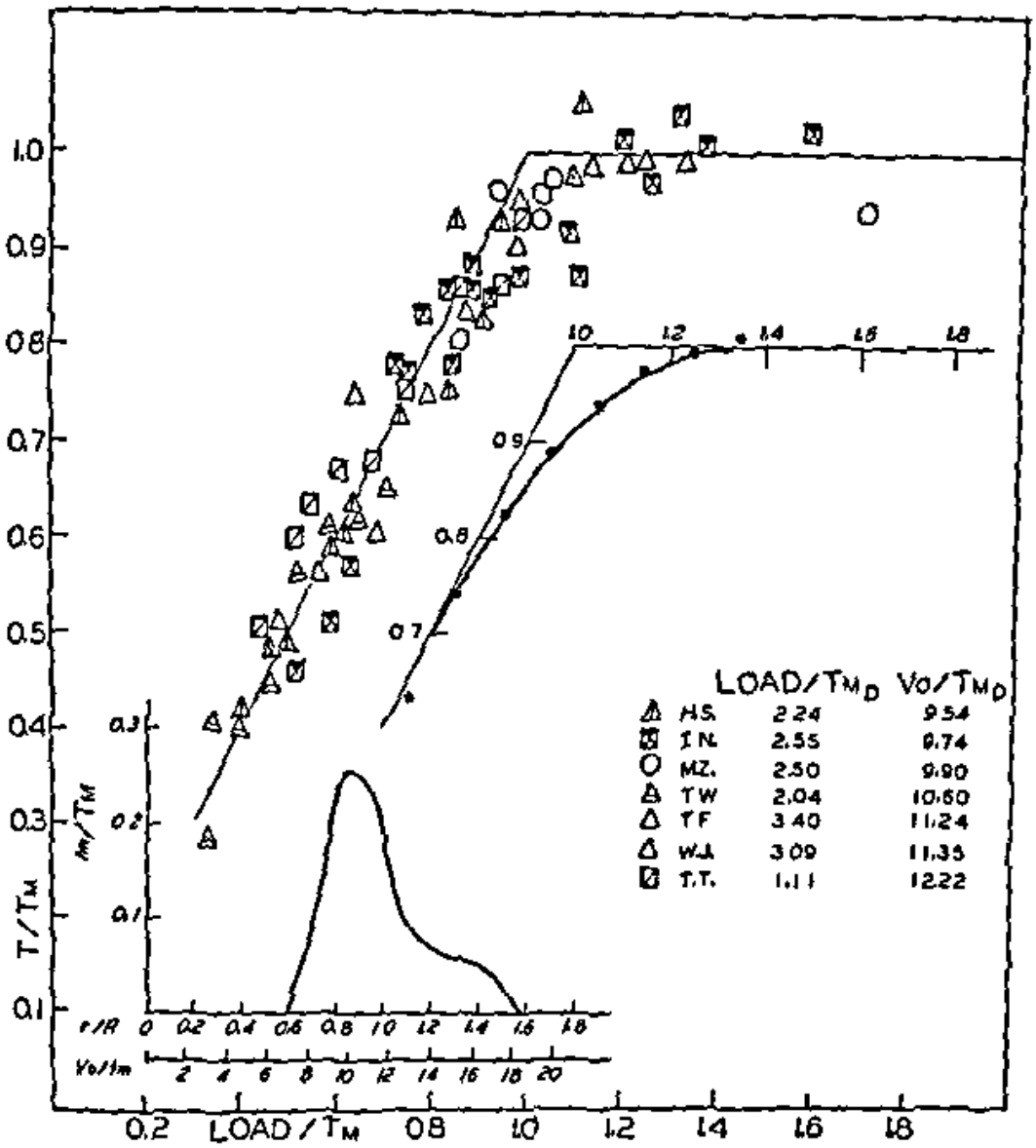

FIGURE 88 Normal dispersion of tubular perfusion Mass plot of diodrast titrations of 7 normal subjects, some of whom were titrated twice The mass plot contains 70 observations which were averaged by blocks of Δ load/Tm = 0 1. The averaged data are shown in the inset, the smooth titration curve being drawn by visual approximation The limits of relative tubular perfusion are conformably placed at 0 66 and 1 66. The lower figure cannot be set with accu-

curve, and hence of the distribution curve, involves only a small percentage of the total tubular tissue.

As in the case of figure 18, the frequency distribution curve is practically identical with the normal frequency distribution curve The same qualifications

flow. That similar uniformity of glomerular activity exists in the dog is demonstrated by the extremely narrow range of plasma concentration in which tubular saturation with respect to glucose is effected, and by the constancy of Tm_G at various filtration rates effected by low and high protein diets,[1863] as well as by the narrow range of plasma phosphate concentration at which tubular saturation is effected and the fact that phosphate Tm is independent of the absolute value of the filtration rate [66]

Application to man of the titration principle with diodrast yields similar results: no appreciable quantity of tubular tissue has a perfusion rate (v_0/tm) below 0 66 or above 1.66 times the mean tubular perfusion (V_0/Tm_D) for the entire kidneys; the relative perfusion rate is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the tubular tissue is perfused at a rate within ±40 per cent of the mean (fig. 88)

On the basis of these data, it must be accepted that glomerular activity, defined relative to tubular activity in the attached nephron, is remarkably uniform in dog and man, and that changes in renal blood flow and filtration rate are the result of a fairly uniform increase or decrease in activity in all glomeruli. There is, therefore, no warrant for speaking of 'glomerular reserve' in the sense of inactive glomeruli or tubules.

Handley, Sigafoos, and La Forge [901] report that when the filtration rate is increased in dogs by the infusion of large quantities (amount not stated) of isotonic saline, Tm_{PAH} and Tm_G may be substantially increased. The C_F/Tm_G ratio remained constant in the one dog examined. Conversely, when dogs were dehydrated by the infusion of 20 per cent glucose solution with or without the use of mercurhydrin, Tm_{PAH} and Tm_G were reduced, the ratio C_F/Tm_G remaining constant in most experiments. Tubular function was not altered at the peak of diuresis (1 hr) but only after the urine output began to decline and sufficient water

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must be applied to the massing of data obtained from different individuals as in the case of glucose titration Accepting the curve as drawn, it may be said

(Smith, Goldring, Chasis, Ranges, and Bradley [1931,1939])

had been excreted to produce moderate dehydration. The depressive effects increased with time as dehydration proceeded. The authors conclude that the changes in Tm_{PAH} and Tm_G represent changes in glomerular activity such as may be involved in the maintenance of fluid balance In the face of the evidence cited above, this interpretation cannot be accepted. Mudge and Taggart [1490] report no change in Tm_G in dogs after the infusion of saline, while the reduction in function during dehydration can scarcely be interpreted as physiological in view of the extreme degree of dehydration used in the experiments above. Modification of endocrine activity and of cellular activity by dehydration of the tubules are, moreover, not excluded.

ANOMALOUS EXTRACTION RATIOS

Van Slyke, Rhoads, Hiller, and Alving [2098] have reported that the oxygen capacity of renal venous blood when drawn by puncture of the renal vein of the explanted dog kidney is generally slightly less than that of the simultaneous arterial blood They attributed this to dilution of the renal venous blood by water absorbed in transit through the kidney. In view of the apparent uniformity of filtration and reabsorption of water, the explanation must remain suspect on a quantitative basis. In some observations the difference in oxygen capacity amounted to 1 to 2.5 cc/100 cc. (with a total oxygen capacity of 23 cc/100 cc), representing *a dilution of renal venous blood by some 5 to 10 per cent, a discrepancy* rather too large to be explained by water reabsorption

Mason, Blalock, and Harrison [1416] also noted that in some experiments the oxygen capacity of renal venous blood was as much as 1.5 cc/100 cc below the arterial capacity. Such differences in oxygen capacity occurred more frequently when the renal venous sample was obtained by puncture of the renal vein of dogs with explanted kidneys than when the sample was obtained by a venous sound.

Reubi and Futcher [1698] report that in dogs the oxygen capacity, hematocrit, and plasma protein content are higher in renal venous blood than in renal arterial blood, a difference which is increased by adrenalin. They suggest that this loss of fluid from the renal blood may occur through the renal lymphatic vessels or other vascular channels by-passing the renal vein. This difference does not obtain between femoral arterial blood (renal arterial blood is not available) and renal venous blood in man.

Van Slyke *et al.*[2098] also observed that in an occasional sample, the extraction ratio of urea might decrease to zero, or the renal venous

blood might contain more urea than the arterial blood. The phenomenon usually affected only one observation in a series. In such samples, however, the oxygen arterial-venous difference remained within normal limits They believed that the phenomenon was due to some reflex initiated by slight trauma connected with puncture of the renal vein, though they were unable to prevent it by cocainizing the vein. Gordon, Alving, Kretzschmar, and Alpert [819] similarly observed occasional concentrations of urea in renal venous blood equal to those in arterial blood in dogs with explanted kidneys

Such anomalous extraction ratios in the case of urea are not so surprising, since the normal extraction ratio is small (0.06) and back diffusion of urea might conceivably occur without corresponding loss of water or creatinine, though why it should occur in isolated samples of blood is not clear.

The phenomenon is less easily explained with inulin, diodrast, and PAH White [2193] reports that, in 1 out of 44 renal venous blood samples drawn from dogs with explanted kidneys, he found a higher concentration of diodrast and of inulin than in arterial blood On 2 occasions the diodrast extraction ratio was zero. He notes that, in 5 instances where extraction ratios below 0 40 were obtained, there had been difficulty in getting the renal venous sample. Apparent addition of diodrast to renal venous blood was also noted in a few instances by Corcoran, Smith, and Page.[428]

Warren, Brannon, and Merrill [2144] report 1 instance in man where, in renal venous blood (?) collected from the renal vein by catheter, the extraction ratio of PAH was zero, with an oxygen arterial-venous difference of such a size (2 4 cc/100 cc) as to indicate that the catheter had not slipped out of the renal vein In view of the non-traumatic nature of this technique, this result is more difficult to explain than low extraction ratios of urea in dogs with explanted kidneys, where compression of the renal veins and possibly of the ureter may be involved during puncture through the skin

Cargill and Hickam [829] were unable to confirm in man the observation of Van Slyke *et al* [2098] in the dog, that there is a difference in the hemoglobin content of arterial and renal venous blood. In man, 22 comparisons of oxygen capacity of paired, simultaneous samples showed a mean difference of 0 2 vol/100 cc , and 71 comparisons of paired hematocrit determinations showed a difference of 0 1 per cent packed red cell volume, differences within the limits of technical error. Breed and Maxwell (pers. com.) also find that in paired hematocrit determinations in ar-

terial and renal venous blood in man the maximal difference in packed red cell volume is no more than 0 1 per cent

The anomalous extraction ratios reported above might be a consequence of the escape of urine from the renal pelvis into the venous system by pyelovenous backflow (ch xxvi), but this explanation is merely speculative. They are recorded here for the sake of the record.

CHAPTER XVI

Renal Function in Infancy and Childhood

THE FETAL KIDNEY

In some mammals, such as the white rat, glomerular development is incomplete at birth, the kidney in the newborn containing numerous anlagen which continue to undergo differentiation, full glomerular development not being reached until the second or third month of life. After this time the glomerular count remains constant until regression begins with senility, roughly at one year of age in this species.[55, 1126]

In man, however, glomerular development is normally completed *in utero*. Cessation of the formation of new glomeruli is primarily dependent on the size attained by the fetus, and only secondarily on the gestational age. Formation of new glomeruli ceases ordinarily when the fetus weighs between 2100 and 2500 gm. and measures from 46.0 to 48.9 cm. in length The kidneys of the majority of fetuses born before the beginning of the thirty-fifth week (from the first day of the last menstrual period) show the presence of incompletely developed glomeruli; in the majority of those born after the beginning of the thirty-fifth week, none are visible. In premature infants glomerular development continues after birth until the potential number of glomeruli has been attained. Potter and Thierstein [1651] accept the state of glomerular development as an index of fetal maturity.

In the adult human kidney, the glomerular capillaries are covered with the thinnest of epithelium, so that there is a minimal barrier to filtration. In fetal life the glomerular loops are matted together and invaginated into a sac of tall columnar to cuboidal cells,* which persist over the peaks of the capillary loops into postnatal life.[382, 830, 915] Transformation of the cuboidal epithelium to the squamous type begins in the juxtamedullary glomeruli and progresses toward the cortex, to reach completion within a few months to two years after birth. This is probably a gradual process, there being no evidence of an abrupt transformation at birth. The presence of this cuboidal epithelium in the visceral layer of Bowman's capsule probably seriously impairs filtration in the embryonic kidney and substantially reduces it in the newborn.[444, 915] The persistence of embryonic epithelium, together with unequal development of the glomeruli and tubules, leads to serious glomerular-tubular imbalance in young infants and poses perplexing problems for the pediatrician

At term, the tubules of the glomeruli near the capsule are still primitive and the loops of Henle are very short The juxtamedullary nephrons are more advanced, but even here the loops of Henle are not fully extended. When the growth (volume) of individual segments of the nephron in the rat is compared to the growth of the sum of its parts, it is found that the proximal segment grows most rapidly in relation to the whole.[1440] This possibly reflects the earlier and fuller development of the juxtamedullary region.

In the newborn rat, the cortex has a peripheral neogenic zone of undifferentiated tissue which is inactive, if judged by the storage of trypan blue, whereas the proximal tubules deeper in the cortex take up this dye in proportion to their age. Dye storage does not occur in the peripheral neogenic zone until 12 days, but by 28 days the peripheral tubules are fully developed. The vital storage of dye is correlated with the acquisition by the proximal tubule cell of brush border.[102] Proximal tubule tissue from the chick and human embryo, the latter from the second or third month of fetal

* Klein,[1129] in 1873, recognized that the visceral glomerular membrane in mature and immature human fetuses is composed of cuboidal to columnar cells, but he did not recognize that this circumstance is unique to the fetal period and not applicable to the mature kidney

life, when grown in tissue culture, secretes phenol red and, although such tissue possesses a rather remarkable capacity to undergo differentiation *in vitro*,[222 242] there is little doubt that it is capable of function in the fetus.

The mammalian kidney begins to function in the formation of urine to a limited extent before birth. The fetal bladder contains urine by the fourth month of gestation, this urine being discharged in great part into the amniotic fluid, which shows a progressive increase in urea and uric acid content, probably of urinary orig The first rarely exceeds 50 mg/100 cc., possibly because of its d fusibility; the latter may accumulate to 40 to 50 mg/100 cc. Th osmotic pressure of the amniotic fluid corresponds to $\Delta = 0.52$ at 2.5 months, 0.515 at 4.5 months, 0.482 at 7.5 months, and 0.46 at 10 months (plasma = 0.55).[881] This decrease in osmotic pressure indicates that it is to some extent osmotically isolated from both the fetus and mother, and may reflect the accumulation of fetal hypotonic urine.

In the fetal rabbit, cat, opossum, chick, and pig, both the mesonephros and metanephros function in the glomerular excretion of ferrocyanide and the tubular excretion of phenol red; the mesonephros and metanephros may function simultaneously, so that renal excretion is a continuous process uninterrupted by the degeneration of the former.[768,769] Wells and his coworkers [165,2165,2166] report that the fetal rat kidney excretes phenol red and responds with mild osmotic (urea) diuresis 16 hr. before term. Shortly before term, the urine was dilute, glucose-free, and showed a urea U/P ratio of 11.7 and a creatinine U/P ratio of 42. Williamson and Hiatt [1226] have shown that the kidney of fetal rabbits *in utero*, 3 to 4 days before term, excreted only traces of phenol red in 1 hr. after subcutaneous injection. When calculated as per cent of the test dose recovered from the bladder in 1 hr., excretion increased rapidly after birth, the rate of increase being about 5 times as great as the rate of increase in renal weight, so that at the end of 10 days of postnatal life dye excretion had increased 100-fold over the prenatal rate, while the weight had increased less than 20-fold. There was no appreciable transmission of dye across the placental barrier in either direction in 1 hr., although Lell and Liber [1224] report that 15 to 30 per cent of a test dose of phenol red injected into

parison cannot be improved upon at the present time.* For the calculation of surface area see chapter XVII.

MATURATION OF RENAL FUNCTION IN INFANCY

Numerous studies are now available on renal function from infancy to adolescence. The earliest of these, by Schoenthal, Lurie, and Kelly,[1798] indicated that the urea clearance in 9 normal infants 2 to 11½ months in age, when corrected to 1 73 sq m. of body surface area, agreed with the normal values reported by Van Slyke and his coworkers for older *children and adults However, Barnett*[90] *found that the inulin* clearance corrected for surface area is about 20 to 40 per cent of normal in infants 4 to 9 days of age, 50 to 90 per cent of normal at 14 days to 7.5 weeks, and essentially normal in children 6 to 10 years of age. The observation that the filtration rate in infancy is less than normal on a surface area basis has been repeatedly confirmed McCance and Young[1207] report an average value of 51 cc per 1 73 sq. m in 3 newborn infants; Dean and McCance[483] 27.2 (16 3 to 44 6) in 6 infants 2 to 8 days old; Barnett, Hare, McNamara, and Hare[92,93] 47.8 (34 8 to 65.9) in 13 premature infants 3 to 21 days old and 67 4 in 9 premature infants 49 to 107 days old; and Young and McCance[2254] 28 8 (9 5 to 61.8) in 7 full-term infants 1 to 8 days old who were possibly dehydrated from gastroenteritis Average figures are, however, not very meaningful since some of the variations are due to differences in water and electrolyte load. Moreover, it is clear from the data above and those of West, Smith, and Chasis[2175] *and Rubin, Bruch, and Rapoport*[1751] *that, beginning at* birth, the filtration rate † increases steadily throughout the first year. After this time it maintains essentially normal values.[90 238,1892,1751]

RELATION OF URINE FLOW TO FILTRATION RATE

McCance and Young[1207 2292,2254] believed that the inulin clearance increased with the rate of urine flow (i e. with the degree of hydration),‡

* This decision is affirmed despite Tanner's[2543] criticism of Houck's[1037] data on the dog.

† Both groups of investigators used mannitol to measure the filtration rate, but both used the periodate oxidation method of Smith, Finkelstein, and Smith[1946] for the determination of mannitol and, since, in the writer's experience, this tends to give higher mannitol/inulin clearance ratios than does the chromotropic acid method of Corcoran and Page,[454] no correction has been made for reabsorption of mannitol West *et al* used a constant intravenous infusion of mannitol and PAH, while Rubin *et al.* infused PAH but used a single injection of mannitol.

‡ A parallel has been drawn between the infant kidney and that of the rab-

of kidney weight is better with surface area than with height or body weight,[1325] the data of Vierordt [2112] and Wald [2124] indicating that this relation is maintained between 5 and 69 years of age. Kunkel [1177] concluded, from studies in several mammals, that the number of glomeruli are more closely related to body surface area than to body weight. Taylor, Drury, and Addis [2048] pointed out that the Addis urea ratio (60 min. clearance) is proportional to renal weight, and hence to body surface area, in rabbits, and McIntosh, Möller, and Van Slyke [1321] have shown that, after the age of 1 to 2 years, the urea clearance is proportional to surface area in children and has the same magnitude as in the adult, an observation which has been confirmed by Schoenthal, Lurie, and Kelly,[1798] Payne and Shukry,[1582] and Cullen, Nelson, and Holmes,[459] Cullen *et al.* reporting that the distribution and mean value of the urea clearance so calculated in 62 children, 5 to 13 years of age, correspond to those of normal adults. Holten [1029] showed that the creatinine clearance in 90 children from 9 months to 17 years of age correlated better with surface area than with body weight, and West, Smith, and Chasis [2175] accepted the surface area basis of comparison. Rubin, Bruch, and Rapoport,[1751] from data on 63 infants and children, decided that the filtration rate correlates poorly with body weight, body height, and calculated metabolic rate; when calculated kidney weight is used, there is a gradual increase in filtration per unit of kidney tissue, with stable ratios being reached between the fourth and fifth months of life; after this age the values more closely parallel the adult values than with any other method of reference; when body surface area is used, occasional adult values are reached around 6 months of age, but the values are not consistently in the adult range until about the second year.

Although kidney weight has much to recommend it, reference to a standard which not only has to be calculated but which itself has a large coefficient of variation (0.18) [2124] would seem to complicate the problem unnecessarily. Absolute values of various renal functions among adults of various ages, when expressed on a surface area basis, have fairly low coefficients of variation (ch. XVII), and this fact, coupled with the considerations stated above, leads the writer to believe that the surface area basis of com-

edly dependent on urine flow than in the adult, the urea/inulin clearance ratio decreasing from about 0.85 at an inulin U/P ratio of 10 to 0.3 or below at an inulin U/P ratio of 90 (fig 89). Barnett and his coworkers state that the clearance ratios reported by others conform with their data, and conclude that the urea clearance alone is without mean-

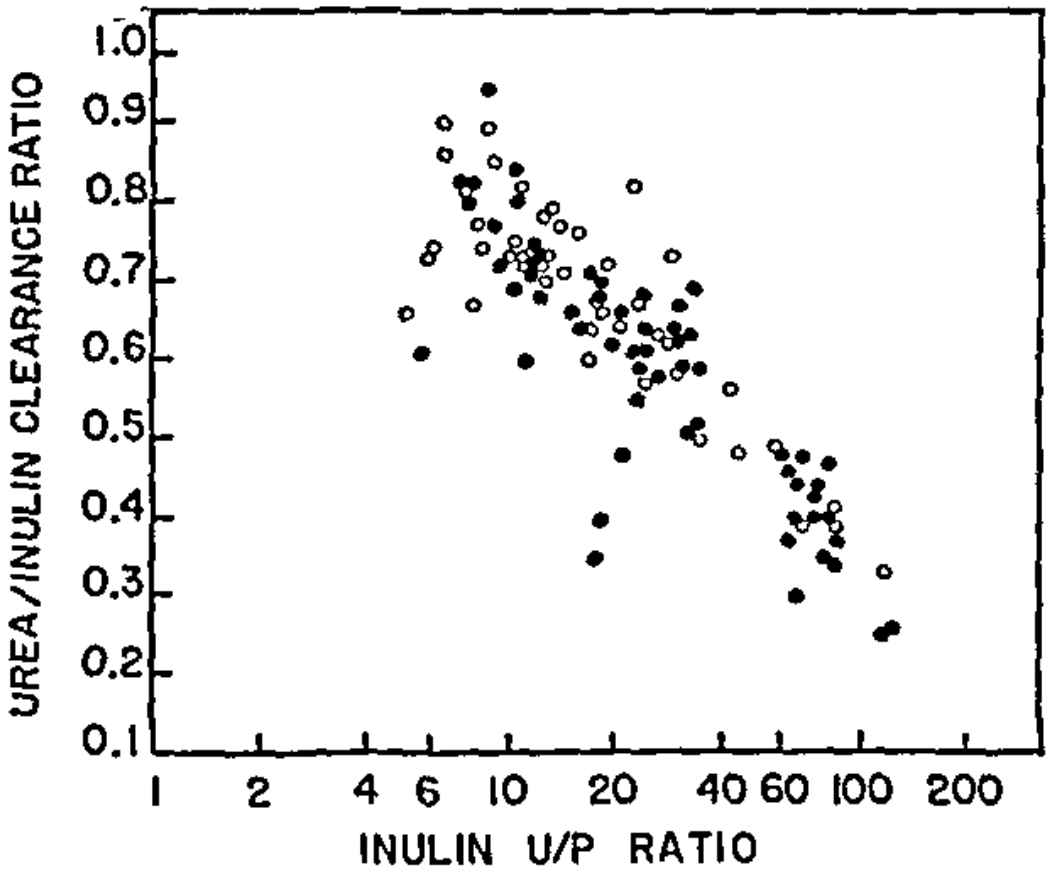


FIGURE 89. Urea/inulin clearance ratio in premature infants In adults this ratio has a value of 0 60 at an inulin U/P ratio of 10, and about 0.48 at an inulin U/P ratio of 100 (Barnett, Hare, McNamara, and Hare [85])

ing; it can be interpreted only when the filtration rate is known, for it is influenced, as in adults, by the filtration rate, by water reabsorption, and by the rate and direction of change of urine flow However, at moderate urine flows (inulin U/P ratio of 10 to 20) the average urea/inulin clearance ratio is about the same (0 5 to 0 6) as in adults.[93,263,1693] In older children, the urea clearance, like the filtration rate, comes up to the adult value.

West, Smith, and Chasis,[2178] and Rubin, Bruch, and Rapoport [1761] have discussed the changes in filtration rate, renal plasma flow, and Tm_{PAH}. Since it is agreed that by the age of 2 years all

a conclusion affirmed by Barnett, Perley, and McGinnis [95] from observations on a newborn infant with extrophy of the bladder, and by Dean and McCance.[483] Dicker and Heller (pers. com) report that the filtration rate increases with urine flow during water diuresis in newborn guinea pigs, but not in adult animals. However, the studies of Barnett *et al.*[91, 93] on premature infants, hydrated and dehydrated, show a change in filtration rate of only 20 per cent between urine flows of 0 05 and 0 7 cc/min. (*c* 0.5 to 7.0 cc/min. per 1.73 sq. m), indicating that there is no special lability of the glomerular apparatus in infancy. No obvious relation between filtration rate and urine flow is apparent in the data of West *et al.*[2175] or Rubin *et al.*,[1751] though these studies were complicated by the diuretic action of mannitol and were not made in dehydrated infants. In a more recent paper, Dean and McCance [485] recognize that, because of the osmotic limitations of the infant's kidney, the filtration rate may well determine the urine flow. As McCance [1296] notes, more information is needed on effects of dehydration on the filtration rate, for, if it is true that glomerular activity is readily reduced by dehydration in infancy, this fact would go far to explain the abnormal electrolyte pattern often observed in the first weeks of life.

UREA CLEARANCE

As would be expected from the low filtration rate, the urea clearance in the newborn is also below the adult figure when calculated on a surface area basis.[93, 483 496, 1307, 1751, 2067, 2283 2284] Gordon, Harrison, and McNamara [815] concluded that the 24 hr. urea clearance, which is lower in premature than in full-term infants, shows no relation to urine flow,* and the urea/inulin clearance ratio did not vary markedly with urine volume in the data of McCance and his coworkers [483, 1307] on full-term infants, or in those of Young, Hallum, and McCance [2283] on premature infants, because both clearances tended to decrease with urine volume. However, the data of Barnett *et al.*,[93] who studied the same infants during hydration and dehydration, show that the urea clearance is even more mark-

bit, but the reported decreased filtration rate at low urine flows in the rabbit, originally reported by Kaplan and Smith [1090] and confirmed by Wilkinson and McCance,[2221] Dicker and Heller,[614] and Forster,[678] has been shown by Brod and Sirota [966] to be in large part a 'physiological anomaly related to renal vasoconstriction elicited by excitement of the animal' (ch. XVII). According to Brod and Sirota, if rabbits are handled with due respect to their unusual psychic sensitivity, the filtration rate proves to be independent of urine flow down to very low values of the latter. The same may also be true of infants

* This may be because diurnal variations in glomerular activity nullify the effects of diurnal variations in water excretion.

figure of 23.3 gm. for the average kidney weight in the newborn, to obtain the ratio 0.26 cc/min. per gm. of kidney. In the adult, this ratio may be taken as 0.46 cc/min. (ch. XVII). Alternatively, on a surface area basis, the average filtration rate in the newborn

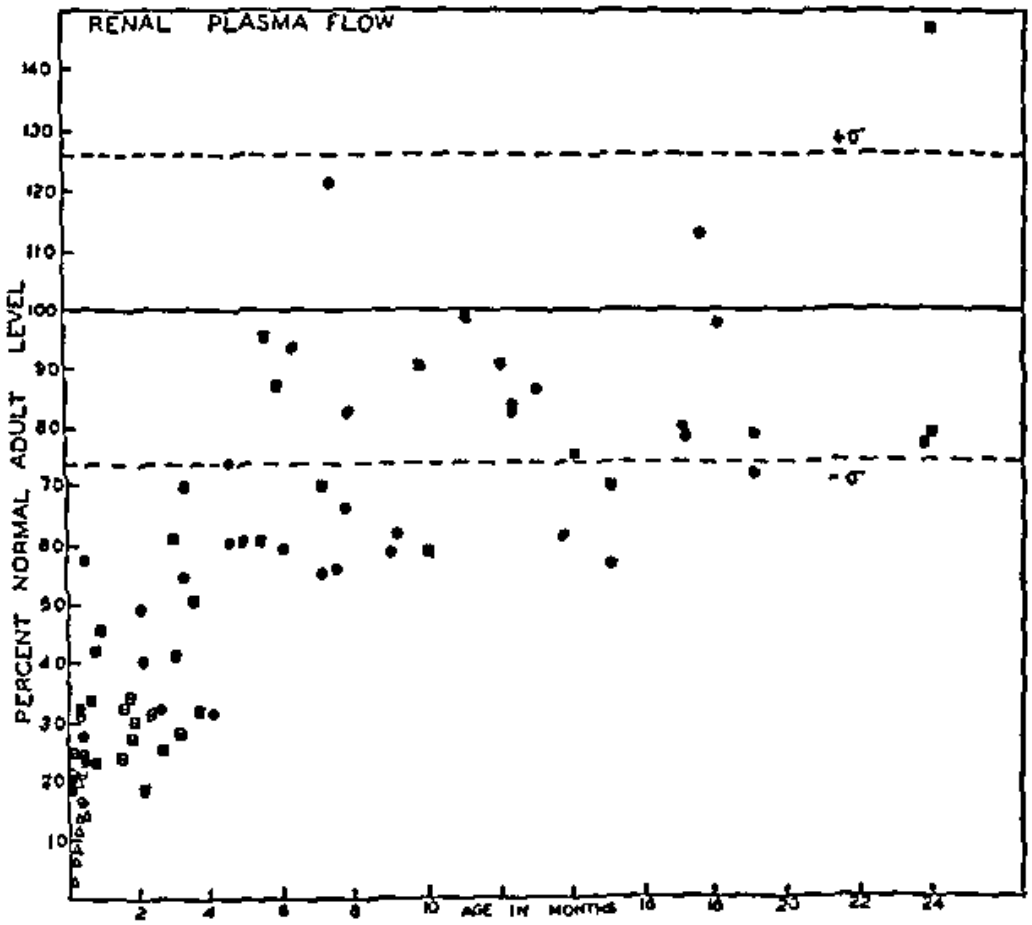


FIGURE 91 Renal plasma flow in relation to age in premature and full-term infants. Symbols as in figure 90

may be taken as no more than 50 cc/min. per 1.73 sq. m. (some observations are as low as 3 cc.[485]), which is to be compared with the adult figure of 127 cc. As noted above, the filtration rate increases to reach the adult value on a surface area basis generally by the end of the first year, and almost invariably before the end of the second year (fig 90).

Dean and McCance [483] obtained an average diodrast clearance of 66 (25.2 to 124.7) cc/min. per 1.73 sq. m. in 7 infants 2 to 8 days old. Barnett *et al* [92] report an average PAH clearance of 148.5 cc.

functions have generally reached adult values on a body surface area basis, data on subjects above this age will not be reviewed here. All data available to the writer have been collated in figures 90, 91, and 92, and the derivative calculations in figure 93.

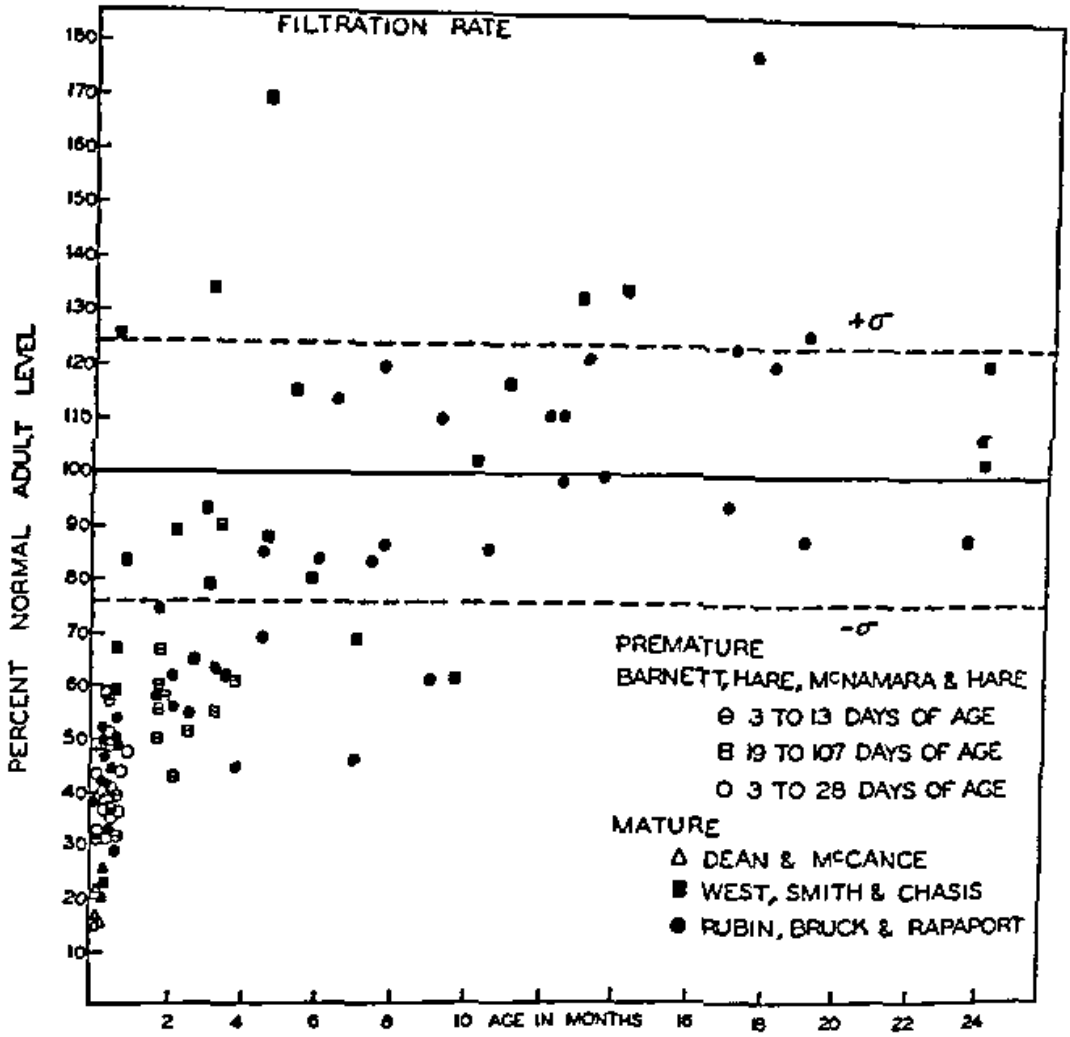
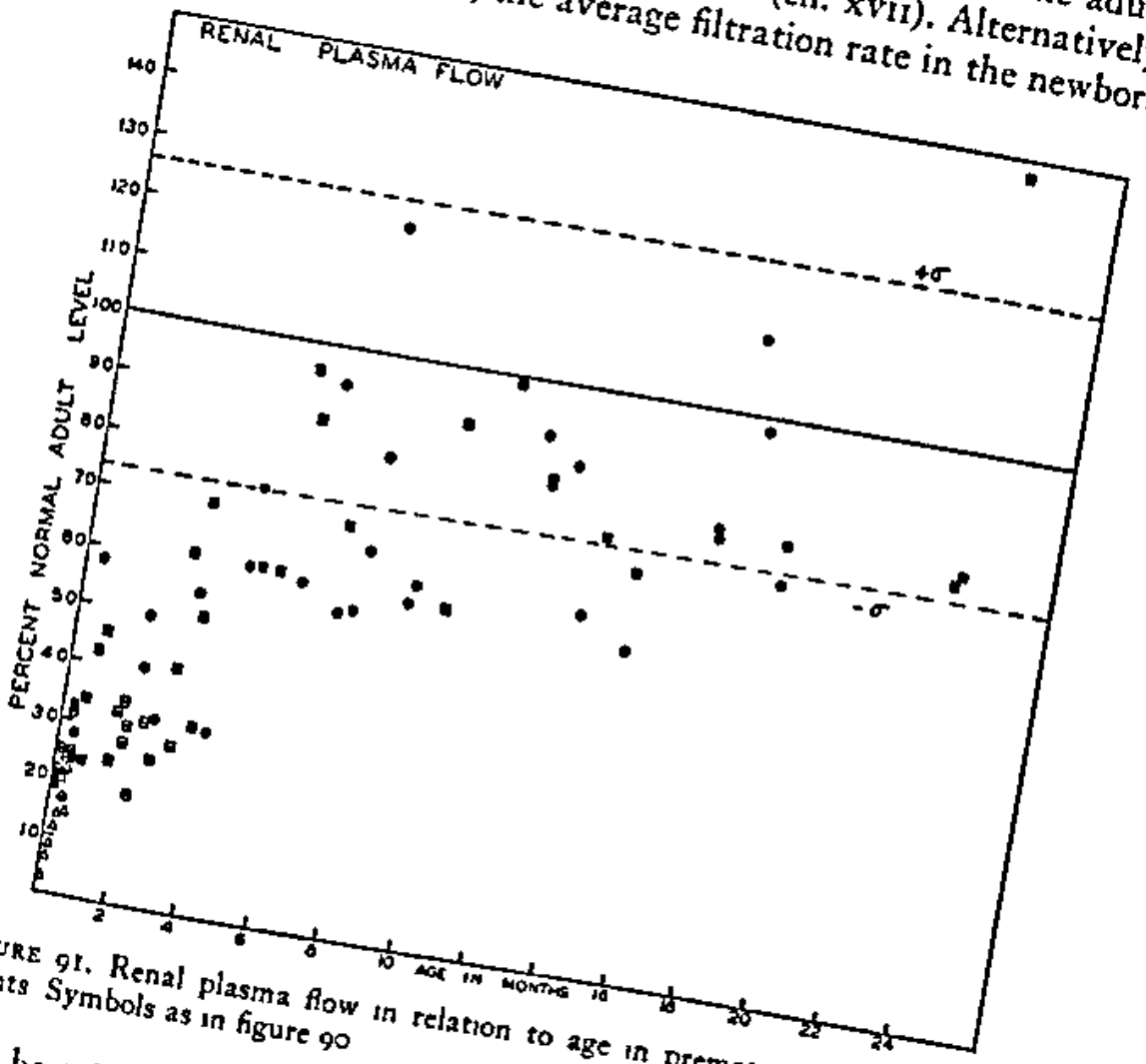


FIGURE 90. Filtration rate in relation to age in premature and full-term infants The data are drawn or recalculated from the authors indicated. The normal adult value is taken from table XII (mixed sexes).

As Rubin and his coworkers demonstrate, in agreement with the studies cited above, whether judged on a basis of kidney weight, body height, or surface area, the filtration rate is relatively low in the newborn infant. Their data on infants under 1 month of age average 0.20 cc/min. per gm. of calculated kidney weight; alternatively, we may divide the average filtration rate of 6.0 cc., as indicated by the data of various observers, by Muhlmann's [1491]

figure of 23.3 gm. for the average kidney weight in the newborn, to obtain the ratio 0.26 cc/min. per gm. of kidney. In the adult, this ratio may be taken as 0.46 cc/min. (ch. XVII). Alternatively, on a surface area basis, the average filtration rate in the newborn



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Dean and McCance [488] obtained an average diodrast clearance of 66 (25.2 to 124.7) cc/min. per 1.73 sq. m. in 7 infants 2 to 8 days old. Barnett *et al.*[92] report an average PAH clearance of 148.5 cc.

in 8 premature infants 3 to 13 days old; in 9 premature infants 49 to 107 days old this figure was 200 cc. Similar low values for the PAH clearance in infancy are shown in the data of West *et al.* . . . Rubin *et al.* (fig. 91). As in the case of the filtration rate, the I

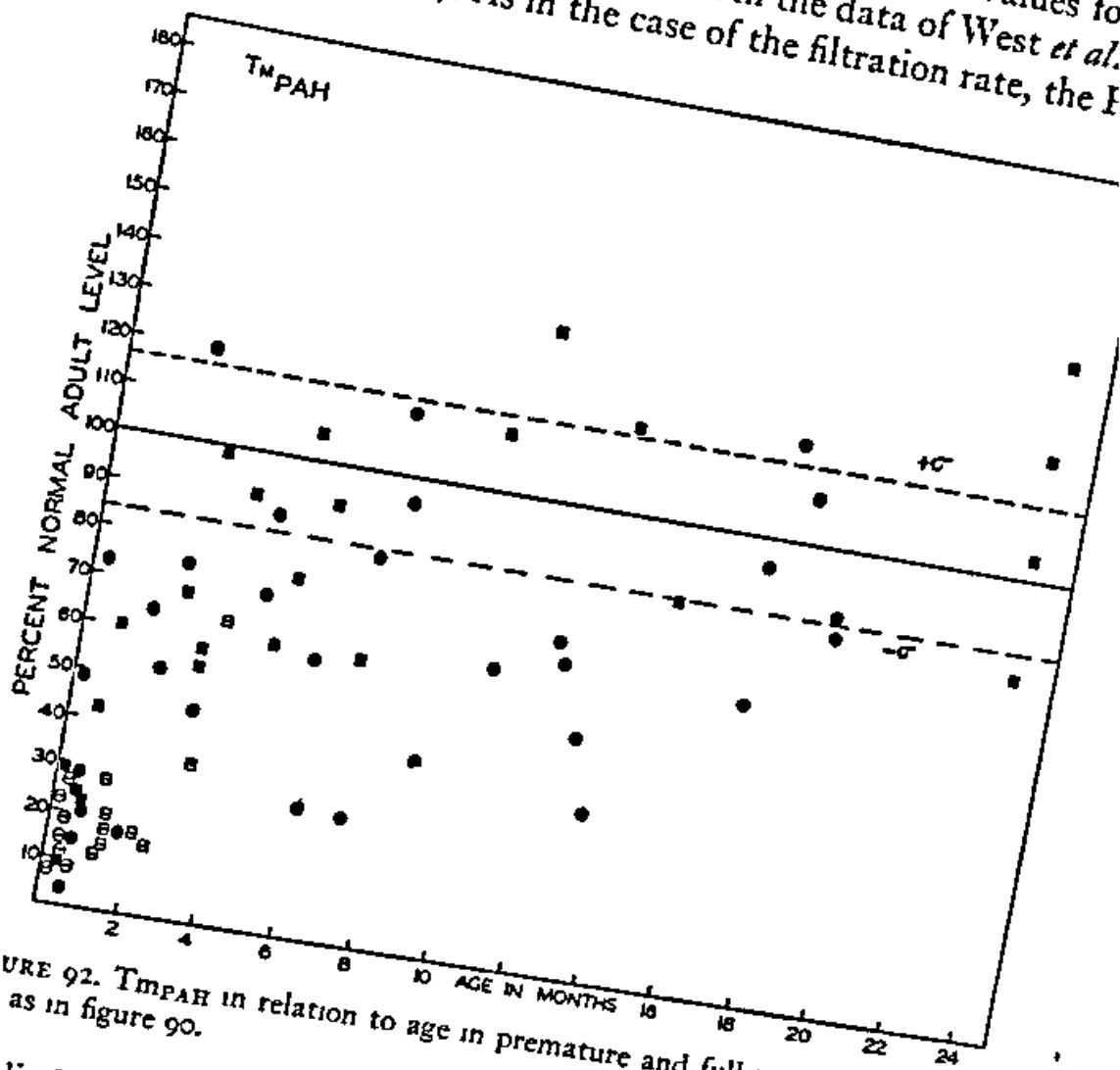

FIGURE 92. T_{m}PAH in relation to age in premature and full-term infants Symbols as in figure 90.

(or diodrast) clearance increases to reach its adult value in many infants by 1 year of age, and in nearly all by the age of 2.

Tudvad and Vesterdal,[2085] in a preliminary abstract, report that during the first days of life the inulin clearance ranged from 12 to 14 cc. and the PAH clearance from 50 to 60 cc. per 1.73 sq. m. The filtration fraction was high (0.22 to 0.55). This value was 0.60 to 0.84 in 1 Mongolian idiot, indicating a high degree of immaturity of the kidney. Galan, Peréz-Stable, Martin, and Faéz[715] report an average diodrast clearance of 695 ± 183 cc., with the normal

filtration fraction of 0.19, in 3 children 8 to 10 years old; the C_{IN}/Tm_D ratio in 2 of these was 3 58 and 2.45, all data within the normal range.

The filtration fraction in Dean and McCance's [482] data averaged 0.427 (0.296 to 0 700); if two exceptions, both 0.70, are excluded, this ratio ranged from 0 30 to 0.47 and averaged 0.38. Because of this high value, they inferred that diodrast is incompletely removed from the renal blood. In the data of Barnett *et al.*[92] the filtration fraction averaged 0.34 in premature infants ranging up to 107 days old As shown in figure 93, the filtration fraction, high initially, decreases and is generally normal at 1 year of age.

As with the filtration rate and effective renal plasma flow, Tm_{PAH} has very low values at birth, but increases rapidly. West *et al.*[2176] believed that normal values were reached by about 30 weeks; a wider scatter is present in the data of Rubin *et al.*[1751] and, while several infants had attained adult values within the first 6 months, there were some in whom this had not occurred at 7 years (fig. 92).

It appears from the relationships above that various aspects of renal function are adjusted at an early age, usually under 1 year, to the metabolic requirements of the body, using the surface area as an approximate index of general metabolism. However, in this readjustment glomerular and tubular function develop at different rates, as is revealed by the changes in the derivative ratios (fig. 93). The problem is to relate this differential functional development to the anatomical development of the kidney.

First, we may consider the possible causes of the low filtration rate at birth. Excluding back diffusion of inulin or mannitol, this low filtration rate might be due to (a) low blood pressure, (b) increased afferent glomerular resistance and resulting low glomerular pressure (which would be accompanied by a low blood flow), and (c) the impediment to filtration offered by the cuboidal epithelium of the fetal-neonatal glomerular membranes.

The changes in blood pressure that occur at birth and during the first year of life are not too well known. The establishment of the adult circulation involves the obliteration of the placental circulation and the functional separation of the systemic and pulmonary circulation It would be expected that the latter process would be

accompanied by substantial and rapid increases in systemic arterial pressure, but such does not appear to be the case. Observations on experimental animals throw little light on the situation in

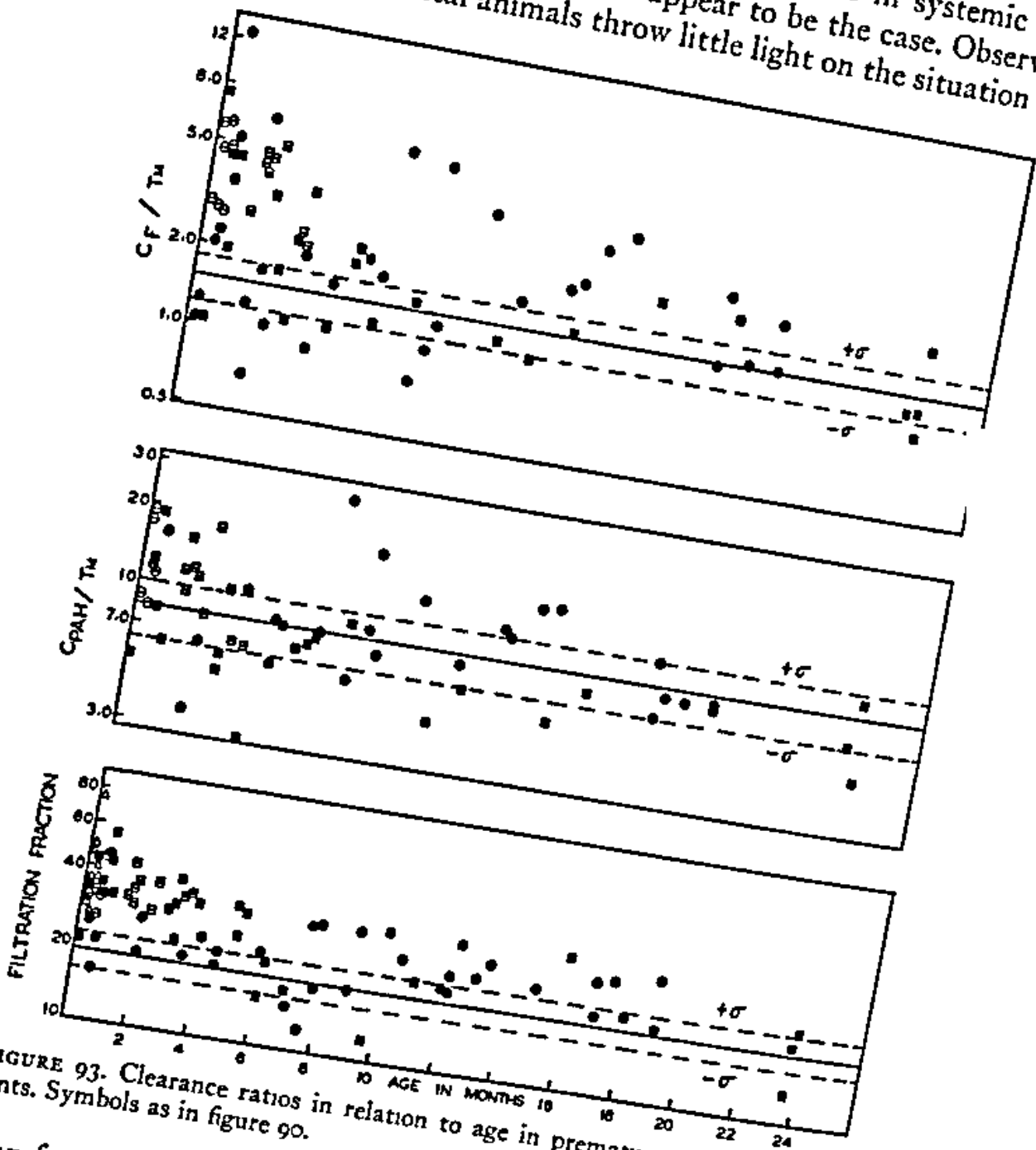

FIGURE 93. Clearance ratios in relation to age in premature and full-term infants. Symbols as in figure 90.

man for, in the dog and rabbit at least, the ductus arteriosus has a valve-like structure which is competent to stop the backflow from aorta to ductus, and after the ductus has been functionally closed for a while adhesions form and the closures usually become

anatomical. In the human fetus there are no valve-like flaps to guard the aortic opening of the ductus; what causes the aortic-ductus flow to stop and the ductus to close is an unanswered question.[397] Whereas closure occurs within a few minutes after delivery in most animals, the process is apparently more leisurely in man. However, an interval longer than 3 hr. is rarely required for the transformation of the fetal circulation into the adult circulation, as judged by the oxygenation of the arterial blood, and it may be much less.[1914]

Citing the data of several investigators, C. A. Smith [1914] gives the pressure in the umbilical artery in infants at the time of premature birth at 5, 6½, 7, 8, and 9 months as 33/21, 55/25, 70/35, 85/45, and 80/46 mm Hg, respectively, i.e the systemic pressure rises toward its postnatal level throughout fetal development. The umbilical pressure immediately after birth averaged 80/46 mm. Hg in 24 normal infants studied by Woodbury, Robinow, and Hamilton.[2272] From these and other data, Smith concludes that the systolic pressure increases about 10 mm during the first 24 hr. of life and by another 10 mm between the first and fourteenth days, with a further increase no greater than 2.5 to 5 mm. during all the rest of the first year It therefore seems unlikely that the continued increase in filtration rate throughout the first year or more of life is related to increasing systolic pressure.

Given adequate blood pressure, a low filtration rate per gm. of kidney might be attributed to a paucity of glomeruli, but full-term human infants apparently have all the glomeruli they are ever going to develop The rate of filtration in these glomeruli would, however, be reduced by either exaggerated afferent arteriolar tonus or persistence of fetal glomerular membranes. In the first case the total renal blood flow would be low; in the second case, the total renal blood flow would be low only if the cuboidal visceral epithelium compressed the capillaries to such an extent as to impede perfusion.

The effective renal plasma flow, as measured by the diodrast or PAH clearances, is in fact lower at birth, relative to adult values, than is the filtration rate, as is shown by the supernormal filtration fractions recorded by all investigators (fig. 93). Nothing is known about the extraction ratios of these compounds in the in-

fant kidney, and in the absence of this information we can only indulge in speculation. That the high filtration fraction is attributable to a low extraction ratio is indicated (though not firmly established) by inference. The infant's blood pressure is below rather than above the adult value, and, even without excessive

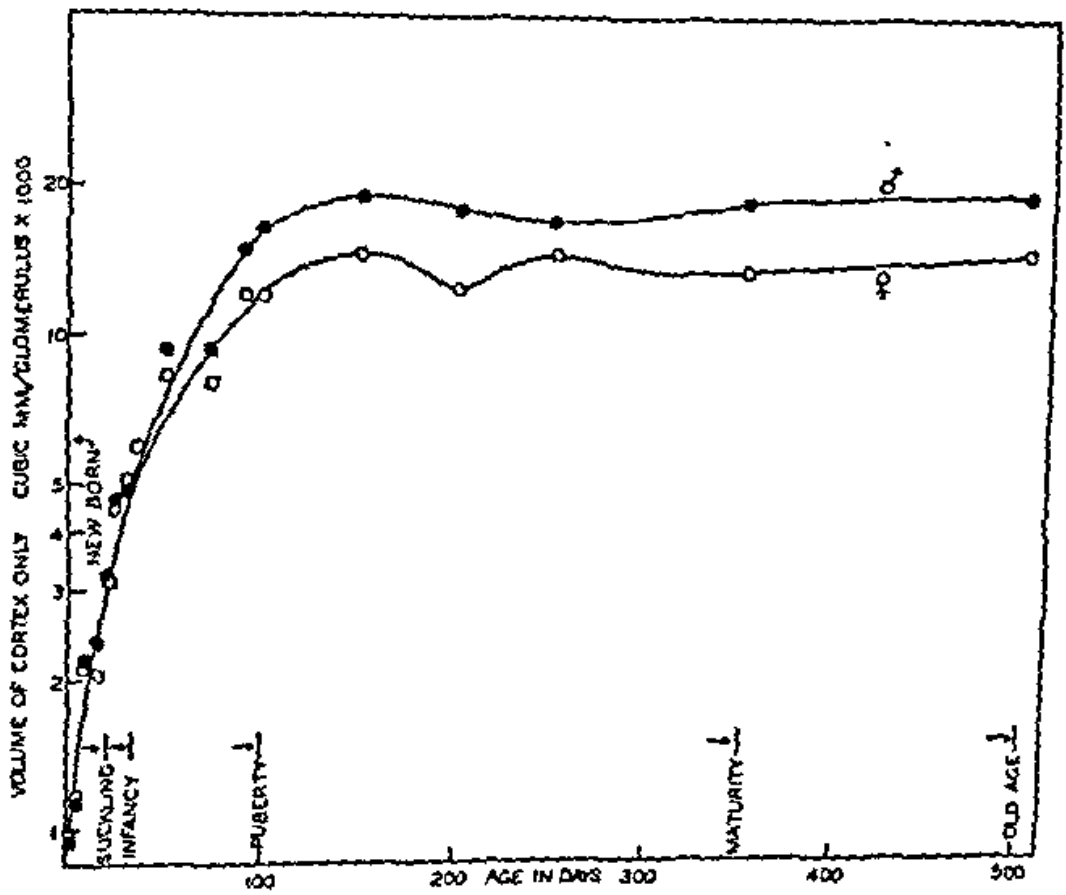

FIGURE 94. Growth of renal cortex (volume) per glomerulus in the white rat. (Recalculated from Arataki [15])

afferent arteriolar resistance, it may be surmised that glomerular pressure is also low; the persistence of fetal glomerular membranes and the fact that the glomerular capillaries are typically underdeveloped would also decrease rather than increase the filtration fraction. Thus, with all these circumstances operating to reduce the filtration rate per unit of total renal blood flow, it would seem that a high filtration fraction could only be the result of deficient tubular clearance of postglomerular blood. The most likely reason for deficient tubular clearance would be that some of this blood, after leaving the glomeruli, escapes into the venous circulation

without being presented to functional proximal tubular tissue. That such is probably the case is indicated by certain features of renogenesis. In early fetal life the medulla, at this stage bearing a large proportion of collecting tubules, develops ahead of the cortex. By the fourth fetal month, the renal tubules begin to differentiate into a thin descending and a thick ascending limb, the long loops extending downward and reaching the papillae by the fifth month, thus contributing to the increased depth and thickness of the medulla. While the medulla is increasing its transverse diameter by 100 per cent, the cortex increases only by 20 to 25 per cent.[622]

Development of the cortex proceeds from the juxtamedullary regions toward the capsule, with progressive elongation of the cortical tubules. This tubular development involves a gross readjustment between glomerular and tubular function, which can best be illustrated in the white rat, the only species in which detailed data are available. From the counts of Kittelson[1128] and Arataki,[55] it appears that the number of fully developed glomeruli increases by nearly 3 fold after birth, the maximal number not being reached until about 100 days. This fact implies that a number of nascent nephrons in the newborn rat are functionally aglomerular, even as all nephrons are functionally aglomerular in the early embryonic period. In addition, however, tubular tissue is developing even more rapidly than glomeruli. Indeed, despite the presence of incompletely differentiated glomerular anlagen in the newborn animal, the extent of tubular development is so meager that one may say (relative to the adult relations) that the kidney is predominantly glomerular.

This imbalance between glomerular and tubular development is well illustrated by Arataki's[55] classical studies. This investigator made glomerular counts and other measurements on the kidney in pairs (1 male and 1 female) of rats from birth up to 500 days of age. The writer has recalculated some of his data for presentation in figures 94 and 95. Figure 94 shows the volume of renal cortex * in cu. mm. per (completely formed) glomerulus in

* This figure is the volume of cortex after fixation, as calculated by microscopic enlargement and planimetry of every other section (20 to 25 μ). Correction for shrinkage would not significantly alter the relations shown.

relation to age; since the glomeruli themselves represent only a small fraction of the volume of the cortex, the latter can be taken to indicate the quantity of tubular tissue per nephron. The notable feature of these data is that between birth and 100 days the

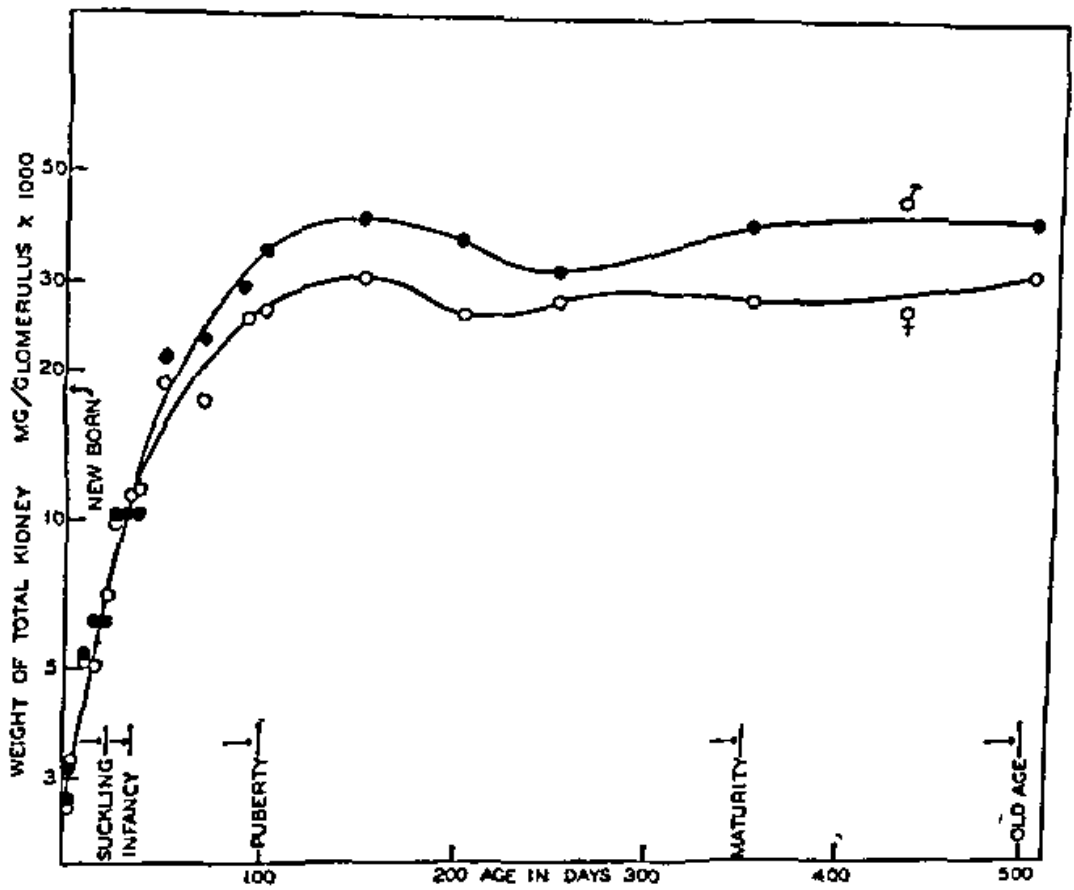

FIGURE 95 Growth of total kidney (weight) per glomerulus in the white rat. (Recalculated from Arataki [65])

quantity of tubular tissue per nephron increases 20-fold; since the tubules do not increase in diameter (fig. 96), this increase can only be effected by elongation of the proximal and distal tubules in each nephron. The same conclusion is reached if one calculates the weight of total kidney tissue per glomerulus (fig. 95).* The two methods of calculation yield essentially the same result because the relative proportions of cortex and medulla (the latter con-

* By both calculations, the adult male has slightly more tubular tissue than the female.

stitutes about 30 per cent of the total kidney volume) are practically constant in Arataki's data from 3 days on.*

As shown in figure 96, the average glomerular diameter increases by a little less than 100 per cent between birth and 100 days, but, even if this is accompanied by doubling of glomerular

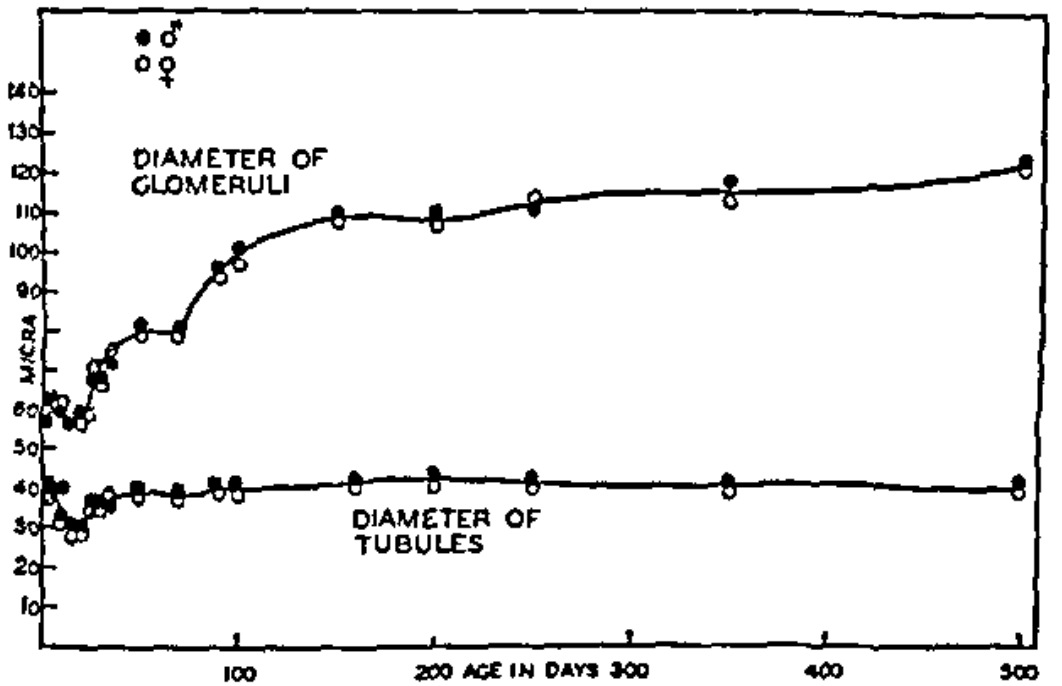

FIGURE 96. Changes in diameter of glomeruli and tubules in the white rat in relation to age. (Arataki [46])

function, in the kidney of the newborn rat glomerular function predominates over tubular function by a ratio of some 10 to 1 because of incomplete elongation of the tubules.† In man an increase in glomerular diameter is evident before the age of 1 to 2 years (table IX).

* In Kittelson's [129] data, the volumetric ratio of medulla to cortex is 1:3.05 at birth, decreasing to 1:1.2 at 12 weeks and increasing again to 1:2.87 in the adult.

† Arataki notes that, as between 350 and 500 days of age, the total number of glomeruli in the kidney decreased from above 30,000 to some 20,000; since the diameter of the tubules and the number of glomeruli per unit volume of cortex remain constant, he concludes that the tubules of the disappearing glomeruli have also been destroyed, i.e. there is no evidence here of the formation of aglomerular nephrons in the senescent kidney.

In the newborn infant, the ratio of the height of the medulla to that of the cortex is about 1:5, in the adult this ratio is about 1:2.4, this proportion being closely approached between the first and second year.[2112] In the cat (no measurements are available in

TABLE IX

The Midsize of the Peripheral and Central Glomeruli in Man, in Micra

(After Kulz, cited by Arataki [56])

Age	Peripheral glomeruli	Central glomeruli
0 days	99	138
9 days	97	135
2 5 months	107	139
5 months	110	138
7 months	121	140
9.5 months	129	139
1¼ years	132	143
2¾ years	157	158
12 years	192	192
16 years	231	229
18 years	213	219
23 years	237	237

man) the relative expansion of the cortex involves a considerable elongation of the proximal tubule relative to the rest of the nephron. According to Sperber,[1959] the proximal tubule constitutes about 30 per cent of the total nephron length in the 12-day-old kitten, some 30 to 35 per cent in the young female cat, and about 45 to 50 per cent in the old male.

That tubular excretion could be carried on by proximal tubule tissue as rapidly as it develops is implied by the demonstrated activity of embryonic mesonephric tissue in *in vitro* cultures, and during its development the proximal tissue of the cortex must have a reasonable supply of blood, no doubt of glomerular origin. It is, however, conceivable that the peritubular capillary plexus is inadequate to present all postglomerular blood to proximal tissue because of incomplete relations between the peritubular capillaries and the rapidly developing proximal tissue; more particularly, the postglomerular blood from the juxtamedullary glo-

meruli, the earliest to develop, may be significantly deficient in this respect.

If the extent of development of proximal tubular tissue may be judged by Tm_{PAH}, the kidney of the newborn is very deficient in this tissue. Tm_{PAH}, like the effective plasma flow, is relatively lower at birth than is the filtration rate, as shown by the supernormal values of the ratio C_{IN}/Tm_{PAH}. The data of Rubin *et al.* indicate that in 7 infants 7 to 22 days of age Tm_{PAH} has a value of 0.10/gm of kidney; using Muhlmann's figure of 23.3 gm. gives a value of 0.13. This figure in the adult may be taken as 0.300 (ch. XVII). Thus, as functionally measured, there is only one-half as much proximal tissue per unit of weight in the kidney of the newborn as will be the case at 2 years of so Either (a) proximal tissue is present but is so poorly perfused by blood that it is not saturated in clinical determinations, or (b) this proximal tissue has not yet developed in proportion to kidney weight or filtering surface. In respect to (a) it has elsewhere been argued (ch. XIX and Smith,[1939]) that every unit of proximal tissue which is active in clearing PAH at low plasma levels must be conceived to be available to blood during the measurement of Tm_{PAH}; i.e. the two terms, C_{PAH} and Tm_{PAH}, have reference to the same excretory units and the same vascular channels Since the ratio C_{PAH}/Tm_{PAH} is normal or slightly high at birth (fig 93), such proximal tubule tissue as is clinically available appears to be normally vascularized and perfused, and we are thus led to reject (a) in favor of (b), namely that proximal tissue is not yet fully developed; the renal circulation at the start is predominantly a glomerular one, the postglomerular blood escaping into the venous circulation without tubular clearance because adequate tubular tissue is not there. This circumstance will lead to a low extraction ratio of diodrast and PAH, to low clearances of these compounds, and to a high filtration fraction. Thus all the facts are at least compatible with a low extraction ratio of PAH.

The supposition above is supported by the data of Williamson and Hiatt [2228] on the rabbit, in which the rate of excretion of phenol red per gm. of renal tissue increases 5-fold in the first 10 days after birth. If this is entirely a matter of increased renal blood flow per gm. of kidney, it requires a greater acceleration of glomerular de-

velopment than is indicated by the anatomical data on other species or by data on the functional activity of the glomeruli in man, whereas the observation conforms with the interpretation that after birth a predominantly glomerular circulation with poor tubular clearance is rapidly transformed by the continuing development of proximal tissue into one in which the postglomerular blood is fully distributed for tubular clearance. With this redistribution, C_{PAH} and Tm_{PAH} increase, roughly in the same proportion, and the filtration fraction falls. These changes are superimposed on a simultaneous increase in the filtration rate promoted by opening up of the glomeruli and regression of the fetal glomerular epithelium.

In brief, then, an interpretation that will fit all the facts is about as follows: glomerular development outruns tubular development in the late stages of fetal life so that, at term, the kidney has its full complement of glomeruli but a deficient quantity of proximal tubule tissue. Although the blood pressure is essentially normal, the filtration rate per gm. of kidney is low at birth because of impedance of filtration by the fetal epithelium. But, despite this functional deficiency in glomerular activity (i.e. relative to the *number* of glomeruli present), the circulation is predominantly a glomerular one because of a greater deficiency in development of proximal tissue, and considerable postglomerular blood escapes tubular clearance, these circumstances leading to (a) a low filtration rate per gm. of kidney, and (b) low values for E_{PAH}, C_{PAH}, and Tm_{PAH}, and high values for C_{IN}/Tm_{PAH} and C_{IN}/C_{PAH}. As proximal tissue develops in the first year or so of life, all postglomerular blood comes ultimately to be presented to proximal tissue for clearance and E_{PAH}, C_{PAH}, and Tm_{PAH} increase, while C_{IN}/Tm_{PAH} and C_{IN}/C_{PAH} decrease to their adult values.

The interpretation given here differs from those offered by West *et al.* and Rubin *et al.* in that emphasis has been placed on the probability of a low extraction ratio. If the extraction ratio in infancy proves to be normal, reinterpretation will certainly be required.

In view of the fact that the medulla and juxtamedullary circulation develop ahead of the outer cortical nephrons, one may anticipate that much of the neonatal atubular circulation is through

the *vasa recta*, along the lines described by Trueta and his colleagues[2083] in the adult rabbit kidney. Replacement of these atubular circuits by circuits promoting tubular clearance of all postglomerular blood might occur to a variable extent during maturation in different species. And if the primordial juxtamedullary glomeruli receive a meager sympathetic innervation, it would perhaps explain their resistance, relative to the glomeruli in the neogenic zone, to vasoconstriction This neuromotor imbalance, so striking in some rabbits, might also represent a fetal pattern which is largely if variably lost in the adults of other species,* explaining the fact that evidence is lacking for the operation of the Trueta by-pass in man (ch. xxv)

This interpretation must await confirmation by the determination of extraction ratios in the infant kidney, and perhaps studies on the distribution of the postglomerular blood in newborn animals.

One difficulty is presented in this view, in that Galán, Peréz-Stable, Martin, and Faéz[735] report that, in 6 children 2 to 11 years old, Tm_G averaged 543 ± 129 (322 to 759) mg., values much greater than those observed in adults (375 ± 79 7 in males and 303 ± 55.3 in females).[1931, 1939] The average Tm_G/C_{IN} ratio in children, 4 35 ± 1 19, is correspondingly greater than in adults (males 2.7 and females 2 5), and is even larger in children with nephrosis.[732] In 2 normal children in whom both Tm_G and Tm_D were determined, the ratio Tm_G/Tm_D averaged 13.0 as compared with 7.32 ± 1.51 in adult males and 8 29 ± 2.09 in adult females These figures would indicate that glucose reabsorptive capacity is much more highly developed, relative to glomerular function and the excretion of diodrast and PAH, in children than in adults. This circumstance would seem to require, by the foregoing interpretation, extraordinary if transitorily enhanced glucose reabsorptive capacity in all available nephrons. However, in premature and newborn babies, Tudvad[2084] reports that Tm_G corrected to 1.73 sq. m. is below the adult value. The C_{IN}/Tm_G ratio averaged 0.47 (0 34 to 0.66) as compared with 0.395 in adults, confirming a relatively low Tm_G value Some uncertainty must, therefore, remain attached for the time being to glomerular-tubular balance with respect to glucose reabsorption.

* It may be repeated that, in respect to vasomotor reactivity, the rabbit appears to be a very unstable creature.

MAINTENANCE OF SALT AND WATER BALANCE IN INFANCY

Although presumably in salt and water balance at *birth (if the* mother is in a state of health—the effects upon the infant of salt and water imbalance in the mother have never been examined), the newborn baby is precipitated toward dehydration by the lapse of some 24 to 48 hr. before it imbibes fluid.[2069] The relatively large surface area of the infant favors extrarenal water loss, although Heller [958] has found that such loss is smaller than was expected in newborn rats at room temperature, perhaps because they are poikilothermous, and evaporation is reduced as the body temperature falls. The practice of giving newborn infants water is not universal, even when they are to be reared from a bottle, and abstinence from fluid for 48 hr. would produce significant dehydration in the adult. The first 3 or 4 postnatal days are attended *by loss of 6 to 10 per cent in body weight, which is perhaps chiefly* attributable to dehydration, and from birth until the third day the plasma concentrations of urea, uric acid, and NPN generally increase. For these reasons, McCance [1296, 1305] concludes that, as a rule, babies do suffer dehydration from the fourth until the thirty-sixth hour of life.

Despite neonatal dehydration,[38] as judged by red cell count, hematocrit, and body weight, the plasma sodium concentration and total base are fairly well maintained; urea and potassium concentrations are, however, elevated in newborn infants and newborn rats; [959, 1307] the bicarbonate concentration is reduced below adult mean values by the presence of organic acids, among which pyruvic acid is important, while respiratory compensation maintains the hydrogen ion concentration at pH 7.4. *Incipient* acidosis is easily aggravated, as for example by a shift from breast milk to more acid cow's milk or by diarrhea, or readily relieved and even excessively compensated *into alkalosis by the administration of bicarbonate.*[1296, 1914]

In adults taking their full complement of fluid, the osmotic *U/P ratio in urine collected during the day will range from 3 to 4,* and the specific gravity from 1.015 to 1.025. During hydropenia, the urine flow is rarely less than 500 cc , this figure depending to a *considerable* extent upon the salt and protein intake, and the

osmotic U/P ratio increases to its maximal value of 4.0 to 4.2, t
specific gravity to 1.028 or higher

Heller [969] has shown that adult rats, when deprived of water, excret
a concentrated urine (specific gravity 1.056 ± 0 002, 2 0 osm or more)
whereas in newborn rats dehydration does not increase the specific
gravity (1 011 to 1.015) of the urine significantly, this failure to effect
concentration being reflected in failure of the U/P ratios of sodium,
chloride, and potassium to increase. Where adult rats increase potassium
excretion during dehydration, newborn rats excrete less potassium.
Adult animals maintained their extracellular fluid by increasing tubular
water reabsorption and by a shift of water from the intracellular space;
such water conservation as was effected by newborn rats, which may be
the result of a decrease in filtration rate, was inadequate to prevent
hemoconcentration and elevation of plasma urea.

According to Thomson,[2069] full-term infants excrete some 20 cc.
of water per day in the first 2 days, this figure rising to 225 cc. by
the twelfth day. These figures would correspond to about 100 and
1125 cc. per 1.73 sq. m/day The specific gravity in the first 2 days
has a wide range (1 008 to 1 020) with a mean of 1.012, it de-
creases thereafter for several weeks and levels off in the range 1.006
to 1.011, with a mean of 1.008 During the first 48 hr. after birth,
the urine is slightly more concentrated than the plasma, the
osmotic U/P ratio ranging from 1.0 to 1.4, * then, from the third
day on, the urine becomes more dilute, the osmotic U/P ratio fall-
ing to 0.3 to 0.7, this decrease in osmotic pressure being only in
part related to fluid ingestion, which is now established at 300 to
500 cc/day.[955 1307] The urine remains dilute for at least a week,
when the kidney begins to do better osmotic work.[955 1307 2282] At
1 month, the specific gravity during water deprivation may rise
to 1.036 and the osmotic concentration to 1.2 osm/liter (osmotic
U/P ratio about 3.6), figures comparable to those of adults, and
by this time over half the water provided by the infant's usual
food can be conserved to cover abnormal losses by other routes of
water removal.[1459]

* The reason for this limitation in osmotic pressure is obscure, for Dean and McCance [441] have shown that at least 2 infants 3 and 4 days old concentrated to an osmotic U/P ratio of 1 5 to 2 0 during hypertonic saline diuresis, and in 1 this value reached 2 5 during urea diuresis. However, these figures are still less than are observed in adults

Thus the kidney of the newborn is unable to make a significantly concentrated urine during the critical period of dehydration immediately after birth. But, as McCance and his coworkers have emphasized, the urine volume remains low, presumably because a low filtration rate reduces the load of sodium chloride and other solutes escaping reabsorption.

The deficiency in concentrating power in infancy is attributed by Heller to relative insensitivity of the distal tubules to ADH, for the concentration of the urine was but slightly affected by the administration of pitressin to full-term infants 2 to 6 days old who were excreting relatively dilute urine. He correlates this lack of sensitivity with the fact that the neurohypophysis of young animals contains relatively little of this hormone.[955, 957] Assay of the pituitary gland in 15 newborn infants revealed only about one-fifth of the antidiuretic and oxytocic hormones per mg. of dry tissue found in the glands of 14 adults. However, Barnett *et al.*[93] obtained inulin U/P ratios as high as 227 in premature infants who were moderately dehydrated, and they suggest that measurements of osmotic pressure and specific gravity are misleading in this connection, since they depend not only on water reabsorption but on the reabsorption of urinary solutes. These investigators found that a 6-day-old, 2200 gm. premature infant deprived of water for 16 hr. showed an inulin U/P ratio of 200; after the intravenous administration of 0.9 per cent saline the U/P ratio fell to 20 and below; immediately after the infusion of pitressin at 1 milliunit/min. the U/P ratio rose to about 60. The experiment indicates some responsiveness on the part of the tubules to ADH.* The distal tubules may appear to be less sensitive to ADH in respect to water reabsorption because the maximal osmotic ceiling may be low, thus placing a low limit upon the degree of concentration of the urine even under maximal ADH activation.

The fact that infants under 3 months of age respond poorly to water diuresis,[1295] a phenomenon also observed in puppies[29] and newborn rats,[958, 1306] is probably related to the low filtration rate

* The use of saline instead of water to hydrate the infant may have produced osmotic diuresis, and one could not expect to obtain as high a U/P ratio with pitressin alone, which may have promoted the excretion of sodium chloride, as on water deprivation with a low load of urinary solutes.

and the delivery to the distal system of a correspondingly small load of sodium and water. In rats, typical water diuresis begins to appear at 4 days, and at 12 days the response is almost indistinguishable from that of the adult, despite the fact that during oliguria the urine remains relatively dilute.[1308] The situation recalls the blunting of water diuresis in Addison's disease (p. 353).

Sodium, chloride, and potassium clearances are relatively low in newborn full-term infants, on the basis of surface area possibly only one-fifth of those of adults. These low clearances also appear to be related to the low filtration rate. At all ages, the chloride clearances tend to vary with the urine flow, which is to be expected if the urine is (for the infant kidney) maximally concentrated and sodium chloride is the chief deterrent to water reabsorption. The phosphate clearance is also low and tends to vary with the urine flow.[1307, 2283, 2284] Young, Hallum, and McCance [2283] have emphasized the potential importance of the low filtration rate, with resulting glomerular-tubular imbalance, in the genesis of low electrolyte clearances, and, in turn, the importance of low electrolyte clearances in the susceptibility of premature and full-term infants to the formation of edema. The situation can be illustrated by the calculation that, if one takes the average filtration rate in the newborn as 50 cc/min. per 1.73 sq. m., and the adult figure as 130 cc., and if one allows for the lower concentrating power (one-third) in the infant kidney, the expected *urine obligatoire* in infants would be of the order of 800 cc/day per 1.73 sq. m. That the observed urine flow is lower (300 cc. or less) may be referable, as McCance [1298] suggests, to the fact that the low filtration rate reduces the load of solutes delivered to the distal tubule.

Isotonic and hypertonic saline are poorly excreted by young animals. When 10 per cent sodium chloride or 20 per cent urea solutions are administered by mouth to adult rats in doses of 5 per cent of the body weight, the animals respond with a diuresis which enables them to excrete 27 per cent of the solute in 5 hr. As in man, the urine during this diuresis becomes relatively dilute, dropping from the range of 2.5 to 3.0 osm. to 1.3 to 1.5. In newborn rats, however, the maximal control concentration is rel-

atively lower (0.5 osm.), and hypertonic saline and urea solutions produce only a slight diuresis, with a slight increase or no change in osmotic pressure.[1206] Newborn infants respond to osmotic diuresis in a similar manner: diuresis is substantially less than in the adult and the osmotic pressure of the relatively dilute urine rises slightly or does not change.[482,485] This inability of the infant to dispose of hypertonic or even isotonic solutions of sodium chloride would appear to issue in the first instance, as McCance and his co-workers emphasize, from glomerular-tubular imbalance, and in the second instance, assuming excretion into the urine, from the inability of the infant kidney to elaborate a hypertonic urine. The infant is faced with a dual danger: first it is handicapped in excreting sodium chloride, and, if the salt is excreted, it is apt to suffer dehydration by excessive loss of water. Sluggishness in excreting saline does not appear to issue from failure of the glomeruli to increase their activity on expansion of the body fluids, for Dean and McCance [486] found that 0.91 gm/kg. of sodium chloride as a 10 per cent solution markedly increased the filtration rate in 2 infants 3 and 4 days old, though the maximal rate attained (20 cc/min. per 1.73 sq. m.) fell far short of the adult value.*

Infants may remain in a state of acidosis for some time after birth. The phosphate clearance is so low [484] that there is available very little substrate buffer for the excretion of acid, and as a result a larger proportion of acid is neutralized by ammonia than in adults. The proportion of free acid as phosphate is also much lower and the proportion as organic acid much higher.[1298]

Dean and McCance [483] obtained exogenous creatinine/inulin clearance ratios ranging from 0.68 to 1.32, and averaging about 1.0, in infants a few days old (the ratio tended to increase in successive periods),† and inferred that the tubular excretion of creatinine is not fully developed. Brod and Sirota [264] report that in somewhat older infants the endogenous chromogen/mannitol clearance ratio averages 0.60 ± 0.066 (0.55 to 0.69), whereas this ratio

* It should be emphasized that adult humans respond very sluggishly to the administration of isotonic saline in comparison with the dog (ch. xi) and possibly the rat, and it may be that part of the trouble with the infant kidney is that it is human.

† This may reflect poor perfusion of some tubules, as is suggested in connection with pyelonephritis (ch. xxvi).

averages 1.0 in normal adults [262] In 15 older children, the creatinine/inulin clearance ratio averaged 1.13.[159,93]

Barnett and his coworkers [95] conclude that there is no significant back diffusion of inulin in the renal tubules of premature infants, because a constant clearance of inulin may be maintained in the presence of wide variations in water reabsorption and the mannitol/inulin clearance ratio is the same (0.883 ± 0.07) as in adults (0.90 ± 0.07).

The limitations of the infant kidney present a liability that can only be offset by judicious restraint in the administration of salt, of saline infusions, and of a high protein diet. Human milk is low in salt, and the relative proportion of protein and fat are such that a large fraction of the total calories are supplied by the latter, thus conserving water from the requirement of urea excretion Conversely, the kidney cannot do much to compensate for increased water loss in fever, vomiting, or diarrhea. Against any factor tending to expand or contract the body fluids, the infant has but a narrow margin of renal functional defense.

CHAPTER XVII

Comparative Physiology of the Kidney

TELEOSTOMI (BONY FISHES)

From the data of paleontology and comparative anatomy it has been propounded [1390 1406, 1923, 1924, 1926, 1931] that the protovertebrates were evolved in the fresh-water rivers of the Cambrian or Ordovician Period, and that the glomerulus represents an adaptation added to the primitive nephrostomatous tubule permitting the excretion of large quantities of water at the expense of energy supplied by the heart. All those fishes which have had a continuous fresh-water history retain well-developed glomeruli; through the Devonian air-breathing fishes (Crossopterygii) the glomerular kidney was transmitted to the Amphibia and their descendants, the reptiles, birds, and mammals. With the exception of the Elasmobranchii, those fishes which one time or another have invaded the sea and made it their permanent home have reversed the environmental osmotic gradient, the higher osmotic pressure of sea water tending to draw water from the body through the gills, oral membranes, and skin The capacity to elaborate a hypertonic urine was not developed until the evolution of the birds and mammals, and in the marine fishes the urine is isotonic with the blood Apart from a very limited quantity of water formed by metabolism, they must replace any water lost through the skin and gills and obtain additional water for urine formation from the sea They do this by drinking sea water, absorbing the sodium chloride and water (magnesium and sulphate are poorly absorbed) from the gut, and excreting the sodium chloride through the

gills, leaving osmotically free water in the body. This circuitous process requires that practically all the sodium in the ingested sea water be excreted by the gills against an osmotic pressure gradient represented by the difference between that of the blood ($\Delta = -0.6$ to $0.8°$ C.) and of sea water itself ($\Delta = -1.86°$ C.), a process which requires a considerable expenditure of energy for each liter of urine formed.* Consequently, where in fresh-water fishes the urine flow is abundant and the filtration rate relatively high, in marine fishes the urine flow is minimal and the filtration rate correspondingly reduced. No longer an advantageous adaptation, the glomeruli in the marine fishes have undergone marked reduction in size and capillarity, and in many forms have disappeared entirely, leading to the formation of the aglomerular kidney. In the daddy sculpin (*Myoxocephalus scorpius*) the glomeruli degenerate during the life of the individual and large (and old) fishes are sometimes entirely aglomerular, excreting no trace of ferrocyanide or inulin (Forster, pers. com.).[839]

The few data available on fresh-water fishes indicate urine flows of 200 to 400 cc/day per kg.[1919, 1923] It is probable that there is little tubular reabsorption of water, and that the filtration rate is correspondingly high. Burgess, Harvey, and Marshall[294] have shown that in the fresh-water catfish (*Ameiurus nebulosus*) ADH has no effect on the rate of urine excretion.

In the marine fishes the urine flow is quite low (2 to 5 cc/day per kg.) and the filtration rate correspondingly reduced. Variations in urine flow are related to and probably regulated by variations in filtration rate.

For reasons not clear, when marine teleosts are kept overly long in captivity and traumatized by nets, live-cars, etc., they develop marked diuresis, with a corresponding increase in filtration rate.[837, 1923] Chloride, normally absent from the urine, is now excreted in increasing amounts along with large quantities of magnesium and sulphate, indicating that the diuresis is a result of increased ingestion of sea water. The sequence of events seems to reflect a breakdown of the defense of the organism against environmental dehydration, or what Graffin called 'osmotic

* The nature of the cells that [illegible] subject of debate. The writer ag[illegible] spiratory epithelium of the gill [illegible] while Keys and Willmer[1118] and [illegible] function to special cells resembling mucous cells. Copeland, however, suggests that these 'chloride' cells are probably concerned only with anion transfer; if such is the case, the transfer of base (chiefly sodium) from blood to sea water must be attributed to the general respiratory epithelium, though how base could be transferred without anion is not clear.

strain.' It is of some interest that normally the urine may be supersaturated with $MgHPO_4 \cdot 3H_2O$, which crystallizes massively on withdrawing the urine from the bladder.[1623]

Clarke[388] found that the xylose * U/P ratio in the sculpin, *Myoxocephalus octodecimspinosus*, tends to remain constant at about 4.0 with progressive diuresis until the urine flow reaches relatively high values, when the U/P ratio falls toward or to 1.0. The normal filtration rate is of the order of magnitude of 14 cc/day per kg., the urine flow about 3 cc. Under conditions of osmotic strain the filtration rate increases to 100 cc/day per kg. It appears that glomerular activity is physiologically reduced in the sculpin by some inhibitory mechanism to a level considerably below the maximum. This may involve intermittent glomerular activity, as in the frog.

ELASMOBRANCHII (SHARKS, RAYS, SKATES, AND CHIMERAE)

The elasmobranch fishes took up life in salt water earlier than and independently of the invasion of the sea by the bony fishes. Although many elasmobranchs reinvade and breed in fresh water (the Chimerae are an exception), the Sub-order appears to have had a continuous marine history from the time of its evolution. As noted in the discussion of the excretion of urea (p. 79), this substance is actively reabsorbed by the renal tubules in all the elasmobranchs, and the concentration in the blood is thereby raised to some 2000 to 2500 mg/100 cc. This 'physiological uremia' increases the osmotic pressure of the blood to a point where small quantities of water can be absorbed osmotically from sea water through the gills and oral membranes, and thus liberates the organism from the task of separating water from sea water by oral ingestion.[1926 1931] The glomeruli are large and well developed. Glomerular function is no disadvantage to the elasmobranchs and there is no evidence of glomerular degeneration among them, as in the marine teleosts.

The data on the control of glomerular activity in the marine elasmobranch fishes are meager, but they indicate that the rate of filtration and the urine flow are relatively large and constant (*c.*80 and 20 cc/day per kg, respectively). There appears to be no inhibition of renal activity in the normal animal, and as collapse occurs in 'sick fish' the filtration rate progressively decreases. It may be that, because of their physiological uremia and superior osmotic position, they have never been faced with the necessity for evolving mechanisms for reducing glomerular activity.[1406]

* Clarke[389] subsequently showed that the xylose/inulin clearance ratio in the sculpin averaged 0.81 (0.70 to 0.95).

Clarke[390] found that theophylline and salyrgan do not produce diuresis in the dogfish. Phlorizin produces moderate diuresis, probably in consequence of the osmotic activity of the glucose in the urine. Adrenalin in large doses induces diuresis and blocks the tubular reabsorption of urea, causing in 1 experiment a 55-fold increase in the urea clearance and a change in urine flow from 16 to 75 cc/day per kg.

Dogfish transferred from undiluted to diluted sea water (70 per cent) showed a progressive increase in urine flow; the U/P ratio of inulin remained remarkably constant, the inulin clearance rising in proportion to the urine flow. One fish, which in sea water had a filtration rate of 90 cc. and a urine flow of 20 cc/day per kg, showed in the second 12 hr. period in 70 per cent sea water a filtration rate of 272 cc. and a urine flow of 61 cc.[390]

In the fresh-water sawfish, *Pristis microdon*, which is identical with the marine species, the urine flow ranges from 150 to 460 (average 250) cc/day per kg.[1926] The filtration rate is unknown, but it is clear that glomerular activity and the filtration of water increase under conditions of hydration.

AMPHIBIA

The Amphibia have had a continuous fresh-water history since their evolution in the Devonian-Carboniferous periods. No marine amphibian, and none living under arid terrestrial conditions, is known, and extant forms, even the land toads, cannot survive water deprivation for long. The glomeruli are large and the capillary tree elaborate and free of invasive tissue. Again, the antidiuretic hormone has no effect on the reabsorption of water by the tubules,[394] and variations in urine flow are mediated almost entirely by variations in the filtration rate.

Forster[874] has shown that in the bullfrog, *Rana catesbiana*, the urine flow is almost a linear function of the filtration rate: the average filtration rate at a urine flow of 1 cc/hr per kg is 3.5 cc/hr per kg., rising to an average of 20 * at a urine flow of 15. By following glucose Tm, Forster[874] demonstrated that the increase in filtration rate involves the recruitment of inactive glomeruli, conforming with the classical observations of Richards and Schmidt[1718] that the glomeruli in the frog are not all active and that glomerular activity can be increased by expansion of blood volume and other means (injection of urea, glucose, sodium sulphate, caffeine, small doses of pituitrin, and section of the sympathetic nerves), and reduced by adrenalin, large doses of pituitrin, or

* These figures were obtained in fall and winter frogs. There appears to be a seasonal variation, for in spring frogs Forster[877] reports filtration rates up to 50 cc/hr per kg.

stimulation of the vasoconstrictor nerves, observations which have been repeatedly confirmed by others.[28,156,593,1709,2186,2187] Bieter[156] has described a short capillary loop in the common frog (*Rana pipiens*) which acts as a shunt, permitting blood to flow across the glomerulus without extensive exposure in the longer capillaries. Forster[677] finds that in the bullfrog with the renal-portal circulation intact the filtration fraction is 6 per cent, when the renal-portal circulation is excluded, this figure is 12 to 15 per cent. The diodrast clearance with the renal-portal circulation intact averages 700 cc., without the renal-portal circulation, 350 cc/hr. per kg.

REPTILES

The reptiles were evolved from an amphibian stock in the arid Pennsylvanian-Permian periods which followed the Carboniferous. They are adapted to living away from water and most of them can survive considerable periods of aridity. Burgess, Harvey, and Marshall[294] found *that pitressin in small doses markedly reduces the filtration rate (xylose* clearance) but obtained no indication that it increases water reabsorption by the tubules.

Friedlich, Holman, and Forster[698] have shown that in the fresh-water turtle, *Psuedemys elegans*, the filtration rate varies with the urine flow. There is no tubular excretion of creatinine, but xylose is reabsorbed to the extent of about 10 per cent. High endogenous glucose plasma levels are attained during experimental manipulation, and lead to glucosuria. *After phlorizination, the reabsorption of glucose is blocked but the per*meability of the tubules is increased, permitting the reabsorption of glucose, xylose, and creatinine (relative to inulin) to the extent of about 15 per cent.

Marshall[1394] found that in phlorizinized iguanas (*Iguana iguana*) the glucose U/P ratio averaged 3.2 and the uric acid U/P ratio 51.4, demonstrating the tubular excretion of the latter. (In the phlorizinized chicken these ratios averaged 12 and 136.4.)

Urea is absent from the blood and urine of the alligator (Alligator mississipiensis), the chief non-protein nitrogenous constituents of both being ammonia, which has an average concentration in whole blood of 61 mg/100 cc. The urine is invariably alkaline (pH 7.18 to 8.02) and rich in bicarbonate (77.6 to 125 mEq/liter), and in fasting animals contains no more than a trace of chloride and very little sodium.[437]

Shannon (pers. com.) obtained inulin U/P ratios of 5.44 to 11.37 (most of them between 5.0 and 7.0) in this species at urine flows of 0.005 to 0.087 cc/min. (3 kg. animal). It is apparent that changes in hydration

are accompanied by changes in filtration rate, as in other cold-blooded animals.

CHICKEN

In the birds, evolved from a primitive reptilian stock, the thin limb of the loop of Henle first makes its appearance in some but not all nephrons, and for the first time the antidiuretic hormone accelerates the tubular reabsorption of water, though large doses (0 5 unit/kg.) also reduce the filtration rate, as in the alligator, though not to the same extent.[294]

Glomerular development is, however, poor The glomeruli are small and heavily invaded by inert tissue, the glomerular tuft sometimes being reduced to a few short capillaries. No aglomerular bird is known, but even the chicken is not far from that state. Functional study of the marine birds, which subsist for long periods (up to 9 months) in the open sea without access to fresh water, might reveal that glomerular function has diminished to close to zero This degeneration of glomeruli is undoubtedly related to the uric acid habitus which is so strikingly developed among this Class and the arid-living reptiles (ch. v).

In the chicken, the massed data of Pitts [1628] and Shannon [1818] show only a slight upward drift of the inulin clearance with urine flows from 0.4 to 1 8 cc/min But, as Korr [1151] points out, these observations were made after the peak and on the descending limb of water diuresis. Korr believes that during optimal hydration the filtration rate averages about 1 22 cc/min per kg , this figure dropping to 0 60 cc. during dehydration and rising to 2 19 cc. through the postdiuretic period But apparently variable reabsorption of water under the influence of ADH is important in diuresis, as in the mammals

Lambert [1194] obtained an average inulin clearance of 1.71 cc/min per kg He has confirmed the excretion of creatinine by the tubules in the chicken, demonstrated the excretion of uroselectan B (iopax), and showed that the administration of uroselectan B depresses the creatinine/inulin clearance ratio Lambert also finds that the filtration rate is decreased in vitamin B deficiency.

DESERT MAMMALS

So far as is known, most desert mammals cannot withstand dehydration much better than can man, the outstanding difference consisting of a better ability to conserve water.[307, 820 2128 2121] To this group belong the antelopes, camel, donkey, and several other herbivores. The rodents, like the desert reptiles and insects, seek cool places during the hot hours of the day instead of using their water for heat regulation. Notable

among the rodents are the kangaroo rats, *Dipodomys merriami* and *D spectabilis*, and Bailey's pocket mouse, *Perognathus baileyi*, studied by Howell and Gersh [1043] and by Schmidt-Nielsen and his colleagues.[1788, 1790, 1791, 1792] These rodents normally live on air-dried seeds and can survive for long periods and gain weight on a diet of dry grain or oatmeal which contains only 5 to 10 per cent free water and affords about 0.6 cc. of water for each gm of carbohydrate oxidized. Temperatures above 35° C. are quickly fatal, but in the burrows a foot or so underground the daytime temperature never exceeds 35° C., and averages about 28° C. These animals have to be taught to drink free water, and while some of them will eat succulent food, *P. baileyi* disdains it and will not eat fresh watermelon. There is no water-storage mechanism in the body, but the kidney elaborates a remarkably concentrated urine In *Dipodomys merriami* the electrolytes, as measured by electrical conductivity, may reach 914 mEq (not chloride, for there is a very low chloride intake), which, as sodium chloride, would have a freezing point of −2.8° C.* and a simultaneous urea concentration of 14 per cent (Δ = *c*.4.22° C.). The average urine figures in *D spectabilis* are 702 mEq. of electrolyte (Δ = *c*.2 2) and 7.8 per cent urea (Δ = 3.4° C.), and in *P. baileyi* (disdaining fresh watermelon in preference to dry grain), 923 mEq of electrolyte (Δ = *c* 2 7° C) and 12 per cent urea (Δ = 3.66° C). Howell and Gersh [1043] report a sample of *D. mohavensis* urine with a urea content of 19.7 per cent These authors suggest that the collecting tubules play an important role in the reabsorption of water in this species. Schmidt-Nielsen *et al.*[1791] report that the highest urea figure in their data (22 1 per cent) occurred simultaneously with the highest electrolyte concentration (1180 mEq); the writer estimates the osmotic pressure of this urine to be 5.68 osmolar (Δ = −10.4° C.), which would give an osmotic U/P ratio of about 17, as compared with a maximal ratio of 4.2 in man. Under the same dietary conditions the white rat (*Rattus norvegicus var. alb.*) loses 52 per cent of its body weight and dies in 15 to 21 days, apparently chiefly because it cannot concentrate the urine to the same degree. The desert rodents cannot endure a high protein diet (pure soy bean), presumably because of the low water/urea ratio in metabolism [1791]

When fed barley dried at 105° C. and containing about 10 per cent sodium chloride, *P. baileyi* survived only 2 to 17 (average 7) days. On the second day on this diet the urine had an electrolyte content of 1220

* In calculating Δ, we take the activity coefficient of NaCl as 1.7, not as 2 0 as Schmidt-Nielsen *et al.* do. Even our estimate is probably high for so concentrated a solution.

mEq (908 mEq. of chloride) and a urea content of 12.5 per cent. The first figure is the highest concentration of electrolyte recorded in the urine of any animal, and is more than twice as concentrated as sea water (585 mEq.). (Adolph[30] gives the maximal concentration of chloride as 600 mEq. for the white rat, 370 mEq. for man, 330 mEq. for the dog, and 320 mEq. for the goat.) *D. merriami* can survive on a diet with a sodium content far below the minimum required by the domestic albino rat, and can survive slightly longer on a diet containing excessive amounts of sodium or potassium. Under both conditions the albino rat shows marked renal injury[1821] *D. merriami*, ordinarily with no taste for water, will take fluid if fed on a high protein diet (soy beans), under which condition it passes into negative water balance because of the large quantity of urea requiring excretion. On such a diet it will drink even sea water, and, at least over a period of a few weeks, does just as well as when drinking fresh water, with no change in plasma concentration of total electrolytes.

MARINE MAMMALS

The marine mammals are, of course, all descendants of terrestrial, fresh-water drinking forms, and it was necessary that adaptation liberate them from dependency on fresh water before the sea could become their permanent habitat.*

Irving, Fisher, and McIntosh[1081] inferred from chloride analyses of urine and fecal material removed from young anesthetized seals that these animals did not drink sea water, water for urine formation being derived from the food. They estimate that out of the 1000 gm. of water made available by 1250 gm of herring (1000 calories), 200 gm. would be required for evaporation from the lungs and for feces. The remaining 800 cc. would be available for renal excretion.

Smith[1977] showed that the rate of urine formation in the fasting harbor seal, *Phoca vitulina*, is normally low, ranging from 0.06 to 0.1 cc/min. in a 40 lb. animal After a meal of herring the rate increased to a maximum of 1 cc/min, maximal diuresis being reached 4 to 7 hr after the meal, the urine flow thereafter decreasing to low levels again. Thus urine excretion increases as water becomes available from the ingested food and falls again to oliguric levels during fasting. Urea is the predom-

* The Eskimos are aware that seals do not drink fresh water, and they con-

[illegible]

tul a hunter

inant nitrogenous substance, along with ammonia, creatinine, and creatine (apparently of exogenous origin). From the composition of the urine and rectal contents it was concluded that the animal does not ingest sea water while fasting, and that no more than traces of sea water are taken in with the food. A seal will frequently swallow large herring under water; apparently the esophagus closes firmly about the morsel of food and any sea water present in the mouth or taken into the esophagus is ejected backward into the oral cavity.

The composition of the urine is in no way remarkable except for the degree of osmotic concentration. The quantity of sulphate in the urine is not excessive (less than 1.85 mM/gm. of nitrogen), the chloride content is that to be expected on a fish diet, and only small quantities of magnesium are excreted. The osmotic pressure ranges from $\Delta = -1.365$ to $-3.988°$ C., the lowest values being observed in the fasting, oliguric state when energy is supplied largely by the oxidation of carbohydrate and fat and when the loads of urea and sodium chloride claiming excretion are minimal. The maximal osmotic pressure does not coincide with the maximal rate of urine formation but at intermediate values of the latter, indicating that it is not solely the osmotic load in the urine that determines the rate of urine formation. The highest osmotic pressure recorded represents an osmotic U/P gradient of about 5.7, as compared with 17 in the kangaroo rat and 4.2 in man.

It seems probable that the evidence on the seal can be generalized to include all marine mammals Even in the whalebone Cetacea, which subsist upon plankton, the urine is no more concentrated than in the seal. The 'comb' of the whalebone whales is adapted to filter microscopic organisms out of the water in such a manner that the material deposited can be licked off by the tongue, which probably 'dries' it by compressing it into a compact bolus before deglutition.

Fetcher [639] subsequently arrived at the conclusion that the seal does not drink sea water from analyses of the total solid content of the urine, but he believed that the conclusion could not be extended to the whalebone whale and other mammals that live on invertebrates. No evidence that such mammals do drink sea water is given, however. Fetcher and Fetcher [640] have shown that the dolphin absorbs more salt than water after the oral administration of 0.5 M sodium chloride.

Hiatt and Hiatt [995] have shown that the postprandial diuresis in the seal is accompanied by a marked increase in the filtration rate, this value increasing from 0.2 cc/min. per gm. of kidney during fasting to 1 cc/min. after a meal of herring, maximal renal function being reached in a few hours. The filtration fraction tends to remain constant, and T_{mG} does

not decrease during fasting oliguria, indicating that the decrease in renal function is not attributable to complete cessation of activity in some glomeruli,* but is shared fairly uniformly by all glomeruli. Hiatt and Hiatt concluded that the effective stimulus to the increased filtration rate and renal blood flow in the fed animal is not available water but probably is associated with the metabolism of the ingested protein.

Irving and his collaborators[1065] have shown that the seal, like other diving mammals, can survive considerable periods of asphyxia during diving by a co-ordinated mechanism which involves respiratory inhibition and maintenance of arterial blood pressure despite marked vagal bradycardia. It is demonstrated in the beaver that during this asphyxial reflex the blood flow to the muscles is decreased and that to the brain increased. Bradley and Bing[225] found that the asphyxial reflex in the seal can be elicited by submerging the animal's head under water, or more simply by holding the nostrils closed with a towel or funnel. They have demonstrated that, during the asphyxial reflex, the filtration rate and renal plasma flow are markedly decreased, the filtration fraction remaining nearly constant. A considerable quantity of blood is thus diverted from the kidneys and made available for circulation to the brain or elsewhere Atropine blocks the reflex bradycardia but does not block the renal ischemia. Bradley and Bing have shown that, as in man and the dog, pyrogenic inulin produces renal hyperemia, increasing the renal plasma flow from the average control value of 1 03 cc/min per gm. KW to 3 27 The hyperemic phase is preceded by a marked vasoconstrictor phase A single dose of amidopyrine (1 3 gm.) blocked the febrile reaction without blocking the renal hyperemia with moderate doses of pyrogen, but with larger doses of pyrogen the body temperature rose to 107° F and the animal died within an hour.

RAT †

The development of a technique for the collection of blood and urine in the rat has presented numerous difficulties. All investigators have used a single urine collection period Some have used a terminal blood sample from single animals or pooled samples obtained from several animals, while others have drawn tail blood in the middle of the urine

* This also excludes a non-glucose reabsorbing shunt.

† The writer does not have much more confidence in the white rat as an experimental animal for comparison with man than he does in the rabbit. It should be noted that the Wistar strain, for example, comes from the King A albino strain established by Helen Dean King at the Wistar Institute in 1904, and has been bred successively for 139 generations. Although in recent years it has been cross-bred rather than inbred, the net biological effect of selection

inant nitrogenous substance, along with ammonia, creatinine, and creatine (apparently of exogenous origin). From the composition of the urine and rectal contents it was concluded that the animal does not ingest sea water while fasting, and that no more than traces of sea water are taken in with the food A seal will frequently swallow large herring under water; apparently the esophagus closes firmly about the morsel of food and any sea water present in the mouth or taken into the esophagus is ejected backward into the oral cavity.

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TABLE X

Renal Clearance Data in Rats

(All values are expressed per 100 gm body weight.)

Filtration rate cc/min.	Effective plasma flow cc/min.	Filtration fraction	Tm_{PAH} mg/min.	Tm_D mg iodine per min.	Authors
0.27 ± 0.06	1.33	0.20		0.142	Friedman, S. M., *et al.*[718]
0.35	2.02	0.17		0.126	Dicker *et al.*[814]
0.347 ± 0.043	2.22 ± 0.28	0.17 ± 0.037		0.132 ± 0.0185	Dicker *et al.*[816]
0.60 ± 0.031	2.66	0.23		0.183 ± 0.0135	Braun-Mendenez *et al.*[847]
0.66 ± 0.028	2.50	0.24			Friedman, M.[708]
0.65 ± 0.019	4.14	0.16	0.18 ± 0.005		Friedman, S. M., *et al.*[709]
0.915 *†	2.63				Lippman[1364]
1.49 *‡	3.38				
0.55 ± 0.085 ‡			0.327 ± 0.016		Corcoran *et al.*[419]
0.61 ± 0.016 *			0.29 ± 0.0056		Corcoran *et al.*[419]
0.43 §					Dicker[813]
0.76 ‖					
0.73 *					Lotspeich[1374]
0.82 *					Boss *et al.*[216]
0.58	1.89	0.31		0.117	Watschinger *et al.*[1151]

* Creatinine
† 'Tail cutting' method
‡ 'Undisturbed' method
§ 18 per cent casein diet
‖ 25 per cent casein diet

collection period, or at the beginning and at the end. Some have used whole blood and some have used plasma. Some have ligated the penis, some have catheterized the bladder and some have expressed the urine with pressure. The use of terminal blood is open to the obvious errors of extrapolation, particularly with diodrast and PAH, while the collection of blood before or during the clearance period runs the risk of reflex excitation of the renal vasoconstrictor paths. In addition to technical difficulties, Dicker [510, 513] has shown that below a certain minimal protein intake in the diet (which itself influences the filtration rate, as in the dog) the inulin clearance increases with urine flow. (In these determinations Dicker used the intramuscular injection of inulin and terminal blood samples.)

The results obtained by various investigators have been summarized in table x. S M Friedman and Livingstone [718] administered diodrast subcutaneously in 4 cc. of 2 per cent sodium sulphate solution, inulin subcutaneously in saline. No water was given orally; the penis was ligated and urine expelled by pressure and a midperiod blood was drawn under ether anesthesia In the calculation of Tm_D, FW was taken as 0.62. The authors give the derived data $C_D/Tm_D = 9.3$, $C_{IN}/C_D = 0.20$. C_{IN} and C_D were independent of urine flow.

Dicker and Heller [514] administered diodrast and inulin subcutaneously in saline, and gave 50 cc/kg. of water orally; urine was expelled by pressure and a terminal blood sample was used. The inulin clearance was constant at plasma inulin levels ranging from 5 to 314 mg/100 cc. of serum, and this and the diodrast clearance were constant at urine flows ranging from 0.0035 to 1.030 cc/min. per 100 gm. BW. The average figures from 104 simultaneous clearances on 35 male rats were: inulin clearance, 0.351 cc., diodrast clearance 2.023 cc., Tm_D 0.126 mg. of iodine per 100 gm. BW. FW was taken as 0.62 after Friedman and Livingstone.

Dicker [510] and Dicker and Heller, [514, 516] using the same technique, report for 134 male rats (mean weight 176.5 gm.): inulin clearance 0.347 ± 0.043, diodrast clearance 2.22 ± 0.281 cc., Tm_D 0.132 ± 0.185 mg. of iodine per 100 gm. BW, filtration fraction 0.17 ± 0.037.

Braun-Menendez and Chiodi [247] administered inulin and diodrast

within the strain for rapidity of maturation, size of litters, docility, etc., has not been evaluated

Had a sibling pair of *H. sapiens* been selected on a similar basis and inbred or narrowly cross-bred for 139 generations (at 25 years to a generation, from 1525 B.C.) few students of physiology would expect them to react to stresses in a manner comparable to *H. sapiens* or *Canis familiaris*, both of which are generally represented in physiological investigations by mongrel individuals.

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0.35	2 02	0 17		0 126	Dicker *et al.*[814]
0 347 ± 0 043	2 22 ± 0 28	0 17 ± 0 037		0 132 ± 0 0185	Dicker *et al.*[810]
0 60 ± 0 031	2 66	0 23		0 183 ± 0 0135	Braun-Mendenez *et al*[817]
0.66 ± 0 028	2 50	0 24			Friedman, M.[708]
0 65 ± 0 019	4 14	0 16	0 18 ± 0 005		Friedman, S. M, *et al.*[720]
0.915 *†	2 63				Lippman[1944]
1.49 *‡	3 38				
0.55 ± 0.085 ‡			0 327 ± 0 016		Corcoran *et al.*[493]
0.61 ± 0 016 *			0 29 ± 0 0056		Corcoran *et al.*[410]
0 43 §					Dicker[812]
0 76 ‖					
0.73 *					Lotspeich[17 4]
0 82 *					Boss *et al.*[214]
0 58	1 89	0.31		0 117	Watschinger *et al.*[2161]

* Creatinine
† 'Tail cutting' method
‡ 'Undisturbed' method
§ 18 per cent casein diet
‖ 25 per cent casein diet

subcutaneously, the former in 3 cc. of saline, and 50 cc/kg of water orally; urine was expelled by pressure and a terminal blood sample was used No statement is made in regard to FW. The inulin and diodrast clearance and Tm_D are all reported to increase with urine flow: $C_{IN} = 14.81V + 0.0916$ and $C_D = 64.56V + 0.661$, where C_{IN}, C_D and V are expressed as cc/min. per 100 sq. cm Tm_D averaged 0.1016 ± 0 041 mg of iodine per 100 sq. cm. The filtration fraction averaged 0.226 (0.117 to 0 502). C_{IN} as given in table x was recalculated by Corcoran *et al.*[410] and Tm_D was recalculated by the writer.

M Friedman[702] gave creatinine orally in 3 doses of water (10, 5, and 5 cc) at 1 hr. intervals, and inulin and PAH subcutaneously; urine was expelled by pressure and pre- and post-clearance blood samples were collected from the tail under ether anesthesia; whole blood was used for creatinine determination, plasma for inulin, the creatinine data being used without correction. C_{IN} in table x was recalculated by Corcoran *et al.* and C_{PAH} by the writer. C_{CR}, C_{IN}, and C_{PAH} increased with urine flow, but regression equations are not given. At equal urine flows, the creatinine and inulin clearances in separate determinations averaged about the same, while in 41 simultaneous determinations the creatinine/inulin clearance ratio averaged 1 023 (0.72 to 1.73); in 12 simultaneous determinations the inulin/PAH clearance ratio averaged 0.24 (0 19 to 0 39), and in 35 simultaneous determinations the creatinine/PAH clearance ratio averaged 0.22 (0.14 to 0.38). The creatinine clearance was independent of the plasma concentration of creatinine between 1.0 and 26 6 mg/100 cc Friedman concluded that there is no tubular excretion of creatinine in this species.*

S. M. Friedman, Polley and C. L. Friedman[720] gave inulin intraperitoneally in 3 cc of saline, and PAH subcutaneously in 2 per cent sodium sulphate; urine was expelled by pressure and a terminal blood sample was collected by heart puncture. FW is taken as 0.8. C_{IN} and Tm_{PAH} in table x were recalculated by Corcoran *et al.* and C_{PAH} by the writer. The data as given by the authors are $C_{IN} = 0\ 36 \pm 0.04$ and $C_{PAH} = 2.31 \pm 0\ 18$ cc., $Tm_{PAH} = 0\ 10 \pm 0.01$ mg. per 100 sq. cm.; $C_{IN}/C_{PAH} = 0\ 157 \pm 0\ 023$; $C_{PAH}/Tm_{PAH} = 22\ 1 \pm 2.0$. They note that the C_{PAH}/Tm_{PAH} ratio is higher than in any other species yet reported, apparently because of the high value of C_{PAH}. No influence of urine flow on clearances was recorded.

* M Friedman's technique for obtaining renal clearances in rats has been criticized by Dicker and Heller,[617] to which criticism Friedman has replied[703] In view of Lippman's[1242] results, it cannot yet be accepted with confidence that there is no tubular excretion of exogenous creatinine in the rat.

Lippman [1243] gave creatinine subcutaneously in 10 cc. of water. Urine was expelled by pressure, and blood drawn from the tail before the clearance period and collected by exsanguination at the end. Chemical determinations were made on pooled samples of plasma and urine. The influence of urine volume was not studied. He found that the endogenous creatinine chromogen clearance averaged 0 237 cc. per 100 gm. BW, in contrast to 0 915 cc for the exogenous clearance. The change in clearance value occurs in the plasma creatinine concentration range of 1 to 2 mg/100 cc. The exogenous creatinine clearance averaged 1.43 cc. per gm. KW.

Corcoran, Masson, Reuting, and Page [410] gave PAH-mannitol-creatinine solution subcutaneously in 2 doses of 1.7 cc/100 gm BW. Heparinized rats were restrained in a holder and catheterized under ether anesthesia, the bladder being rendered insensitive with intracaine Blood was collected from the tail after warming the animal at 45° C. for 3 min. before and at the end of the clearance period. They suggest that the greater variability in the data of Corcoran and Page [422] as compared with their present data presumably reflects the effects of light anesthesia and inaccuracy due to single blood sampling. They present data on 10 animals showing that, in successive determinations over a period of 4 weeks or more, C_{CR} and Tm_{PAH} remain fairly constant.

Lippman,[1244] in a second paper, compares clearances by two methods. In 'undisturbed' animals, which under ether have received 10 cc. of saline subcutaneously containing creatinine, urea, and PAH, urine was collected by having the animal sniff ether, and only a terminal blood sample was used The 'tail cutting' method is that given above. The 'undisturbed' clearance method gave average PAH, creatinine, and urea clearances of 3 38, 1.49, and 0 703 cc/100 gm. BW; by the 'tail cutting' method these figures were 2.63, 0 915, and 0 458. The 'undisturbed' clearance method gave PAH, creatinine, and urea clearances of 4.82, 1 06, and 2.27 cc/gm. KW; for the 'tail cutting' method these figures were 4 17, 0 669, and 1 43 cc. There was no relation between clearances and urine flow in either method. Recognizing that no method of clearance determination in the rat is entirely satisfactory, he recommends the 'tail cutting' method because the variability is less, and despite the depression in clearances involved in this technique.

Elsewhere Lippman [1246] asserts that, using the 'tail cutting' method, the subcutaneous administration of PAH in 10 cc. of saline depresses the simultaneous inulin clearance, the extent of this depression increasing in proportion to P_{PAH} Conversely, the subcutaneous administration of inulin depresses the PAH clearance roughly in proportion to the

value of P_{IN}. He believes that, with available preparations, C_{IN} and C_{PAH} or Tm_{PAH} cannot be determined simultaneously in this species.

Dicker, Heller, and Hewer [519] found that, in rats fed on a protein-deficient vegetable diet and suffering from severe hypoproteinemia, the filtration rate varies with the urine flow, contrary to Dicker and Heller's [514] observations on rats receiving a standard diet; while Dicker [510] has shown that saline trebles the filtration rate on a standard diet. Dicker [512] has re-examined this urine flow problem in greater detail. Using the technique of Dicker and Heller,[514] he administered 1 cc/100 gm. BW of inulin-saline solution intramuscularly and gave 50 cc/kg. of water *per os*. Urine was expelled by pressure and a terminal blood sample was used. The young animals were reared to the required weight (101 to 150 gm.) on the stipulated diet, and a series of adult rats were fed on the different diets for 9 weeks They conclude that the plasma protein concentration of the adult rat varies with the amount of protein in the diet, and that in young and in adult rats with a plasma protein concentration below 6.8 gm/100 cc. the filtration rate increases with the urine flow. In adult rats fed on a diet containing 18 per cent or more of casein, and having a plasma protein concentration above 6.8 gm/100 cc., the filtration rate is independent of urine flow. High plasma protein concentrations are accompanied by higher mean rates of filtration.

Boss, Birnie, and Gaunt,[216] in a preliminary note, give an average creatinine clearance of 0.820 cc/min. per 100 gm. BW.

Watschinger and Werner,[2151] using Dicker and Heller's technique, report average inulin and diodrast clearances to be 0.58 and 1.89 cc/min. per 100 gm. BW, with a filtration fraction of 0 117.

Lotspeich,[1274] using the technique of S. M Friedman *et al*,[720] reports an average creatinine clearance of 0 513 cc/min. per 100 sq. m.

In view of all the variables—diet, saline, hydration, tail cutting, anesthesia (even 'light' as the authors say), the alleged effect of PAH on the inulin clearance and *vice versa*, and extrapolation of plasma concentrations and possible differences in strains—it is surprising that five groups of investigators arrive at about the same figure for the filtration rate (0.60 to 0.76 cc/min. per 100 gm BW). The comparison of 'undisturbed' and 'tail cutting' methods by Lippman must await clarification of some of the other variables, and until that time figures for the effective renal plasma flow in the rat must remain uncertain.

Taking the best figure for the filtration rate from table x as 0.6 cc/100 gm. BW, 8 0 gm. of kidney per kg (*vide infra*) gives 0.75 cc/min. per gm. KW. (Lippman [1243, 1244] gives 1.49 and 1.43 cc., but his figures are out of line with all others, as shown in table x.) The corresponding best

figure for renal plasma flow appears to be 2.2 cc/100 gm. BW or 2 75 cc/gm KW, and for Tm_{PAH} 0.30 mg/100 gm BW and 0.375 mg/gm. KW. Taking the surface area on a 200 gm rat as 0.0301 sq. m., the data above give a filtration rate of 39 9, plasma flow of 146 cc., and Tm_{PAH} of 20 mg/sq. m.

The whole blood urea clearance in the rat is reported by Farr and Smadel [827] to be 10 9 ± 3 1 cc., and by Herrin [930] as 19 3 cc/sq m The average figure obtained by MacKay and Roulston [1334] is 0.33 per gm. KW (using decapsulated kidneys).

RABBIT

Hayman and Starr [842] concluded by intravital staining that the number of active glomeruli in the anesthetized (urethane and sometimes ether) rabbit varies widely, and may be increased to a maximal extent by caffeine and salt solution and reduced by adrenalin and other agencies which induce vasoconstriction No correlation was observed between the number of active glomeruli and the volume of the kidney The complexity of such a study is revealed by the following functional studies, and by the discussion of the juxtamedullary circulation in chapter xxv.

Kaplan and Smith [1000] reported that in the rabbit the inulin and creatinine clearances (which are identical in this species) increase with urine flow These investigators administered water by stomach and kept their animals restrained on an animal board. They found that, if water in quantities greater than 3 successive doses of 40 cc/kg at 30 min. intervals is given, the animal is apt to develop oliguria which is frequently followed by convulsions and death (water intoxication?) Reviewing their own data and the observations of others on the injection of dyes, etc , they concluded that in this species, contrary to the situation in the dog and man, hydration is accompanied by a marked increase in glomerular activity.

W W Smith,[1367] however, found no relation between the filtration rate or diodrast clearance and the urine flow at values of the latter ranging from 0 4 to 7 0 cc/min. per 100 gm KW (0 072 to 1.26 cc/min per kg BW) Mannitol diuresis increased the filtration rate by 20 to 50 per cent and the diodrast clearance by 15 to 75 per cent, but this fact has little bearing on the question of glomerular activity in relation to hydration *per se* No explanation of the discrepancy between her results and those of Kaplan and Smith was apparent, as she noted. The average inulin clearance in 8 rabbits was 0 66 cc. (0.38 to 0.94) and the average diodrast clearance 2.50 cc/gm. KW (1 23 to 3 78), and the average filtration fraction 0.273 (0.19 to 0.40).

An apparent relation between filtration rate and urine flow in the rabbit was, however, again recorded by Dicker and Heller,[514] Wilkinson and McCance,[2221] and Forster.[678] The latter found that fair urine flows could be obtained in rabbits by feeding them an abundance of cabbage and other green food for 24 hr. before an experiment. Under these conditions, he found no change in filtration rate or renal plasma flow dur-

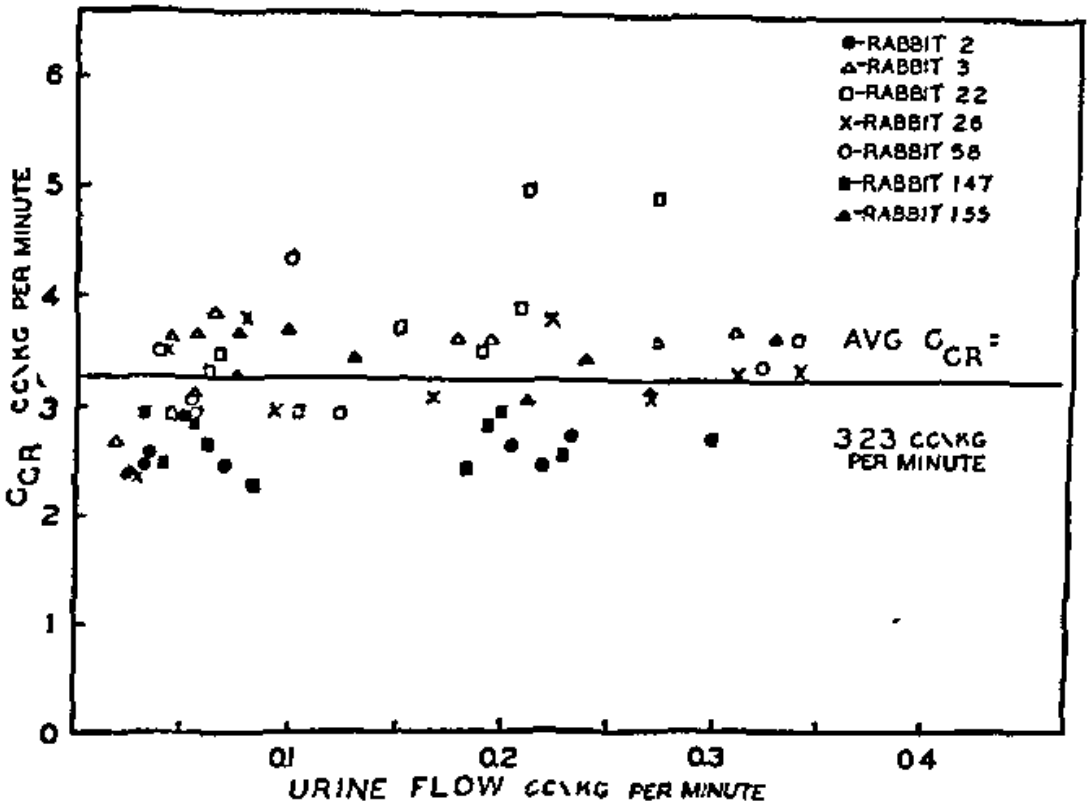

FIGURE 97. Relationship between filtration rate and urine flow in undisturbed rabbits. *A 16-fold increase in urine flow during water diuresis is possible without significant variation in the filtration rate* (Brod and Sirota[265])

ing moderate variations in urine flow, and no differences were observed in renal function as between the prone and sitting positions However, *the administration of water (50 cc/kg) to rabbits* that had been kept on a diet of dry food led to an increase in filtration rate (14 3 to 20 2 cc/min.) and renal plasma flow (70 to 104 cc/min) in the next hour. Glucose Tm also increased from 37 to 64 mg., parallel with the increase in filtration rate, and Forster concluded that the increased renal function was accompanied by recruitment of inactive glomeruli. *Introduction* of mannitol into the infusion had no effect on filtration rate, renal plasma flow, or glucose Tm, although it greatly increased the urine flow by reducing the reabsorption of water. Theophylline similarly had no

effect on filtration rate and renal plasma flow, though it produced diuresis Forster inferred that not all the glomeruli in the rabbit are active and that water diuresis increases glomerular activity, mannitol and *theophylline having no such effect.*

Brod and Sirota,[261] on re-examining the problem, concluded that the results obtained by Kaplan and Smith were attributable to renal vasoconstriction induced by excitement when water was administered by stomach tube, this vasoconstriction is of course accompanied by oliguria and as the vasoconstriction recedes the filtration rate and urine flow increase together. The presumed relationship between filtration rate and urine flow observed by Kaplan and Smith and others they considered to be a fortuitous consequence of autonomic excitation and renal ischemia If precautions were used to prevent autonomic excitation, it was found that the filtration rate remained unchanged despite a sixteenfold variation in urine flow between 0 02 to 0.32 cc/min per kg (*c.*0.1 to 1 5 cc/min. per sq. m.), and regardless whether the urine flow was increasing or decreasing (fig. 97). Although the strength of the stimulus required to produce emotional disturbance varied with the excitability of individual animals, fright or painful stimuli of sufficient intensity always caused antidiuresis by renal vasoconstriction, as a result of which there was a marked reduction in renal plasma flow and filtration rate with little change in the creatinine U/P ratio. During this renal ischemia, water intoxication with convulsions and rapid death was easily obtained and many animals died in convulsions *

Renal denervation did not appreciably reduce the renal response to the usual excitatory stimuli. Adrenalin in large doses (400 μ) had the same action as emotional excitation, smaller doses (50 to 120 μ) failing to have consistent effects. Dibenamine (5 mg/kg. intravenously) did not block the vasoconstriction in 3 animals with renal nerves intact, but in 3 out of 4 animals with denervated kidneys the renal plasma flow and filtration rate increased immediately after its administration. Pitressin in physiological doses (2 milliunits intravenously) produced antidiuresis with little effect on the renal plasma flow.

Brod and Sirota conclude with W W. Smith that in the rabbit, as in the dog and man, uncomplicated water diuresis is mediated by changes in the tubular reabsorption of water with little or no contribution from changing glomerular activity. This conclusion is supported by the report of Wills and Main [227] that in rabbits anesthetized with nembutal the filtration rate does not vary with urine flow

Dicker and Heller [116] have replied to Brod and Sirota that the condi-

* This might be called psychosomatic death

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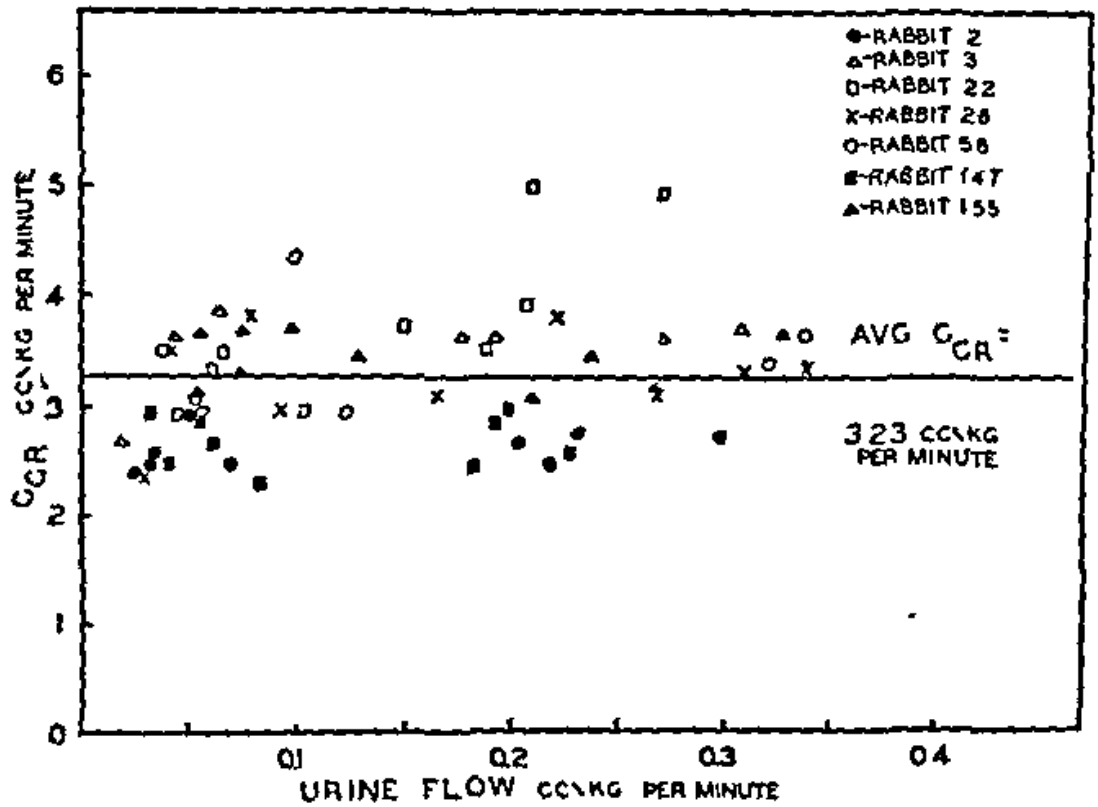

FIGURE 97. Relationship between filtration rate and urine flow in undisturbed rabbits. A 16-fold increase in urine flow during water diuresis is possible without significant variation in the filtration rate. (Brod and Sirota [384])

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Dicker and Heller[818] have replied to Brod and Sirota that [illegible]

* This might be called psychosomatic death.

tions of their original experiments were not such as to be interpreted in this manner. Reanalysis of their data leads them to affirm that in the adult rabbit changes in glomerular activity play an important role in regulating water excretion during hydration as well as changes in tubular reabsorption They point out that such glomerular participation has been demonstrated not only in the Amphibia but in young and newborn rats and newborn guinea pigs, and was indicated by earlier studies on human infants. The implication is that the kidney of the adult rabbit behaves toward hydration in an infantile manner.

Thus there is at the moment wide disagreement on renal function in this species Until the issues have been resolved, we shall tentatively accept Brod and Sirota's average data. Their averages for 69 clearances (each an average of 3 periods) on 21 male rabbits, including control observations, were: creatinine 3.12 ± 0 058 cc., PAH clearance 18.2 ± 3.4 cc/kg , filtration fraction = 0.17. Taking the KW/BW ratio as 6.4 (*vide infra*), these data give 0.488 and 2 85 cc/gm. KW. W. W. Smith's[190] direct ratios of 0.66 and 2 5 cc/min. per gm. KW (as used in table xiv, p 568) are probably more reliable calculations (although both used Carworth Farms white rabbits), since they do not involve an indirect calculation. On a surface area basis, Brod and Sirota's figures give a filtration rate of 50 2 ± 9.2 cc. and a renal plasma flow of 296 ± 59 cc/min per sq. m.

In anesthetized (urethane) rabbits, Laake[1188] obtained much lower values: his average filtration rate was 24.4 ± 6.5 cc/sq. m (10.38 to 38 86) In unanesthetized rabbits the average diodrast clearance was 194.3 ± 3 8 cc. (187 to 202) and Tm_D averaged 33 45 ± 2 13 mg. of iodine per sq m. Tm_G averaged 78.71 ± 13 4 mg/sq. m. (Self-depression of the diodrast clearance begins at a plasma concentration of about 25 mg. of iodine per 100 cc.)

The whole blood urea clearance in the rabbit during urea diuresis averages 0 294 cc/gm. kidney, or 25.5 cc/sq. m.[2048]

The creatinine clearance/Tm_G ratio is about 0 27.[1952]

The writer has heard pathologists and others comment that the rabbit gives highly variable results in certain experimental procedures He adheres to the prejudice that the species possesses a degree of autonomic instability which leads to intense sympathetic discharge under circumstances in which the dog and man remain quiescent.

CAT

Wirz[2249] records the inulin clearance in unanesthetized cats as ranging from 33 to 94 cc/sq. m. (SA = 10 $BW^{0.66}$) with a mean value of about

50 cc The filtration rate appears to be independent of the urine flow. In this species the inulin U/P ratio may reach values as high as 700.

DOG

Corcoran and Page[411] report 77 observations on 7 female dogs maintained on 1 daily feeding of dog biscuit (Purina Dog Chow) and weekly supplements of lean meat. All observations were made after 18 hr. of fasting and at least 36 hr. after meat had been fed. No water was administered to produce diuresis, but sodium sulphate (2 per cent) was added to the priming and sustaining infusion in order to insure moderate urine flows One would say that the dogs were 'basal' and unhydrated. The mean data were: filtration rate 69 ± 14 8, renal plasma flow (from phenol red) 250 ± 61, whole blood 460 ± 118 cc/min per sq m, the last two figures being corrected for E_{PR} and the whole blood figure agreeing with that calculated from E_{IN} by 1 per cent The mean filtration fraction was 0.297. The figure for renal plasma flow agrees well with that cited by Houck,[1037] but the filtration rate is lower Corcoran, Taylor, and Page[432] give the average ratios RBF/Tm_D = 23.78 ± 3 65, C_{IN}/Tm_D = 2.68 ± 0 402 The last ratio is close to that in women, 2 81 ± 0 535, and identical with that in men, 2 63 ± 0.344, while the first is slightly less than the value in man estimated on a hematocrit of 0 46 (26 3 female and 25 9 male). (This similarity in these ratios is surprising, in view of the fact that the dog kidney does not excrete as much PAH per unit of filtrate as does man Thus the Tm_{PAH}/C_F ratio in the dog is 0 236, whereas in man this ratio is 0.624 (table XII). The data indicate a deficit in the dog relative to PAH excretion not applicable to diodrast.

Houck has tabulated the creatinine and PAH clearances in 75 mongrel female dogs maintained on a mongrel diet of dog biscuit, hospital scraps, etc, the data representing observations collected in the writer's laboratory by various investigators over a period of several years These data are illustrated in figures 98 and 99 against the 70 per cent ellipse * with corresponding data in man (fig 100) The average figure for filtration rate is 84 4 ± 19 1 and for renal plasma flow 266 ± 66 cc/min per sq m, or 4 29 ± 1 01 and 13 51 ± 3 26 cc/min per kg. BW The average filtration fraction is 0 317. Allowing for 90 per cent extraction of PAH, the true filtration fraction would be 0.285. It is of interest that Medes and Herrick,[1428] using the thermostromuhr method, obtained a filtration fraction of 0 31, and Van Slyke *et al.*,[2092] using E_{CR} and E_{IN} in the explanted kidney with the other kidney removed, obtained 19 9

* See footnote page 547 for the derivation of this ellipse.

and 22.3 per cent. The last two figures are unquestionably lowered by renal hyperemia associated with hypertrophy of the remaining kidney.

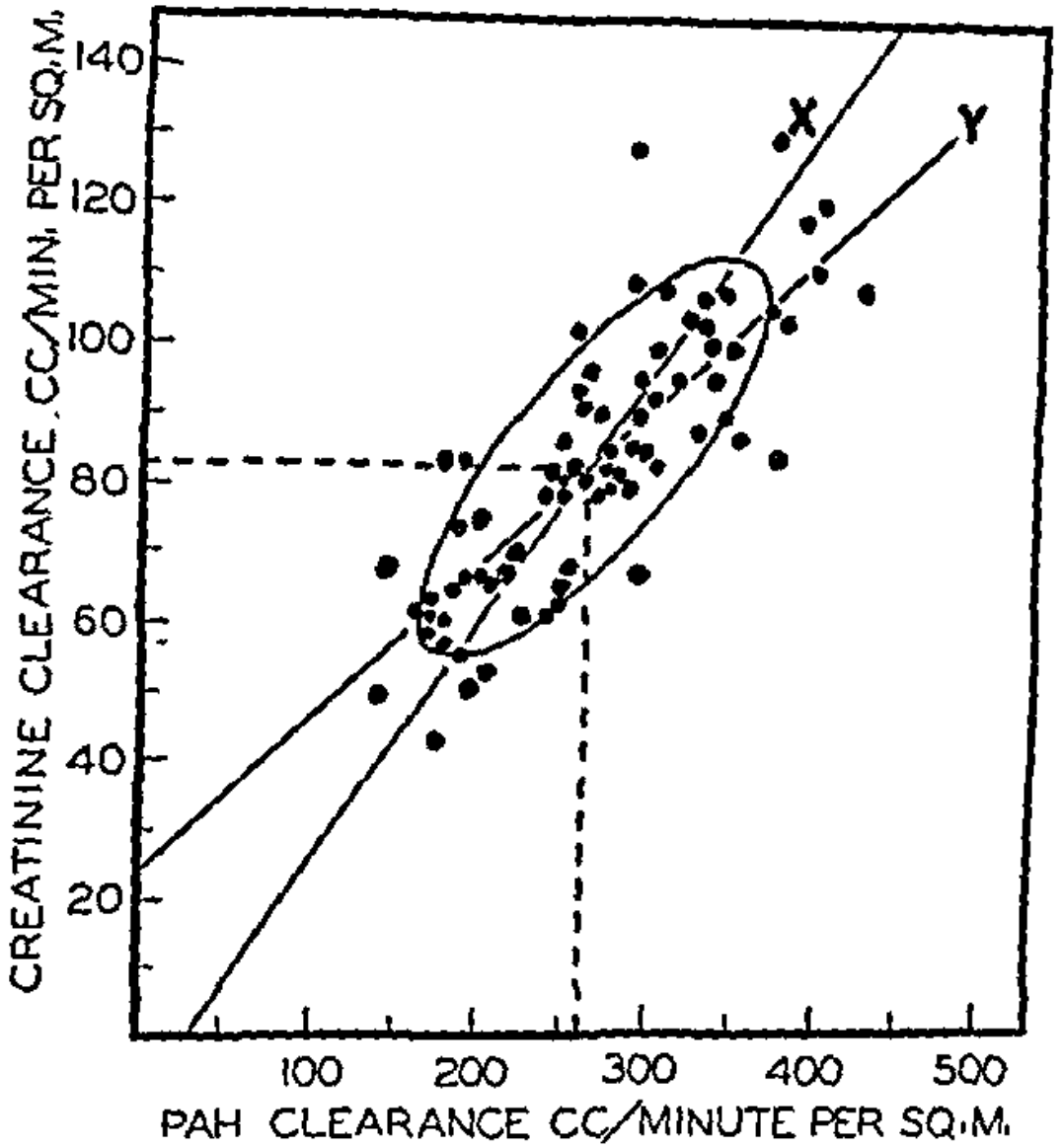


FIGURE 98. Comparison of filtration rate and renal plasma flow as related to body surface area in 75 normal dogs. Each point represents a different dog and is the average of from 1 to 19 clearance observations. Dashed lines are the means for each function. The ellipse delimits the area of a scatter diagram within which 70 per cent of the points may be expected to fall by chance alone, assuming normal bivariant distribution. X represents the regression of renal plasma flow on filtration rate (i e the variation along the x axis for a given value of y) and *vice versa*. (Houck [1021])

Stamler, Katz, and Rodbard,[1977] in their study of normotensive and hypertensive dogs, report for 6 normal male dogs an average filtration rate of 104 ± 15 (86 to 127), a PAH clearance of 295 ± 58 cc/*min.* per sq. m. (range 86 to 127), with a filtration fraction of 0.353. These values

are slightly higher than those of Houck on female d[illegible]
ences are not statistically significant. The average [illegible]
perhaps significantly higher.

Moustgaard [1183] on 118 dogs records the average [illegible]
0 64 ± 12 and the plasma flow as 1.91 cc/min per [illegible]
tion fraction as 0 335

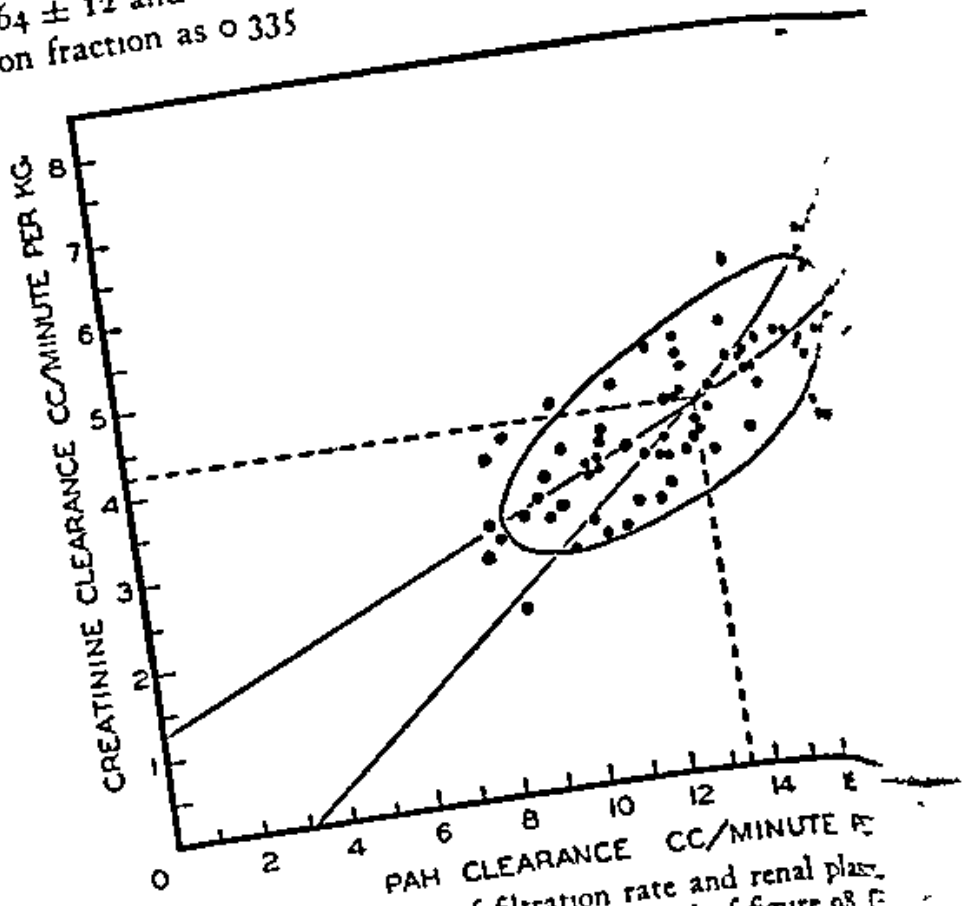


FIGURE 99 Comparison of filtration rate and renal plas[illegible]
body weight in 75 normal dogs See legend of figure 98 [illegible]

Taking the KW/BW ratio as 7 1 gm/kg. (*vide in*[illegible]
for filtration rate and renal plasma flow would be
cc/gm of kidney Both figures are in remarkable ag[illegible]
of Moustgaard, and we have used the average of t[illegible]

The writer has assembled the data on T_{mPAH} re[illegible]
Gaudino and Levitt,[750] Handley, Telford, and La
Sigafoos, and La Forge,[901] and White, Heinbecker
other data kindly supplied by Drs. Richardson, Sch[illegible]
to supply the statistics given in table XI.* It may b[illegible]

* The writer is indebted to Mr Charles Crowder, Jr
and for many others cited in subsequent pages

TABLE XI

Tm_{PAH} *in Female Dogs*

	Number	Mean	σ	$100\,\sigma/m$
C_{CR}/kg.	67	3.84 cc.		
C_{PAH}/kg.	51	12.5 cc.		
Tm_{PAH}/kg.	83	0.97 mg.	0.091	9.4
C_{CR}/Tm_{PAH}	67	4.24	0.66	15.6
C_{PAH}/Tm_{PAH}	51	12.9	2.43	18.8

efficient of variation of Tm_{PAH} per kg. (9.4 per cent) is the smallest one on record in renal physiology.

Houck's [1037] average ratio of sq. m. surface area to kg. body weight for 75 dogs is 19.7, which would give Tm_{PAH} = 19.1 mg/min. per sq. m., while this value would be 0.137 mg/gm. KW.

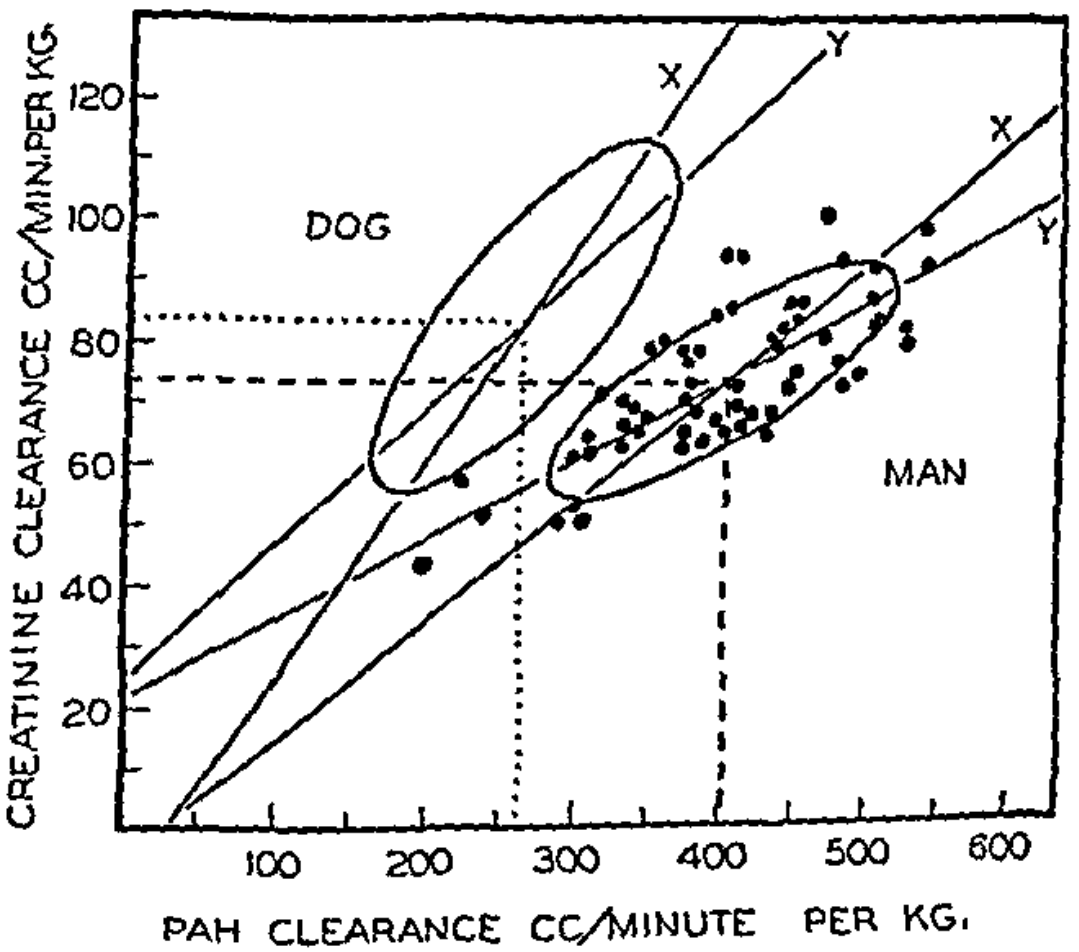


FIGURE 100. Comparison of filtration rate and renal plasma flow, as related to body surface area, in dog and man. The ellipse and lines of regression for the dog are transposed from figure 99 *Those for man were calculated from the* data of Smith *et al.*[1021] (Houck [1037])

TABLE XII

Statistics on Filtration Rate and Renal Blood Flow in Man

Clearances, Tm_D, and Tm_{PAH} corrected to 1 73 sq m. and Tm_D and Tm_{PAH} corrected to 98 5° F. rectal temperature. Figures in parentheses show the number of subjects studied. No subject is counted twice Figures in bold-face type show weighted averages.

MALES

Method	Age range years	Plasma clearances: Inulin cc/min.	Plasma clearances: PAH cc/min	Renal blood flow cc/min	Tm_{PAH} mg/min	Filtration fraction × 100	C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	Authors
CI	16–49	(34) 124 1±25 8	(30) 654±163		(35) 79 8±16 7	(31) 19 2±3 5	(30) 8 44±2 45	(33) 1 6±0 44	Smith (see text)
CI	21–32		(9) 613±107						Chapman *et al* 153
CI		(8) 130±15 4	(8) 628±44 8		(8) 65 6±8 7				Brun *et al* 276
			(8) 603±84 4						Heller *et al* (see Chapman *et al*)
Weighted average					(43) 77 2		(30) 8 44	(33) 1 6	
							C_D/Tm_D	$C_{IN}Tm_D$	Smith & Smith *et al* 1931 1939
					Tm_D		(34) 14 0±2 16	(40) 2 63±0 344	Hogeman[1024]
			Diodrast						Shock *et al.* (pers. com., see text)
CI	16–60	(67) 131±21 5	(61) 697±136	(61) 1209±256	(40) 51 8±8 73	(61) 19 0±2 44			Findley *et al* 646
CI	20–50	(36) 124±13 3	(36) 449±40 1‡	(36) 853±63 9‡		(36) 27 6±0 5‡			Brun *et al* 276
CI	20–39	(18) 119±14 4	(18) 631±99 7		(18) 52 8±9 25				Foà *et al* 665
CI	–40	(17) 117	(17) 544	(17) 1010	(9) 40 1	(11) 20 5	(9) 13 6†	(9) 2 91†	Steinitz[1999]
CI	21–25	(10) 125±4 4	(10) 600±106		(10) 50 6±6 5	(10) 21 4±3 48	(10) 12 1±2 3	(10) 2 51±0 332	Friedman *et al* 714
CI	22–56	(7) 117		(7) 1060	(5) 40 2	(7) 18 2	(5) 16 2	(5) 3 08	Hilden[1001]
CI	19–41	(6) 128	(6) 688			(6) 18 6			Hilden[1000]
CI	22–50	(4) 124	(6) 761	(6) 1288		(4) 17 8			Foà *et al* 664
SC			(12) 617‡						Berger *et al* 128
SC	22–31		(5) 552‡						Josephson *et al* 1084
SC			(6) 566‡	(6) 987‡	(6) 39‡	(6) 15 0‡	(6) 15 9‡		
CI		(26) 126±17 1							
CI	18–45	(25) 140±32							
Weighted average		(258) 127	(179) 655	(91) 1166	(82) 49 9	(130) 19 3	(58) 13 8	(64) 2 7	

FEMALES									
		PAH			Tmpah		Cpah/Tmpah	Cin/Tmpah	
CI		(16) 108 8±13 5	(11) 592±153		(16) 77 2±10 8	(11) 19 4±3 9	(11) 7 85±1.46	(16) 1 43±0 20	Smith (see text)
Weighted average					(16) 77 2		(11) 7 85	(16) 1 43	
			Diodrast		Tmd		Cd/Tmd	Cin/Tmd	
CI	20–50	(20) 119±12 8	(20) 436±10‡	(20) 763±66 4‡	(14) 42 6±9 46	(20) 27 4±0 7‡	(14) 14 2±2 36	(14) 2 81±0 56	Hogeman[1024]
CI	16–55	(21) 117±15 6	(17) 594±102	(17) 982±184	(10) 44 2±4 83	(17) 20 2±3 1	(10) 14 3±2 54	(10) 2 69±0.412	Smith & Smith *et al* [illegible]
CI	19–27	(10) 118±13 9	(10) 628±100			(10) 18 9±1 74			Brun *et al* [illegible]
CI	25–40	(5) 126	(5) 669	(5) 986		(5) 19 0			Friedman *et al* [illegible]
CI			(9) 518	(9) 836					Chesley *et al* [illegible]
SC		(13) 127	(6) 619‡			(6) 19 9‡			Brun *et al* [illegible]
SC			(12) 608‡						Hilden[1001]
IM		(6) 114	(4) 609‡			(4) 19 0‡			Brun *et al* [illegible]
IM	19–30		(5) 595‡	(5) 940‡	(5) 36 0‡				Hilden[1000]
SC			(5) 566‡						Foà *et al* [illegible]
Weighted average		(91) 118	(57) 600	(31) 940	(29) 42 0	(43) 19 5	(24) 14 3	(24) 2 76	
MIXED SEXES									
		PAH			Tmpah		Cpah/Tmpah	Cin/Tmpah	
CI		(50) 116 5±28 1	(40) 640±164		(40) 78 9±13 2	(40) 18 2	(41) 8 28±2 2	(49) 1 54±0.4	Smith (see text)
CI		(32) 129±40	(35) 626±165			(32) 20 6±5 6			Merrill[1418]
SC		(6) 133	(6) 701	(6) 1165		(6) 19 1			Aas *et al* [2]
Weighted average		(13) 129*‡	(13) 538‡		(40) 78 9		(41) 8 28	(49) 1 54	Hamburger *et al* [illegible]
			Diodrast		Tmd		Cd/Tmd	Cin/Tmd	
CI	20–50	(56) 122±13 2	(56) 444±41 6‡			(56) 27 5±3 0‡			Hogeman[1024]
CI		(8) 120	(8) 537			(8) 23			Black *et al* [184]
CI	18–54	(5) 148	(4) 738		(4) 53 2	(4) 21 2			Talbott *et al* [illegible]
CI		(?) 128±20 2	(?) 674±128	(?) 1075±233	(?) 49 4±8 8	(?) 19±2 4	(?) 15 3±6 4	(?) 3 01±0 64	Corcoran *et al* [illegible]
CI	2–12	(?) 133±14 9	(?) 695±183		(?) 53±11	(?) 19±2			Galán *et al* [illegible]
SC		(15) 123‡							Ahlborg[illegible]
Weighted average		(157) 123	(93) 634	(6) 1165	(4) 53 2	(90) 19 7			

CI = constant intravenous infusion, SC = subcutaneous injection, IM = intramuscular injection.
* Mannitol.
† Not on same individuals.
‡ Omitted from weighted means

TABLE XII

Statistics on Filtration Rate and Renal Blood Flow in Man

Clearances, Tm_D, and Tm_{PAH} corrected to 1 73 sq m. and Tm_D and Tm_{PAH} corrected to 98 5° F. rectal temperature. Figures in parentheses show the number of subjects studied. No subject is counted twice. Figures in bold-face type show weighted averages.

MALES

Method	Age range years	Plasma clearances: Inulin cc/min	Plasma clearances: PAH cc/min	Renal blood flow cc/min	Tm_{PAH} mg/min	Filtration fraction × 100	C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	Authors
CI	16–49	(34) 124.1±25 8	(30) 654±163		(35) 79 8±16 7	(31) 19 2±3 5	(30) 8 44±2 45	(33) 1 6±0 44	Smith (see text)
CI	21–32		(9) 613±107						Chapman *et al* [352]
CI		(8) 130±15 4	(8) 628±44 8		(8) 65 0±8 7				Brun *et al* [278]
CI			(8) 603±84 4						Heller *et al* (see Chapman *et al*)
Weighted average					(43) 77 2		(30) 8 44	(33) 1 6	
			Diodrast		Tm$_D$		C_D/Tm_D	$C_{IN}Tm_D$	
CI	16–60	(67) 131±21 5	(61) 697±136	(61) 1209±256	(40) 51 8±8 73	(61) 19 0±2 44	(34) 14 0±2 16	(40) 2 63±0 344	Smith & Smith *et al* [1931 1939]
CI	20–50	(36) 124±13 3	(36) 449±40 1‡	(36) 853±63 9‡		(36) 27 6±0 5‡			Hogeman[1024]
CI	20–39	(18) 119±14 4	(18) 631±99 7		(18) 52 8±9 25				Shock *et al* (pers com, see text)
CI	-40	(17) 117	(17) 544	(17) 1010	(9) 40 1	(11) 20 5	(9) 13 6†	(9) 2 91†	Findley *et al* [648]
CI	21–25	(10) 125±4 4	(10) 600±106		(10) 50 6±6 5	(10) 21 4±3 48	(10) 12 1±2 3	(10) 2 51±0 332	Brun *et al* [278]
CI	22–56	(7) 117		(7) 1060	(5) 40 2	(7) 18 2	(5) 16.2	(5) 3 08	Foà *et al* [665]
CI	19–41	(6) 128	(6) 688			(6) 18 6			Steinitz[1959]
CI	22–50	(4) 124	(6) 761	(6) 1288		(4) 17 8			Friedman *et al* [714]
SC			(12) 617‡						Hilden[1001]
SC	22–31		(5) 552‡						Hilden [1000]
SC			(6) 566‡	(6) 987‡	(6) 39‡	(6) 15 0‡	(6) 15 9‡		Foà *et al* [664]
CI		(26) 126±17 1							Berger *et al* [128]
CI	18–45	(25) 140±32							Josephson *et al* [1088]
Weighted average		(258) 127	(179) 655	(91) 1166	(82) 49 9	(130) 19 3	(58) 13 8	(64) 2 7	

FEMALES										
					T_{mPAH}		C_{PAH}/T_{mPAH}	C_{IN}/T_{mPAH}	Smith (see text)
					(16) 77 2±10 8	(11) 19 4±3 9	(11) 7 85±1.46	(16) 1 43±0 20	
		PAH						(16) 1.43	
		(16) 108 8±13 5	(11) 592±153		(16) 77 2		(11) 7 85		
					T_{mD}		C_D/T_{mD}	C_{IN}/T_{mD}	Hogeman[1024]
CI			Diodrast			(20) 27 4±0 7‡			Smith & Smith *et al* [1031, 1032]
Weighted average			(20) 436±10‡	(20) 763±66 4‡	(14) 42 6±9 46	(17) 20 2±3 1	(14) 14 2±2 36	(14) 2 81±0 56	Brun *et al* [276]
			(17) 594±102	(17) 982±184	(10) 44 2±4 83	(10) 18 9±1 74	(10) 14 2±2 54	(10) 2 69±0 412	Friedman *et al* [714]
CI	20–50	(20) 119±12 8	(10) 628±100			(5) 19 0			Chesley *et al* [272]
CI	16–55	(21) 117±15 6	(5) 669	(5) 986					Brun *et al* [281]
CI	19–27	(10) 118±13 9	(9) 518	(9) 836		(6) 19 9‡			Hilden[1001]
CI	25–40	(5) 126	(6) 610‡						Brun *et al* [282]
CI			(12) 608‡			(4) 19 0‡			Hilden[1003]
SC		(13) 127	(4) 609‡		(5) 36 0‡				Foà *et al* [664]
SC			(5) 595‡	(5) 940‡					
IM		(6) 114	(5) 566‡		(29) 42 0	(43) 19 5	(24) 14 3	(24) 2 76	
IM	19–30			(31) 940					
SC									
Weighted average		(91) 118	(57) 600						
MIXED SEXES									
					T_{mPAH}		C_{PAH}/T_{mPAH}	C_{IN}/T_{mPAH}	Smith (see text)
					(40) 78 9±13 2	(40) 18 2	(41) 8 28±2 2	(49) 1 54±0 4	Merrill[1436]
		PAH				(32) 20 6±5 6			Aas *et al* [2]
						(6) 19 1			Hamburger *et al* [891]
		(50) 116 5±28 1	(40) 640±164						
		(32) 129±40	(35) 626±165	(6) 1165					
		(6) 133	(6) 701				(41) 8 28	(49) 1 54	
CI		(13) 129*‡	(13) 538‡		(40) 78 9				
CI							C_D/T_{mD}	C_{IN}/T_{mD}	Hogeman[1024]
SC					T_{mD}				Black *et al* [184]
Weighted average						(56) 27 5±3 0‡			Talbott *et al* [1043]
			Diodrast			(8) 23			Corcoran *et al* [432]
						(4) 21 2			Galán *et al* [736]
			(56) 444±41 6‡		(4) 53 2	(?) 19±2 4	(?) 15 3±6 4	(?) 3 01±0 64	Ahlborg[38]
CI	20–50	(56) 122±13 2	(8) 537		(?) 49.4±8 8	(?) 19±2			
CI		(8) 120	(4) 738	(?) 1075±233	(?) 53±11				
CI	18–54	(5) 148	(?) 674±128						
CI		(?) 128±20 2	(?) 695±183						
CI	2–12	(?) 133±14 9							
SC		(15) 123‡		(6) 1165	(4) 53 2	(90) 19 7			
Weighted average		(157) 123	(93) 634						

CI = constant intravenous infusion, SC = subcutaneous injection, IM = intramuscular injection.
* Mannitol
† Not on same individuals.
‡ Omitted from weighted means.

TABLE XII

Statistics on Filtration Rate and Renal Blood Flow in Man

Clearances, Tm_D, and Tm_{PAH} corrected to 1 73 sq. m. and Tm_D and Tm_{PAH} corrected to 98.5° F. rectal temperature. Figures in parentheses show the number of subjects studied. No subject is counted twice. Figures in bold-face type show weighted averages.

MALES

Method	Age range years	Plasma clearances: Inulin cc/min	Plasma clearances: PAH cc/min	Renal blood flow cc/min	Tm_{PAH} mg/min	Filtration fraction × 100	C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	Authors
CI	16–49	(34) 124 1±25 8	(30) 654±163		(35) 79 8±16 7	(31) 19 2±3 5	(30) 8 44±2 45	(33) 1 6±0 44	Smith (see text)
CI	21–32		(9) 613±107						Chapman *et al* [362]
CI		(8) 130±15 4	(8) 628±44 8		(8) 65 6±8 7				Brun *et al* [278]
CI			(8) 603±84 4						Heller *et al* (see Chapman *et al*)
Weighted average					(43) 77 2		(30) 8.44	(33) 1 6	
					Tm_D		C_D/Tm_D	C_{IN}/Tm_D	
			Diodrast						
CI	16–60	(67) 131±21 5	(61) 697±136	(61) 1209±256	(40) 51 8±8 73	(61) 19 0±2 44	(34) 14 0±2 16	(40) 2 63±0 344	Smith & Smith *et al* [1021, 1039]
CI	20–50	(36) 124±13 3	(36) 449±40 1‡	(36) 853±63 9‡		(36) 27 6±0 5‡			Hogeman[1024]
CI	20–39	(18) 119±14 4	(18) 631±99 7		(18) 52 8±9 25				Shock *et al* (pers com, see text)
CI	–40	(17) 117	(17) 544	(17) 1010	(9) 40 1	(11) 20 5	(9) 13 6†	(9) 2 91†	Findley *et al* [646]
CI	21–25	(10) 125±4 4	(10) 600±106		(10) 50 6±6 5	(10) 21 4±3 48	(10) 12 1±2 3	(10) 2 51±0 332	Brun *et al* [278]
CI	22–56	(7) 117		(7) 1060	(5) 40 2	(7) 18 2	(5) 16.2	(5) 3 08	Foà *et al* [665]
CI	19–41	(6) 128	(6) 688			(6) 18 6			Steinitz[1038]
CI	22–50	(4) 124	(6) 761	(6) 1288		(4) 17 8			Friedman *et al* [714]
SC			(12) 617‡						Hilden[1001]
SC	22–31		(5) 552‡						Hilden [1000]
SC			(6) 566‡	(6) 987‡	(6) 39‡	(6) 15 0‡	(6) 15 9‡		Foà *et al* [664]
CI		(26) 126±17 1							Berger *et al* [122]
CI	18–45	(25) 140±32							Josephson *et al* [1063]
Weighted average		(258) 127	(179) 655	(91) 1166	(82) 49 9	(130) 19 3	(58) 13 8	(64) 2 7	

Statistical Analysis of Renal Function

Statistical analyses of the filtration rate, renal plasma flow, and Tm_D have been recorded by numerous investigators and are summarized in table XII.

A limited number of data are available for the description of renal function relative to Tm_{PAH}. The writer has recalculated Tm_{PAH} of table 1 of Chasis *et al.*[362] and Bolomey *et al.*[207] with appropriate correction of Tm_{PAH} for the chemical error in the mannitol method,[84] and combined these with table 2 of Chasis *et al.*[362] and with 29 observations supplied by Michie and 8 observations supplied by Earle, to obtain the data for mixed and separate sexes given in table XII. From these data a 70 per cent ellipse * has been calculated for the mixed sexes, as shown in figures 101 and 102. The number of observations available for the separate sexes does not warrant a separate treatment of this ellipse.

The basic data for the reconstruction of these ellipses are given in the legend of figures 101 and 102. The number of observations

4 or more for Tm Technical errors as well as physiological changes, which might otherwise be overlooked, are thus frequently revealed

* The area on a scatter diagram within which we may theoretically expect 70 per cent of the observations to fall by chance alone is an ellipse formed by the equation

$$\chi^2 = \left(\frac{x^2}{\sigma_x^2} - \frac{2rxy}{\sigma_x\sigma_y} + \frac{y^2}{\sigma_y^2}\right)\frac{1}{1 - r^2},$$

[illegible]

above, x is the distance from mx along the x axis, y is the distance from my along the y axis, σ_x and σ_y are the standard deviations of the distribution in the x and y direction respectively, and r is the coefficient of correlation x is determined for various values of y by resolving the above equation in the quadratic.

$$x = \frac{-ay}{2} \pm \sqrt{\left(\frac{a^2}{4} - b\right)y^2 - c}$$

and writing

$$a = -\frac{2r\sigma_x}{\sigma_y}, \quad b = \frac{\sigma_x^2}{\sigma_y^2}, \quad c = -(1 - r^2)\chi^2\sigma_x^2$$

An ellipse on a scatter diagram within which 70 per cent of the observations may be expected to fall by chance corresponds roughly to a distance from -1σ to $+1\sigma$ on a linear scale for 1 variable (68 per cent of the observations).

The mean values of renal clearances at their peak levels in determinations extending over a 24 hr. period, as recorded by Sirota, Baldwin, and Villarreal,[1904] are lower than the short period clearance data recorded in table XII; in 16 male subjects the inulin clearance averaged 119 ± 23 cc., and in 10 male subjects the PAH clearance averaged 597 ± 124 cc. These subjects were allowed water *ad libitum* but were not hydrated prior to observation. The series is small, but perhaps indicates that the routine hydration used in short period clearance determination may increase both the filtration rate and renal plasma flow significantly.

Clearance Variation

Koepf, Hubbard, and Loomis [1145] record a statistical analysis of simultaneous inulin and diodrast clearances in 79 separate 15 min. test periods upon 19 subjects. The inulin clearance showed greater constancy than did the diodrast clearance, which the authors attribute to closer regulation of the filtration rate.

Davies and Shock [473] have made clearance determinations on each of 2 days, separated by 1 week to 1 year intervals, on 40 subjects ranging from 27 to 89 years of age. Older subjects showed less variation, both from period to period on the same day, and from day to day, than did younger ones They find evidence of a systematic decrease in measurements made in successive periods on the same day. (It has been the experience of investigators in the writer's laboratory that the filtration rate and renal plasma flow tend to drift downward in long tests, a phenomenon which has been loosely attributed to discomfort, restlessness, and fatigue on the part of the patient, though decreasing hydration may play a part) Measurements in successive collection periods on the same individual on the same day will group themselves around the average value with a standard deviation of the mean of 6.1 cc for C_{IN}, 33 cc. for C_D, and 2.9 mg. of iodine for Tm_D, all per $\overline{1.73}$ sq. m. The variation of an individual from day to day is significantly greater than the experimental (period to period) variation, as might be anticipated Davies and Shock suggest, because of the large individual day-to-day variation, that the number of collection periods in any one test makes only a moderate contribution to the total variance, and increasing the number of periods beyond 2 or 4 does not greatly reduce the error.*

[illegible] clearance technique [illegible] a high [illegible] writer would take the liberty to suggest that others who may [illegible] t of an equal competence would do well to rely on 3 periods for the filtration rate and

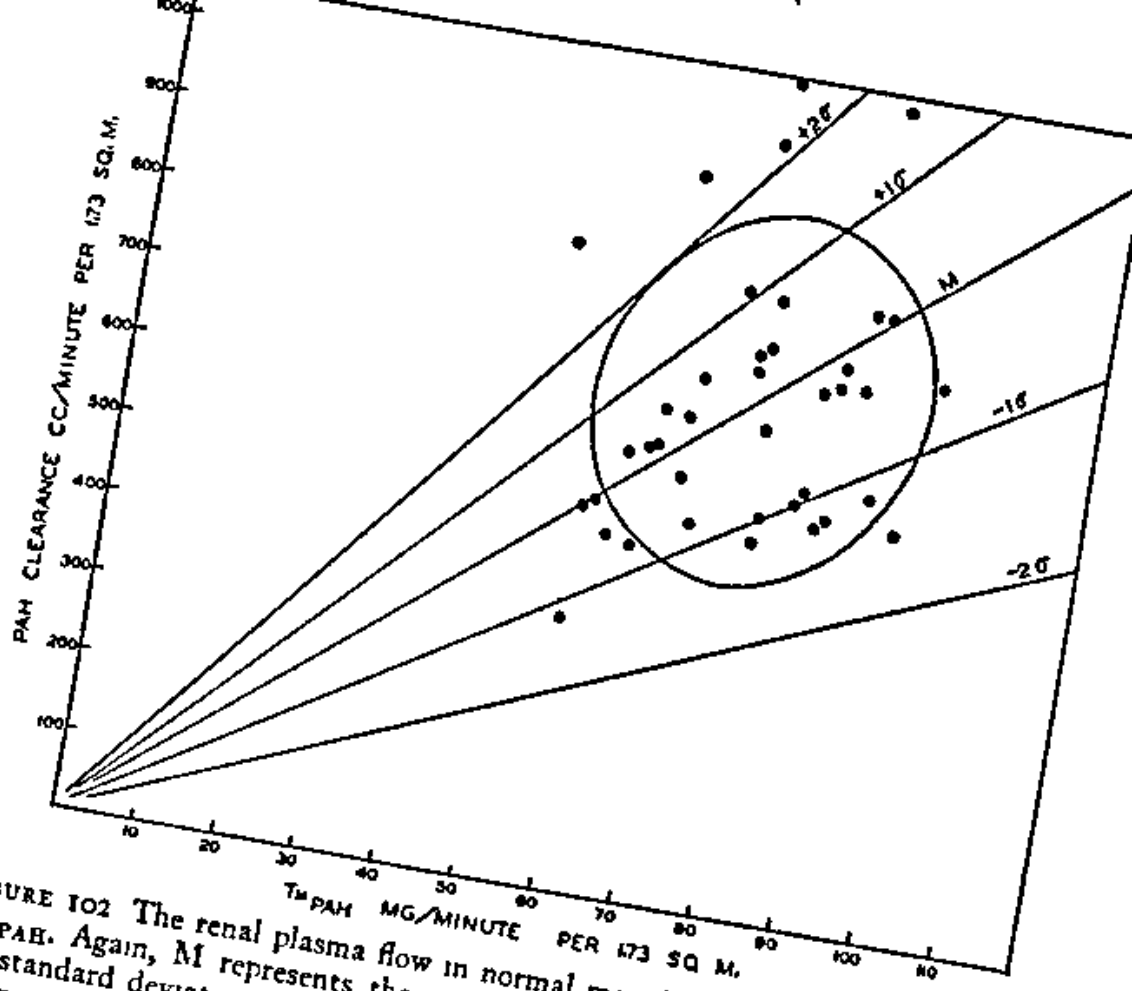


FIGURE 102 The renal plasma flow in normal man (mixed sexes) as related to Tm_{PAH}. Again, M represents the mean ratio C_{PAH}/Tm_{PAH}, ± multiples of the standard deviation The ellipse is calculated to contain 70 per cent of the observations (corresponding to $\pm\sigma$) and actually contains 80 per cent The basic data used are $C_{PAH} = 640 \pm 164$ and $Tm_{PAH} = 78.3 \pm 13.4$ (40 observations), $C_{PAH}/Tm_{PAH} = 8.15 \pm 2.0$ The derived data for plotting the ellipse are

C_{PAH}	Tm_{PAH}
407	75 9
415	80 9
440	72 5
465	86 9
490	66 [illegible]
540	89 4
590	63.6
610	92 1
640	61 3
690	95 7
740	58 7
790	97 9
815	57 6
840	98 7
865	57 4
873	99 0
	57.6
	99 0
	58 7
	97 9
	60 9
	95 4
	64 5
	93 3
	67 6
	90 0
	70 2
	84 9
	75.7
	81 2

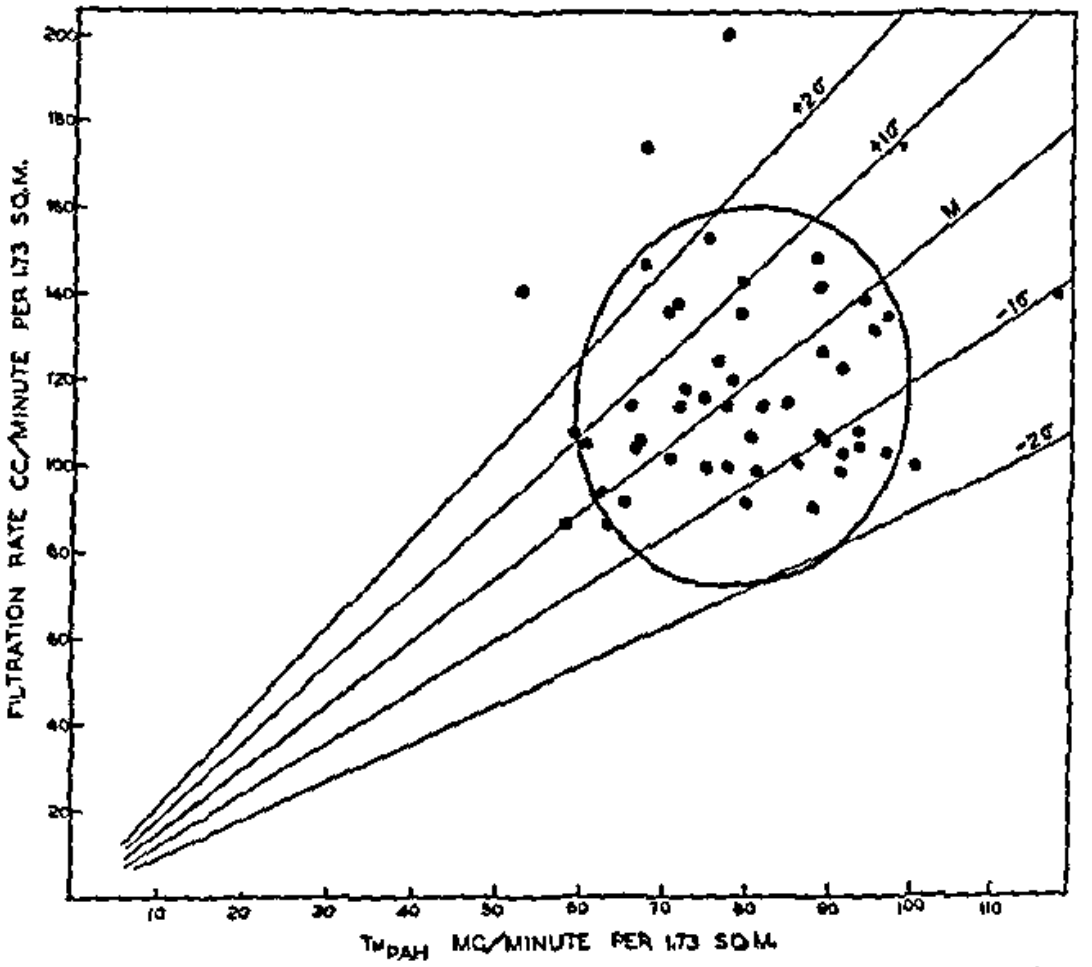


FIGURE 101. The filtration rate in normal man (mixed sexes) as related to Tm_{PAH}. M represents the mean ratio C_F/Tm_{PAH}, ± multiples of the standard deviation. The ellipse is calculated to contain 70 per cent of the observations (corresponding to $\pm\sigma$) and actually contains 84 per cent.

The 70 per cent ellipse is calculated by the equation given in the text. The basic data used are $C_F = 116.5 \pm 28.1$ and $Tm_{PAH} = 79.0 \pm 12.9$ mg (50 observations), $C_F/Tm_{PAH} = 1.5 \pm 0.3$

The derived data for plotting the ellipse are.

C_F	Tm_{PAH}	
72.8	77.6	
76.5	86.8	68.6
81.0	90.3	65.9
86.5	92.9	63.1
96.5	96.3	60.4
106.5	98.2	59.1
116.5	99.0	59.0
126.5	98.8	59.8
136.5	97.6	61.7
146.5	94.9	65.1
152.0	92.1	67.9
156.5	89.4	71.2
160.1	80.4	

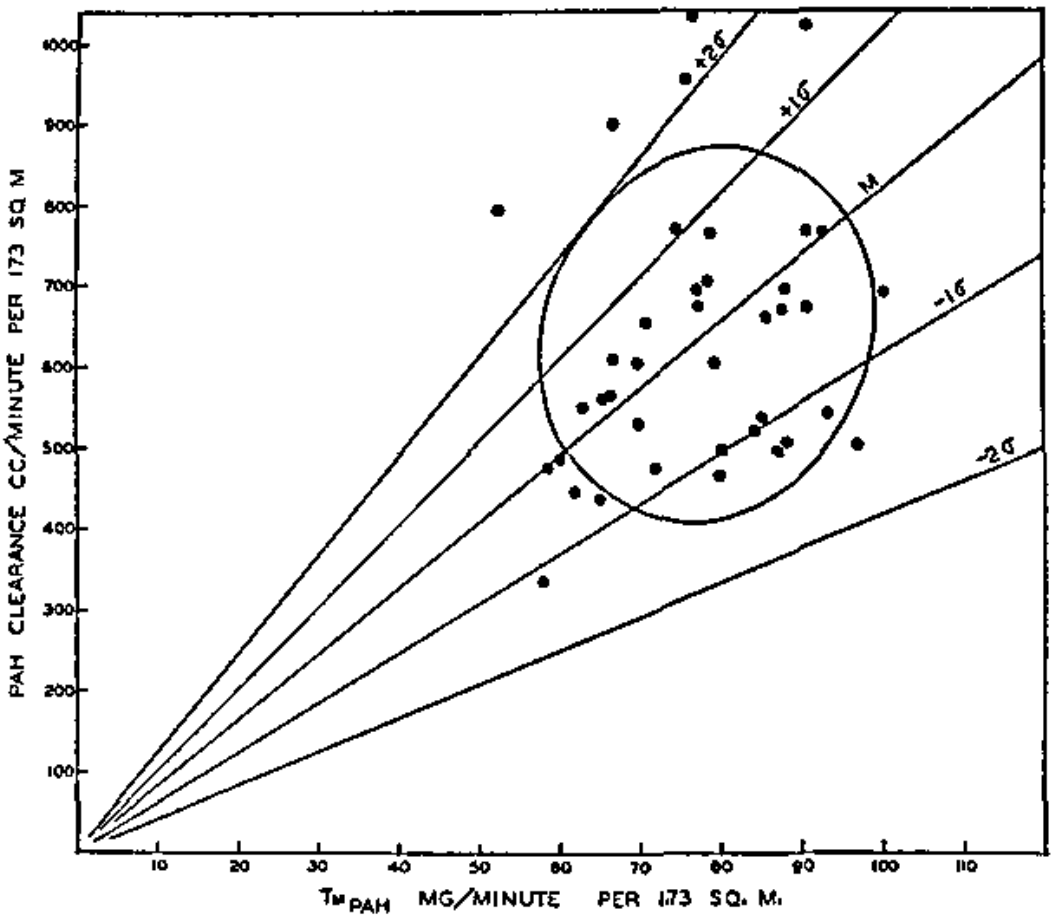


FIGURE 102 The renal plasma flow in normal man (mixed sexes) as related to Tm_{PAH} Again, M represents the mean ratio C_{PAH}/Tm_{PAH}, ± multiples of the standard deviation The ellipse is calculated to contain 70 per cent of the observations (corresponding to $\pm\sigma$) and actually contains 80 per cent.

The basic data used are $C_{PAH} = 640 \pm 164$ and $Tm_{PAH} = 78.3 \pm 13.4$ (40 observations), $C_{PAH}/Tm_{PAH} = 8.15 \pm 2.0$

The derived data for plotting the ellipse are:

C_{PAH}	Tm_{PAH}	
407	75.9	
415	80.9	72.5
440	86.9	66.7
465	89.4	63.6
490	92.1	61.3
540	95.7	58.7
590	97.9	57.6
610	98.7	57.4
640	99.0	57.6
690	99.0	58.7
740	97.9	60.9
790	95.4	64.5
815	93.3	67.6
840	90.0	70.2
865	84.9	75.7
873	81.2	

of Tm_{PAH} against C_{PAH} in the same patients is 40, of Tm_{PAH} against C_F is 50. The mean Tm_{PAH} in these two series is 78.9 mg., a figure not far different from the average of the means of the sexes treated separately (78.5 mg.) and consequently the figure 78.9 ± 13.2 has been entered in table XII as an appropriate mean for mixed sexes. The values of C_{PAH}/Tm_{PAH} and C_{IN}/Tm_{PAH} entered for the mixed sexes in table XII are the weighted means of the separate sex data.

It is of course to be expected that, as the number of observations on any physiological value increases, the mean and related parameters will shift. However, mere multiplication of the number of observations does not increase the accuracy of these parameters unless all observations are physiologically comparable. Thus the use of single injection methods is apt to lead to erroneously low results for both the filtration rate and renal plasma flow (ch. III), and such data have been excluded from the weighted mean.* These means have been calculated by multiplying each datum by the number of subjects and taking the mean of the whole. Where investigators have not reported the number of subjects studied, their average figure has also been omitted from the weighted mean.

Brun, Hilden, and Raaschou[276] record for 8 males C_{IN}/Tm_{PAH} = 2.01 ± 0.32, C_{IN}/C_{PAH} = 0.206 ± 0.0296, C_{PAH}/Tm_{PAH} = 9.49 ± 0.75, and Tm_{PAH}/Tm_D (mEq.) = 1.77. This last ratio (corrected) in the 10 normal subjects reported by Chasis *et al.*[362] averages 2.51 (range 1.87 to 3 12).

Body weights were not readily available in preparing the data in table XII, but a rough conversion to body weight basis can be made by assuming 60 kg weight in women and 70 kg. in men. Thus calculated, the filtration rate, renal plasma flow, and Tm_{PAH} average 1.81 cc., 9.35 cc., and 1.1. mg., respectively, in men, and 1 97 cc., 10 0 cc., and 1.28 mg. per kg. in women.

Sex Differences

Brun, Hilden, and Raaschou[275] note that in their data there is no sex difference in the diodrast clearance, a probable difference in the filtration rate, and a fairly positive difference in Tm_D. But the weighted av-

* The data of Hogeman on the diodrast clearance are so far out of line with other observations that these data and all derived calculations have also been omitted from the weighted mean.

erages in table XII indicate a significant difference in all three functions when compared on a surface-area basis. Taking the adult kidney weight as 313 gm. in men and 257 gm. in women (*vide infra*) the C_{IN}/KW, C_D/KW, Tm_D/KW, and Tm_{PAH}/KW ratios in men are 0.406, 2.09, 0.16, and 0.247; and in women, 0.46, 2.33, 0.163, and 0.30, suggesting that all functions are slightly higher in women per gm. KW. The data are too few to warrant any firm opinion, however.

The Fraction of the Cardiac Output Delivered to the Kidneys (Renal Fraction)

The renal blood flow is so large that it is a matter of considerable interest to know what fraction this comprises of the total cardiac output in health and disease. Numerous opinions, based on non-simultaneous data, have been expressed. One approach is to divide the average renal blood flow figure recorded by Smith, Goldring, Chasis, Ranges, and Bradley,[1939] of 1209 cc/min. per 1.73 sq. m., by the average cardiac output recorded by Cournand and his co-workers,[439] as determined by the direct Fick method, of 5.29 liter/min. per 1.73 sq. m., which yields the value of 22.9 per cent. Correction of this figure for a 90 per cent extraction of diodrast of PAH from the renal blood would raise the renal fraction to 25.3 per cent. This method of estimation is obviously uncertain, since average figures for renal blood flow and cardiac output vary with the size and composition of the population sample.

Bradley, working in the author's laboratory, endeavored to obtain simultaneous data on a number of subjects, determining the cardiac output by means of the ballistocardiograph; the renal fraction corrected for extraction ratio worked out in the range of 25 to 30 per cent. When it became clear that the ballistocardiographic method was not too reliable for such calculations, this approach was abandoned.

Lauson, Bradley, and Cournand,[1217] in their study of the renal circulation in shock, attempted to establish figures for the normal renal fraction by the simultaneous determination of renal clearances and of cardiac output by the direct Fick method. In 6 subjects they obtained an average value of 16.6 per cent (range 14.4 to 21.2 per cent). Subsequently, Bolomey, Michie, Michie, Breed,

Schreiner, and Lauson [207] completed a series of 18 non-hypertensive and 19 hypertensive subjects, using the direct Fick method. The average cardiac index in the normal subjects was 4.07 liters (or 7.04 liter/min. per 1.73 sq. m.), a figure substantially higher than that of Cournand *et al.* (5.29 liter/min.). The average renal fraction (uncorrected) was 15.6 per cent (range 10.2 to 26.9). However, the multiple procedure of saline infusion, bladder catheterization, and venepuncture for clearance determination, coupled with catheterization of the right heart and the collection of expired gases, is not conducive to physiological quiescence, and it would seem that the inevitable effect would be to increase the cardiac output above the basal level, and possibly to decrease the renal blood flow, thus decreasing the renal fraction. Moderate anemia of some of the subjects in this series may also have led to some reduction in the renal blood flow,[236] and consequently the authors expressed their belief that their figure for the renal fraction might be on the low side.

It is the writer's opinion that a true figure for the renal fraction cannot be determined by these multiple procedures because of the psychological and physiological effects on the subjects, and in the absence of more reliable data he would venture the opinion that the true renal fraction in subjects at rest and with normal hematocrits, and corrected for renal extraction ratios, is between the two figures, namely about 20 per cent.

The data collected by Bolomey *et al.* serve, however, to show that the renal fraction is substantially reduced in hypertensive disease, in consequence of the destruction of renal parenchyma, falling below 10 per cent in many subjects and reaching 1 to 2 per cent terminally.

Senescence

Lewis and Alving [1237] have reported studies on normal men, 20 in each decade from 40 to 89 years, 2 of 91 years, and 1 of 101 years. The whole blood urea clearance declined from 100 per cent of the average normal value (standard clearance = 54 cc., maximal clearance = 75 cc. per 1.73 sq. m.) at 40 years to 55 per cent at 89 years (fig. 103). The urea nitrogen content of the blood increased from 12.03 mg. per cent at 40 years to 17.62 mg. at 89

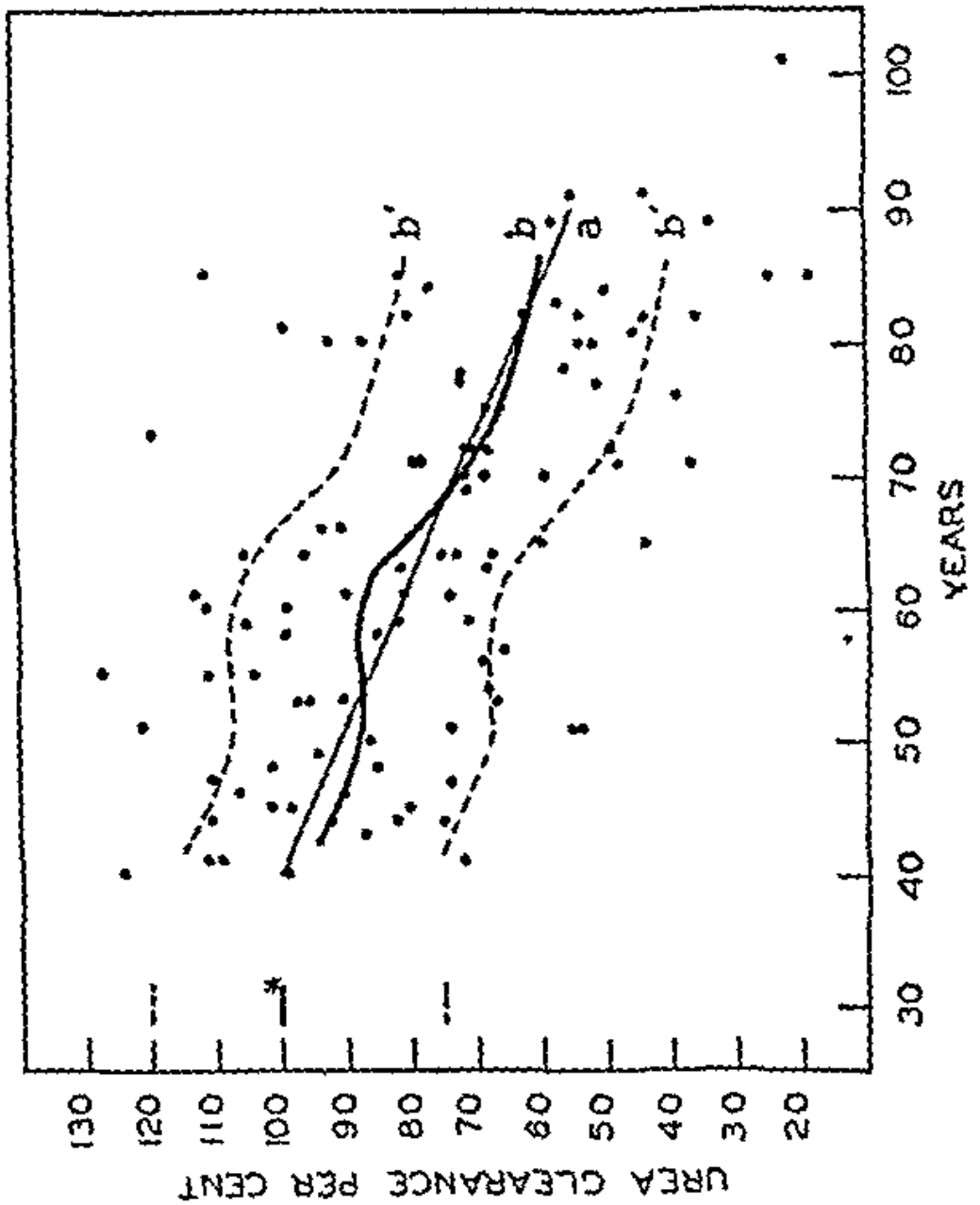
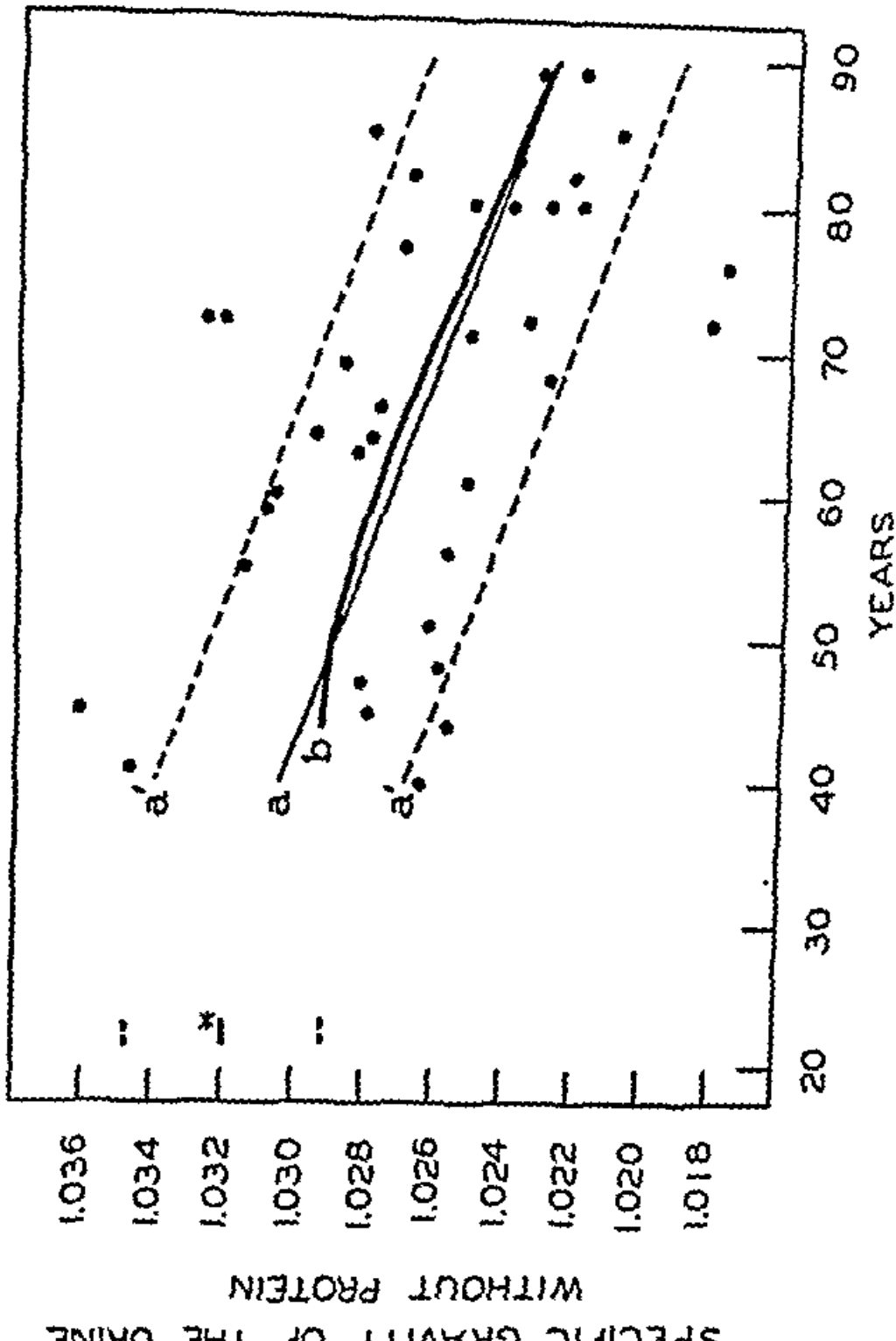


FIGURE 103 Urea clearance in relation to age in normal men over 40 years of age Dots represent individual values (averages of 2-hr. clearance tests), *a* is the straight line regression, 40 to 89 years, *b* is the smoothed regression of 5-year means, with limits, *b'* (dashed lines), of standard error of estimate, 40 to 89 years, the asterisk represents the average in young normal men, with limits of variation (short dashed lines). (Lewis and Alving [111])



[illegible] in normal men over [illegible] ears, [illegible] hed regression of 10-year means; the asterisk represents the average in young normal individuals, with limits (short dashed lines) of standard deviation. (Lewis and Alving [1327])

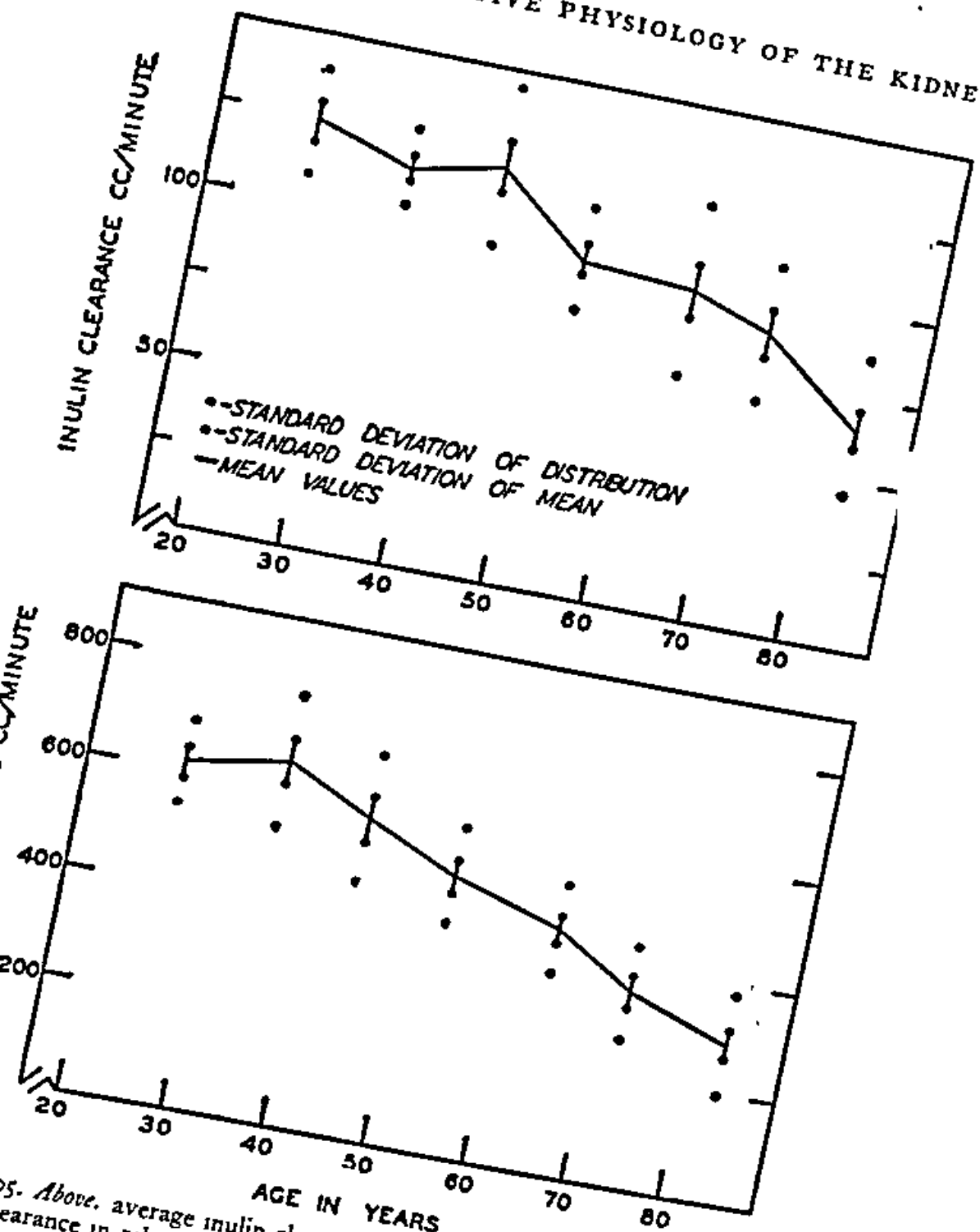
years. The concentrating ability of the kidneys, as shown by the urine specific gravity (corrected for protein) in 38 men after 24 hr. of dehydration, declined from 1.030 at 40 years to 1.023 at 89 years (fig. 104). The specific gravity does not fall below the lower limit of 1.026 observed in younger subjects before the sixty-fifth year, but after this age values in the range 1.023 to 1.026 are more common.

Hilden [1001] gives data on the plasma urea clearance in 8 men 57 to 79 years of age. This clearance ranged from 102 down to 72 per cent of normal and the diodrast clearance from 95 down to 65 per cent. In 8 women 51 to 78 years old, the urea clearance ranged from 90 down to 63 per cent of normal and the diodrast clearance from 84 down to 52 per cent. The urea/diodrast clearance ratio remained at 0.131 in both groups, the same value as obtains in young adults.

Shock [1879] and Davies and Shock [472] report an extensive study of renal function * in 70 males aged 24 to 89 years of age The subjects were carefully selected to exclude recent or remote renal disease, cerebrovascular accident, coronary artery disease, syphilis, rheumatic heart disease, hypertension, or any recent alteration in body weight. At the higher ages, blood pressure was not considered hypertensive unless the diastolic pressure exceeded 90 mm. Hg, since systolic hypertension with increased pulse pressure may result from dilatation and loss of elasticity in the larger arteries, a change commonly associated with aging. Nevertheless, only 2 tests were done on patients with systolic pressures greater than 160 mm. Hg.

With increasing age there is a progressive diminution in the inulin clearance, diodrast clearance (fig. 105), and Tm_D (fig. 106). Although wide individual differences in the effects of age on renal function are apparent, few subjects in the oldest group gave values as great as those observed in the youngest group.† The regression rates of function on age are given in table XIII.

* The standard error of measurement for the tests made: inulin clearance,



5. *Above*, average inulin clearance in relation to age. *Below:* average earance in relation to age. (Davies and Shock [172])

TABLE XIII

Regression Rates of Kidney Functions in Adult Men

(Davies and Shock [173])

$Y = aX + b$, where Y = the function, X = age

Function and units	n *	a †	b ‡	Regression rate	r ‖
		units/yr		per cent §	
Glomerular filtration rate, cc/min.	70	−0 96	153 2	0.722	−0.68
Effective renal plasma flow, cc/min	70	−6 44	840 0	0 906	−0 65
Tm_D, mg iodine per min.	70	−0.40	66.7	0 678	−0.66

* Number of cases
† Slope and regression rate of function on age.
‡ Extrapolated value of Y when age is 0
§ Per cent regression per year based on value at age 20.
‖ Coefficient of correlation by product moment formula.

The significances * of the differences between any single adjacent or non-adjacent decades have been summarized in figure 108. Values of the critical ratio as shown in this figure greater than 2.3 are significant at the 5 per cent level.† Examination of this figure shows that the inulin clearance, diodrast clearance, and Tm_D in general show more significant changes between adjacent decades beyond the age of 40 than in early adult life. When alternate decades are examined, the significance of the differences is high for all but young adults; i.e. significant changes occur over 20-year intervals of time.

The filtration fraction, C_{IN}/C_D, does not change significantly between the ages of 20 and 60 (fig. 106). Beyond the age of 60 a small but significant increase occurs. The elevated filtration fraction of the 70 to 79 year group may be owing to sampling errors, since two aberrantly high values occurred in this age category.

* Critical ratios were calculated by the formula:

$$CR = \frac{Mn_1 - Mn_2}{\sigma(Mn_1 - Mn_2)}$$

† Significant at the 5 per cent level means that, if the experiment were repeated a large number of times, a difference as large as (or larger than) this could be expected by chance (where no true difference existed) in 5 per cent of the observations

Both subjects had lower filtration fractions on later tests, but the data from the first test was used to maintain uniformity.

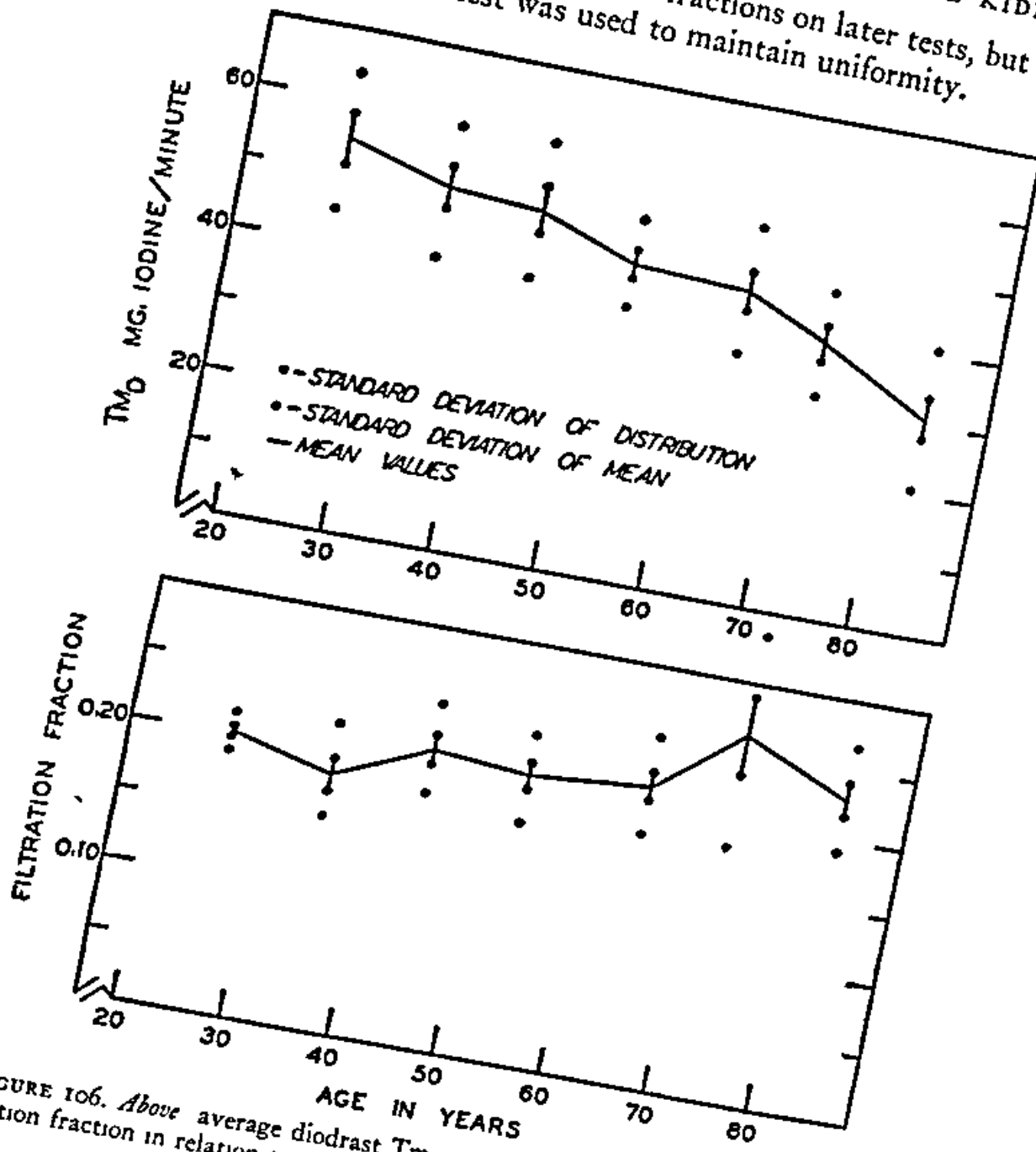


FIGURE 106. *Above* average diodrast Tm in relation to age *Below*· average filtration fraction in relation to age. (Davies and Shock [478])

The C_{IN}/Tm_D ratio remains constant between the ages of 20 and 90 * (fig. 107), but the C_D/Tm_D ratio decreases from an aver-

*A critical ratio of 0.3 was found by comparing the average value for 20 to 49 year olds with that of the 70 to 89 year olds

age value of 12.6 at age 30 to 39, to 9 7 at age 80 to 89 (fig. 107). The critical ratio of this difference is 4.2 ($P < 1$ per cent).

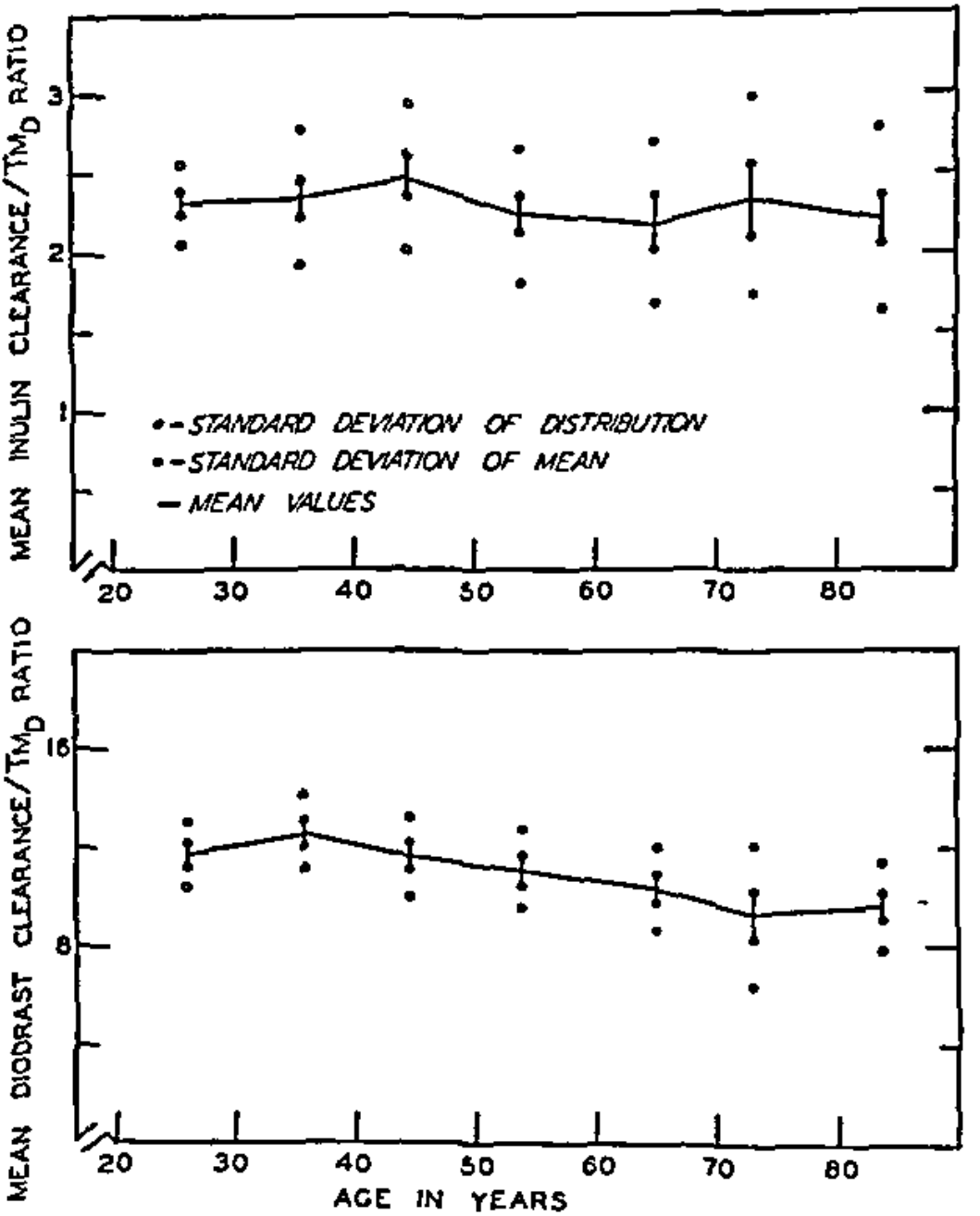


FIGURE 107. *Above* average C_{IN}/Tm_D ratio in relation to age. *Below* average C_D/Tm_D ratio in relation to age (Davies and Shock [473])

The data show that the filtration rate in the men 80 to 90 years of age is approximately half of that in the 20 to 30 year age group. To demonstrate whether or not the mean clearance remains con-

stant between 20 and 40 would require a much larger number of subjects than the present sample. It is safe to say only that there appears to be less difference between mean values of adjacent decades in early adult life than between those of later decades. Although the data presented by Goldring *et al.*[197] are generally higher than the present series when analyzed by age groups, the mean filtration rate of the 50 to 60 year age group is significantly lower than that of the third decade.

Similarly there is a decline in the renal plasma flow in this series, amounting to 53 per cent between the ages of 20 and 90 years. The diodrast clearances reported by Goldring *et al.*[197] are significantly higher than those of the present group in the third decade (critical ratio = 3.55), fifth decade (CR = 2.79), and the sixth decade (CR = 2.41). However, the mean value for the 50 to 59 year group is significantly lower than that for the 20 to 29 year group in the New York subjects as well as in the Baltimore group.

The change in Tm_D (fig. 106) from a mean value of 54.6 mg. of iodine in the 20 to 29 year age group down to 30.8 mg. in the 80 to 89 year group suggests an earlier initial decrease, but subsequently a gentler slope than occurs in renal plasma flow. The differences between the mean values for the two extremes of the age span are highly significant, but somewhat less significant than for analogous decades of inulin and diodrast clearances. For this function a straight line easily fits between the points representing plus or minus 1 standard error of the mean for each decade. Changes in filtration rate and diodrast clearance with age are not so clearly linear. However, with the exception of the 20 to 29 year group in diodrast clearance and the 40 to 49 year age group in inulin clearance, a straight line would fall within a single standard error of the mean of each decade. Although it is improbable that a straight line would represent the true curve reflecting the changes in these functions with age, it is evident that none of them shows a geometric regression.

A marked rise occurs in the filtration fraction of the 70 to 79 year age group over the previous decades. As mentioned above, this may be owing chiefly to the effect of 2 subjects who later returned toward normal, but a slight elevation does occur in the ninth decade. It is safe to assume that a number of subjects in the

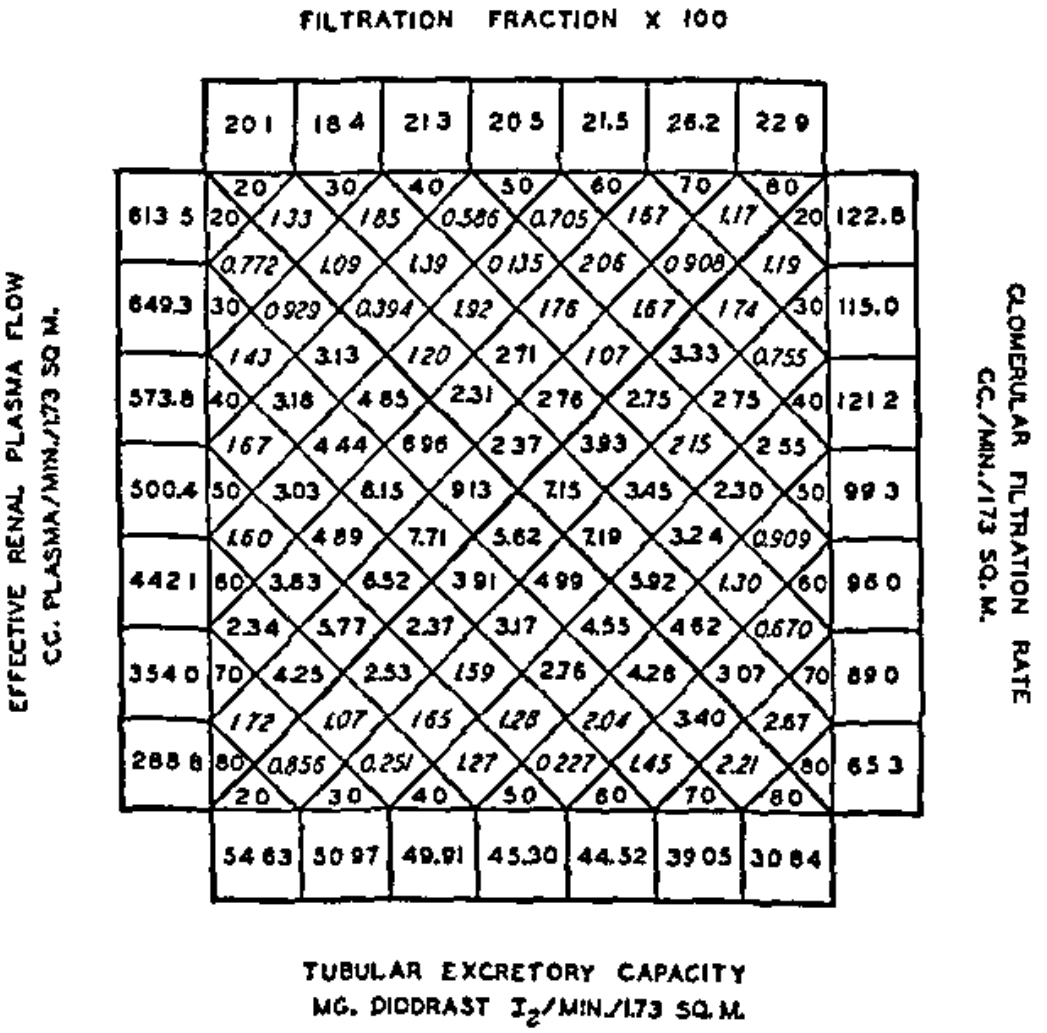


FIGURE 108. Significance of functional differences in relation to age. Average functional values by decades may be found as follows: left-hand vertical column, diodrast clearance; right-hand vertical column, filtration rate, top row, filtra- [illegible]

face vertical figures.

Example 1. To find significance of the difference between the twenties and forties for diodrast clearance, start at the number 20 in the left-hand margin and follow the column diagonally downward to the intersection with the column [illegible]

eighties is found by starting at the triangle 30 along the bottom of the figure and following the column upward diagonally to the right until it meets the column rising diagonally to the left from the triangle 80. These columns meet at 4 99 shown in bold-face numbers The difference in diodrast Tm between the 30- and 80-year-old groups is thus significant. (Davies and Shock [473])

ninth decade could be found who have a filtration fraction no higher than that of young adults, but in the general population higher fractions may be most common because of the incidence hypertension and heart disease. The tendency for the filtrati fraction to rise may be due to arteriolar sclerosis.

The constancy of the C_F/Tm_D ratio over 7 decades indicate that the nephron loses its function as a unit and without the for. mation of aglomerular tubules.

The steady decline in the C_D/Tm_D ratio beyond the fourth decade reveals that the renal tubules of men in the ninth decade are receiving a mean plasma flow of 9.17 cc. per unit of functional tubular tissue, as compared with 12.6 cc. in men in their thirties. This decrease in renal plasma flow with increasing age cannot be attributed to a reduction in cardiac output, since no estimates of cardiac output, crude as they may be, have indicated a reduction of this order of magnitude in elderly subjects.[1236] Nor can it be attributed to decreased mean blood pressure, since this tends to rise slightly with advancing age. It probably reflects progressive vascular changes in the renal parenchyma.

No data are available on renal function in relation to senescence in women. Such data will be awaited with interest.

Davies[472] reports that the urea clearance decreases with age after the fifth decade in a manner parallel to the decrease in filtration rate and Tm_D Tubular reabsorption declined throughout the 7 decades studied, most of this decline being related to the decreased filtration rate. Urea production does not decrease with age, and hence the blood urea shows a moderate increase. From this preliminary note, one infers that decreased renal function in old age is not related to decreased protein metabolism.

CALCULATION OF BODY SURFACE AREA AND KIDNEY WEIGHT

For inter- or intraspecies comparisons of various animals, it is desirable, as one mode of expression, to use the body surface area. The formula relating surface area to volume

(1)
$$SA = k' \times \text{volume}^{0.66}$$

was developed by Meeh in 1879; if the specific gravity is assumed to be constant, body weight (BW) may be substituted for volume:

(2)
$$SA = k \times BW^{0.66}$$

where SA is in sq. cm and body weight in gm. This relationship subsequently came into widespread use as an approximation equation by Rubner and other students of metabolism The values of k as determined by various investigators for numerous species were collected by Benedict and are reported by Dubois:[548] rat, 9 1; cat, 10.0; rabbit (without ears), 9 0, dog (under 4 kg), 11.2 (over 4 kg.), 10 1; man, 11.0.

Mice: Warren[2143] gives the kidney weight in male mice 35 to 195 days of age as 15 2 mg/gm , in females 12.9 mg/gm.

Rat Lee[1222] prefers the use of the exponent $BW^{0\ 60}$ and a value of k = 12 54 over previously published data. (A formula using a nutritional factor is somewhat more accurate.)

The writer calculates the KW/BW ratio in Wistar rats 50 days of age or older in Arataki's[55] data to be 8.04 gm/kg. in males and 8 08 gm/kg in females. Dicker[513] obtained a KW/BW ratio of 7 5 to 8 8 gm/kg depending on the protein content of the diet Taking this ratio as 8.0 and using Lee's formula, a 200 gm. rat would have 130 gm. of kidney per sq m.

In view of some apparent differences in function in different strains, it is of interest that in the older Wistar strain[536] $KW = 0.00718\ (BW_{gm} - 3) + 0\ 132 \log (BW_{gm} - 3) - 0\ 009$ for male rats, which yields for a 300 gm. rat about 8.3 gm/kg This ratio in rats 110 days old or more in the data of MacKay and MacKay[1237] in decapsulated, sectioned, and blotted kidneys is 5 44 gm/kg in males and 5 68 gm/kg. in females, figures not to be compared with those of other investigators who did not decapsulate the kidney but only freed the capsule of fat. The data of MacKay and MacKay show that adult male rats have 35.6 gm , females 31 0 gm , of decapsulated blotted kidney per sq. m The right kidney is a trifle heavier than the left in both sexes[55,1340]

Kirkman and Stowell[1121] estimated the total filtration surface in the male albino rat to be 11,704 sq. mm (6890 sq. mm. per gm of kidney) and from available data inferred that the urea clearance in the rat and man (using Book's estimate of filtration surface in the latter) agree within 18 per cent in terms of kidney weight, and 0.2 per cent in terms of surface area.

Cat: No formula is known to the writer which improves on the Meeh-Rubner equation.

Hall and MacGregor[889] give the formula for kidney weight as

$$KW_{gm} = 9.825 \times BW_{gm}^{\ 0\ 71} - 1.09 \tag{3}$$

or with almost as much accuracy for medium-sized animals,

$$KW_{gm} = k \times BW_{kg}. \tag{4}$$

For males weighing 3.0 to 3.5 kg, $k = 9.4$; for females weighing 2.5 to 3.0 kg, $k = 7.2$. The markedly larger figure in male cats should be noted. In old males the figure is still larger (10.2).

Rabbit: Kaplan and Smith [1090] calculated from the data of Taylor, Drury, and Addis [2049] on 17 rabbits that

(5)
$$KW = 8.9 \times BW_{gm}^{0.66}$$

The figure is probably valid only between 2 and 4 kg. From these same data the writer obtains the relationship:

(6)
$$KW_{gm} = 6.4 \times BW_{kg}$$

(7)
$$KW_{gm} = 89 \text{ gm/sq. m.}$$

while W. W. Smith [1947] gives for 8 rabbits

(8)
$$KW_{gm} = 5.6 \times BW_{kg}$$

Dog Cowgill and Drabkin [442] made a careful study of the dog, and presented a nomogram which is superior to the Meeh-Rubner formula and which is almost universally used. As an equation they recommend

(9)
$$SA_{sq\ cm} = 2.268 \times BW_{gm}^{0.367} L_{cm}$$

where L is the length from nose to anus measured over the belly.

Stewart's [2005] data on 5 dogs (5 to 18 kg), in which he measured the surface area, yield the relation, according to Cowgill and Drabkin,

(10)
$$SA_{cm} = 6.63\ BW_{gm}^{0.71}$$

and Thomas' data on 6 dogs yield

(11)
$$SA_{cm} = 7.48\ BW_{gm}^{0.71}$$

Graphical analysis of Kunkel's data for 13 dogs (5.2 to 20.0 kg) indicates the relationship

(12)
$$SA_{cm} = 11\ BW_{gm}^{0.66}$$

though K might well be 10.

Stewart gives the KW/BW ratio as 7.2 gm/kg for 8 dogs below 8 kg, and 3.4 for 4 dogs above this weight. In his larger series (table 4) this ratio was 7.2 below 10 kg. and 5.8 above. Calculation * from Stewart's larger series shows that, in 16 dogs weighing from 7 to 18 kg., the KW/BW ratio is 6.28 gm/kg. In Kunkel's [1177] 9 dogs, weighing from 5.30

* The writer is indebted to Mr. Charles Crowder, Jr., for these and other calculations.

to 20.00 kg., KW/BW = 7.3 gm/kg. Moustgaard's [1483] series of 88 dogs in the weight range of 5 to 10 kg, 10 to 15 kg., 15 to 20 kg., 20 to 25 kg, [illegible] and [illegible]

data It is probable that differences in diet as well as differences in preparing the kidneys for weighing may play a part in giving rise to this discrepancy.* The best figure based on the above data appears to be

$$KW_{gm} = 7.1\ BW_{kg} \tag{13}$$

Dividing (12) by (13) yields 141 gm/sq. m, a figure in fair agreement with (16) below

Several calculations are possible on a surface-area basis. (a) Stewart's data for 5 dogs between 5 and 18 kg. give 105 gm/sq. m. as measured. (b) Calculation of surface area by (12) yields, for 15 dogs weighing from 5 to 19 kg, 131 gm/sq. m. (69.9 to 176 6). (c) Kunkel's data [1117] on 9 [illegible]

an average value of 100 gm/sq m; (e) the surface area as calculated by (9) on 88 dogs yields 135 gm/sq m.; (f) if surface area is calculated by (12) these 88 dogs yield 110 gm/sq. m (g) Moustgaard, from data on 88 dogs, arrives at the relation

$$KW_{gm} = 0\ 15 BW_{kg}^{0\ 63}\ L_{cm} \tag{14}$$

Dividing this equation by (9) we obtain

$$KW_{gm/sq\ m} = 8\ 53\ BW_{gm}^{0\ 263} \tag{15}$$

If we divide (15) by (12) the resulting expression

$$KW_{gm/sq\ m} = 3.4\ SA_{sq\ m}^{0\ 395} \tag{16}$$

yields 129 gm for 1 sq m The correspondence between this figure and those obtained by calculations (b), (c), and (e) is remarkably good, and we take the kidney weight in the dog to be about 130 gm/sq m. Sex was not specified in any instance

Man: Dubois [848] has presented the widely used nomograms relating surface area to height and weight in adults and children. As a rough [illegible]

approximation he recommends k = 10.79 in the Meeh-Rubner formula for adults and 10.3 for children. The Meeh-Rubner formula is close enough for general purposes, but slightly more accurately in adults is

$$SA = BW_{gm}^{0.425} H^{0.725} 71.84 \quad (17)$$

Surface area in infants is given by Klein and Scammon [1128] as 5.188 $BW_{gm}^{0.75}$

MacKay [1325] calculates from the data of Vierordt [2112] that man has 171 gm. of kidney per sq. m., but does not say whether he used the data on males, females, or both, and in the calculation he used average data from two independent series on body height and weight. The writer has recalculated Vierordt's data for the age groups 20 to 25 years, multiplying the number of observations by the renal weight in each group, and obtained an average of 302 gm in men and 276 gm. in women. Greenwood and Brown [857] give the average weight of the kidney in healthy males 25 to 55 years of age as 303 gm. (σ/m = 0.1921). (The same sources may have been used in these two series.) In Wald's [2124] data on subjects dying within 24 hr. of accident, with no history of illness or pathologic abnormality, at 20 to 29 years the average kidney weight in males is 313 ± 59.0, at 30 to 39 years 323 ± 57.0, at 40 to 49 years 316 ± 54.4 gm., while in females the corresponding figures are 257 ± 54.5, 250 ± 47.6, and 258 ± 52.8 gm. Taking all age groups in Wald's data, the weight of the kidney in women averages 82 per cent of that in men. For present purposes we shall take Wald's figures of the second decade (313 for men and 257 for women) as applying to 1.73 sq. m.; using 70 and 60 kg. respectively, these would give 4.47 and 4.29 gm/kg.

Lattimer reports the kidney weight in men to be 6.68, in women 5.99 gm/kg. between the ages of 20 and 40 years In infants these figures are 10.2 in males and 9.90 in females All these coefficients appear to be high and may represent emaciated individuals.

GLOMERULAR COUNTS

It is of interest to relate the basal function in the rat, rabbit, dog, and man to the glomerular and tubular development of the kidney. This can only be accomplished by combining the data of various investigators. The number of glomeruli in one kidney of the adult animal (the number of animals is shown in parentheses) is recorded as follows (the number of glomeruli in the adults of all species studied remains fixed, and there will therefore be no correlation between number of glomeruli and body size within species):

Rat: 28,000 (3);[1126] 31,000 (12);[65] 33,826 (1);[2114] 30,750 (2);[1177] 25,300 (4);[2058] 30,800 (8).[1761] Kunkel[1177] from his data on 2 rats estimated an average of 2,118,000 glomeruli per sq. m , or 27,000 per gm. KW. Arataki's[65] 6 males 100 days or more of age give 27,000, and 6 females give 35,100

Vimtrup's count[2114] on 1 rat gave 32,200 glomeruli per gm KW. The weighted mean of these figures gives 30,600 per gm. KW.

The total number of glomeruli in the white rat decreases by about 30 per cent in senile animals[66,1474]

Rabbit 212,269 (10);[1501] 202,850 (2);[1177] 207,000 (?).[1761] Hayman and Starr's[942] maximal figures range about 200,000 Kunkel found 2,030,000 per sq. m. in 2 animals For a 2 kg. rabbit, Nelson's figure and k = 9 0 would give 1,490,000 per sq. m. For a 2.0 kg rabbit, equation 5 gives 6.4 gm for one kidney, and the mean of the figures above gives 33,300 glomeruli per gm. KW. (Kunkel obtained 33,000 in 1 rabbit with a 6.5 gm KW.)

Cat 182,600 (3),[2114] 199,300 (?).[1761] Vimtrup obtained 15,200 glomeruli per gm KW, Kunkel 9,000 (male with large kidney?) and 23,000 (female?)

Dog Kunkel determined the number of glomeruli in one kidney in 14 dogs to be 426,000; Rytand[1761] obtained 408,100 in 1 dog (9 1 kg), and Vimtrup[2114] 457,500 in 2 dogs Kunkel calculates for 14 dogs (both kidneys) 1,920,000 glomeruli per sq m. (as measured), or 117,000 per kg body weight; in 9 Kunkel obtained 13,350 glomeruli per gm. KW; Vimtrup 13,700 in 2 dogs.

Man. 1,040,000 or 7,170 per gm KW (1);[1126] 955,434 (range 833,992 to 1,233,360) (5).[2114] The writer has excluded from Moore's[1473] series 2 cases of miliary tuberculosis and 1 of rheumatic heart disease, leaving 14 kidneys from patients 1 to 38 years old; the average is 874,448 (range 651,596 to 1,040,671) Moore's data indicate that the glomerular count decreases by one-third to one-half by the seventh decade * Vimtrup's[2114] figures on 2 human kidneys (sex unspecified) give 6,060 and 7,470 glomeruli per gm. KW The best figure appears to be about 7000 per gm. KW, or 2,190,000 in man and 1,800,000 in women, assuming that the

* Moore gives the number of glomeruli per gm of cortex, but the counts were made on individuals dying of diseases many or some of which were severely wasting (chronic tuberculosis, lobar pneumonia), and the kidneys had been perfused with fresh water and were edematous These figures, however, averaged 15,839 in 7 women and 11,009 in 15 men In the 7 women the total glomerular count averaged 793,038 per kidney, and 763,264 in the men. The data suggest that the female kidney has the same number of nephrons as the male kidney but each nephron is smaller, accounting for the smaller kidney weight.

TABLE XIV

Comparison of Renal Function in Mammals

(Sources of data are discussed in the text.)

	KW/sq. m.	Glomeruli per gm. KW	Per glomerulus × 100,000			Per gm. KW			Per kg. BW			Per 1.73 sq. m.		
			C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.	C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.	C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.	C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.
Rat	130	30,600	2.45	8.99	1.22	0.75	2.75	0.375	6.00	22.0	3.0	69.9	253	34.6
Rabbit	89	33,300	1.98	7.50		0.66	2.50		3.12	18.2		87.0	512	
Dog	130	13,350	4.64	14.3	1.03	0.62	1.91	0.137	4.29	13.5	0.97	146	460	33.0
Man *	149	7,000	6.56	33.3	4.29	0.46	2.33	0.300	1.97	10.0	1.28	118	600	77.2

* Women, for comparison with female dogs.

difference in renal weight is entirely referable to a difference in the number of nephrons.

Moore [1472] records that the number of glomeruli in the human kidney decreases with age; in the seventh decade it is one-third to one-half the number in young adult men.

Data from the calculations above have been brought together in table XIV to afford a comparison of renal function in different species. These data indicate that, per unit of body surface area, the rat, the dog, and man have about the same quantity of renal tissue. But man has the smallest number of nephrons (glomeruli), so that each nephron must have more tubular tissue attached to it, an inference confirmed by the higher value of Tm_{PAH} per nephron. The filtration rate per glomerulus in man is also higher than in the rat, and possibly than in the dog These differences almost entirely cancel out when comparison is made on the basis of kidney weight.* In all species, each gm. of kidney makes about the same quantity of filtrate and has about the same value of Tm_{PAH}. Per unit of body weight, renal function is higher in small animals, a fact which may be related to the circumstance that metabolism is greater per unit of body weight in small than in large animals. These differences are reduced, if not abolished, when total function is compared on a surface-area basis, reflecting the applicability of the surface-area law to metabolism. The difference between the last methods of calculation in favor of the surface-area basis lends further warrant to this method of comparison within a species and as between young and adult animals.

Kunkel [1177] gives data on the number of glomeruli in the monkey, opossum, ground hog, pig, ox, cat, rabbit, rat, mouse, and guinea pig. The number of glomeruli in his series correlated more closely with body surface area than with body weight.

Rytand [1761] gives glomerular counts on 1 elephant and 4 to 8 male mice, albino rats, and kangaroo rats, and measurements of the unfixed glomeruli suspended in serum. Combining his data with those of Kunkel, he calculates the total glomerular volume (TGV) and relates it to kidney weight and body weight, as shown in table XV.

He finds that TGV is almost a linear function of the kidney weight, as shown by the constancy of the ratio of the two in table XV; hence

$$TGV_{cu\ mm} = 0.044\ KW_{mg.}^{1.0} \tag{18}$$

Rytand apparently drew his curve by visual fit and included the ele-

* It has been noted above that, relative to man, the dog is deficient in respect to Tm_{PAH} (as judged per unit of filtrate) but not deficient in respect to Tm_{D}.

TABLE XV

Body Weight, Kidney Weight, Glomerular Size, and Glomerular Number in Several Mammalian Species

The data for the mouse, albino and kangaroo rats, and elephant are Rytand's.[1161] The data for man are taken from the text, and data for other species were recalculated by Rytand from Kunkel.[1117]

Animal	Body weight	Weight of one kidney	Glomerular radius	Number of glomeruli in one kidney	Total glomerular volume in one kidney	Total glomerular volume in 1 gm. of kidney
	gm.	mg	μ		cu mm	cu mm.
Mouse	20	123	36.7	12,430	2 6	21.1
Kangaroo rat	66	295	48.4	18,840	8 9	30 3
Albino rat	241	746	61 2	30,800	29 5	39 5
Guinea pig	565	1,900	63	75,700	79 3	41 7
Ground hog	1,210	1,800	69 5	96,000	135	75
Opossum	2,000	5,200	87.5	91,200	256	49 2
Rabbit	2,320		71	207,000	310	
Cat	2,750	8,000	66	184,000	227	28 3
	3,500	25,500	75	214,500	379	14 9
Monkey	3,860	9,000	83	186,600	447	49 7
Dog	9,100	31,300	90	408,100	1,247	39 9
Pig	46,650	76,700	83	1,193,000	2,859	37 3
Man	70,000	156,500		1,095,000	4,599	29 4
Ox	410,000	640,000	122	3,992,000	29,860	46 7
Elephant	4,545,000	3,650,000	169	7,510,000	151,900	41 6

phant and excluded the mouse (fig. 109). The writer has calculated the regression line, omitting the elephant and including the mouse, and obtains practically the same slope but a slightly smaller constant:

$$TGV_{cu\ mm} = 0\ 0296\ KW^{1.024} \tag{19}$$

The elephant remains in line with this equation (fig 109).

The exponent is so close to 1 0 that it is approximately correct to say, with Rytand, that on the average there are 30 cu. mm. of glomerular volume (eq. 20) in each gm. of kidney. The cat is way out of line, probably because of large tubules. Using Vimtrup's[2114] figure for the average glomerular volume in man of 0.0042 cu. mm., 7000 glomeruli per gm would give 29 4 cu. mm per gm.—an agreement with Rytand's generalization that is too good to be true.

Rytand also derives the following relations (N is the number of glomeruli) for 1 kidney:

$$N = 508\ KW_{mg}^{\ 0\ 65} \tag{20}$$

(21) $$KW_{mg} = 8.22\ BW_{gm}^{0.85}$$

(22) $$TGV_{cu\ mm} = 0.36\ BW_{gm}^{0.85}$$

Recalculation of (22), omitting the elephant and including the mouse as in figure 109, gives

(23) $$TGV = 0.1987\ BW_{gm}^{0.9287}$$

All these relations * are probably approximate only Equation 22 would yield for a 70 kg man 250 gm. total kidney weight, which would be about right for women.

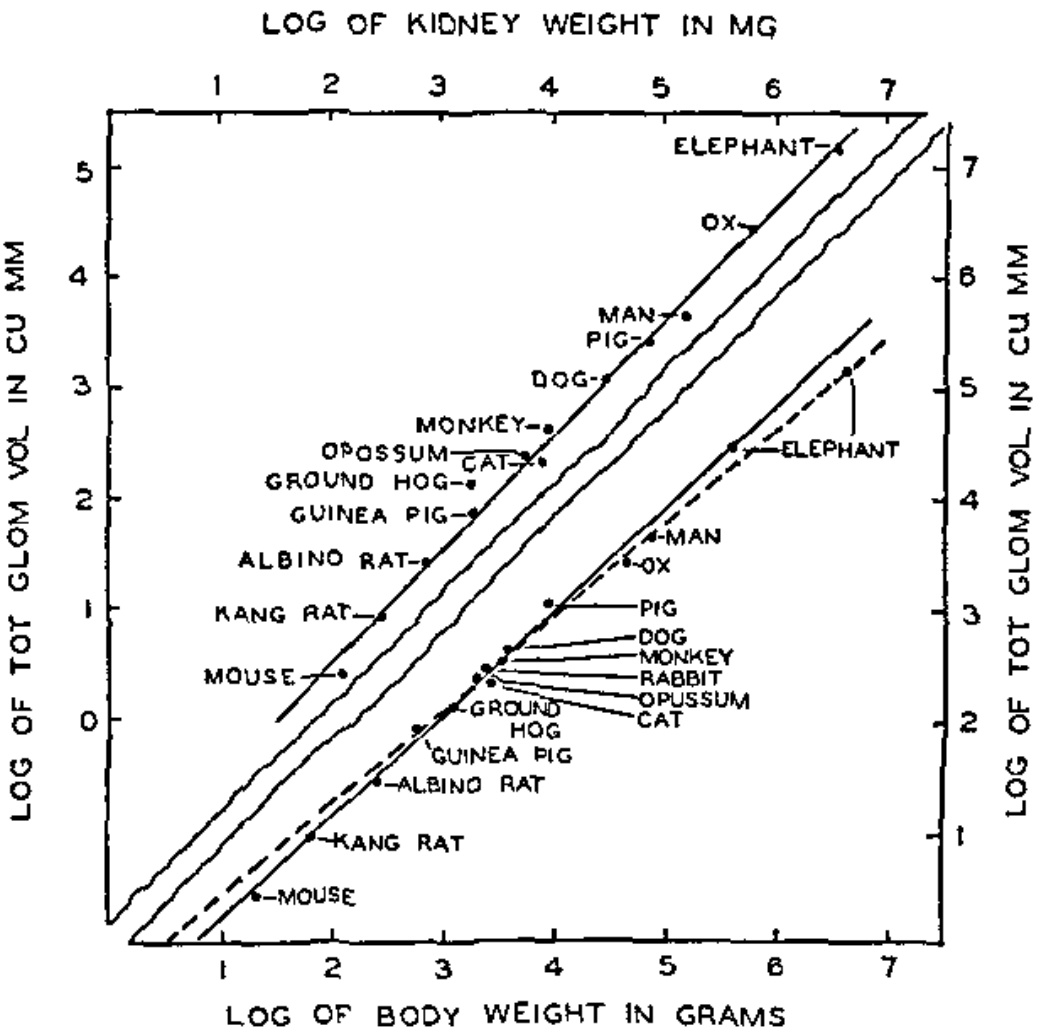


FIGURE 109 Total glomerular volume in relation to kidney weight (above) and body weight (below) in mammals. The data on man are calculated in the text (Rytand [1761])

* The fact that the exponent in the last three equations is less than 1 0 indicates lack of simple proportionality. It should be noted, however, that a log-

Rytand's inference that TGV, which he finds is fairly constant per gm. of kidney, should be closely proportional to glomerular function, is supported by the constancy of the filtration rate per gm. of kidney, as shown in table XIV.

COMPARISON OF LOWER AND HIGHER VERTEBRATES

In closing this chapter, it will be of interest to the student of comparative physiology to compare renal function in the mesonephros and metanephros, particularly with reference to the relative importance of glomerular and tubular activity.

It will be recalled that, in Pisces, Amphibia, Reptilia, and Aves, the definitive kidney, or mesonephros, receives a copious supply of blood from the veins of the posterior part of the body, this venous blood perfusing the tubules and mingling with the postglomerular blood in the venous channels draining the kidneys (ch. 1). Unfortunately no functional data are available on the fresh-water fishes, where the arterial-glomerular circulation could be expected to dominate over the renal-portal circulation.

Nash [1600b] has shown that total glomerular volume is much larger per unit of surface area in fresh-water teleosts than in marine forms, the marine elasmobranchs and cyclostomes resembling the former.

It may be surmised that under conditions of threatened dehydration, such as would be faced by the anadromous salmon or catadromous eel during the marine phase, glomerular activity is reduced to low levels in order to conserve water It is, however, doubtful that glomerular activity ceases entirely, since it does not do so in most permanently marine forms, and the development of the aglomerular state in old sculpin must be looked upon as a developmental phenomenon related to biological degeneration rather than atrophy in the individual from lack of function. But comparison of urine flow in the salt- and fresh-water elasmobranchs, as noted earlier in this chapter, indicates that such an adjustment occurs in this Sub-class.

Glomerular function can be evaluated by the filtration rate, C_F, and tubular function by phenol red Tm, the only substance which has been studied in the lower vertebrates. Of equal importance is the rate of perfusion of the tubules, since this would comprise both the renal blood flow through both the postglomerular and renal-portal circulation. For such comparisons, we have calculated the tubular perfusion, C_T, from

log relationship is precarious, for almost any 2 progressive variables will yield an approximately linear relationship when so treated, large absolute deviations showing up as only small departures from the apparent logarithmic relationship.

data on the phenol red clearance, corrected for an extraction ratio of 0 50 (an assumed and doubtless inaccurate value). Since so little phenol red is excreted by filtration, neglect of this term introduces no significant error.

The data in table XVI show that glomerular clearance is, of course, zero in the aglomerular toadfish and goosefish. In the glomerular dogfish (marine) the filtration rate is very low, the ratio C_T/C_{IN} very high. In the fresh-water bullfrog, the filtration rate is better than 10 times as great as it is in the marine dogfish, probably reflecting differences in hydration rather than in glomerular development, for the glomeruli are

TABLE XVI

The Excretion of Inulin and Phenol Red in Various Vertebrates, Showing the Relative Importance of Glomerular and Tubular Function

	C_F cc/min per kg	C_T cc/min. per kg.	C_T/C_{IN}	Tm_{PR} mg/day per kg.	Tm_{PR} mg/100 cc. of filtrate
Cold blooded, Mesonephros					
Toadfish *	0	1	∞	13 6	∞
Goosefish *	0	1	∞	9 3	∞
Dogfish † (salt water)	*0 05*	*2 25*	*45*	*18 0*	*25*
Frog ‡ (fresh water)	0 66	11 6	16 0	120 0	12 6
Warm-blooded, Mesonephros					
Chicken §	1 84	50 0	26.0	1643 0	62
Warm-blooded, Metanephros					
Rat ‖	6 0	22 0	3.7		
Rabbit ‖	3 12	18 2	5.8		
Dog ‖¶	4 29	13 5	3 1	495	8
Man ‖**	1 97	10 0	5 0	288	10

* C_T at best a rough guess, estimated from Shannon's[1867] figures, assuming E_{PR} = 0 5, other data from same source

† C_{IN} from Shannon[1844] and W W Smith,[1945] C_T from W W Smith taking E_{PR} = 0 5, Tm_{PR} from same source

‡ C_{IN} from Forster[677] on summer frogs C_D from same source, taking E_D = 1 0, Tm_{PR} from Forster[675] In Forster's earlier paper[674] he gives the inulin clearance in winter frogs as 0 33 cc/min per kg during maximal water diuresis

§ C_{IN} and C_{PR} from Pitts[1628] taking E_{PR} as 0 5, Tm_{PR} from the same source

‖ Data from table XIV, taking E_{PAH} as 1 0

¶ Tm_{PR} from Shannon[1847]

** Tm_{PR} in one subject only, from Smith, Goldring, and Chasis[1938]

well developed in the latter. Tubular perfusion is, however, increased fivefold, possibly because of an abundant postglomerular flow. Tm_{PR} per kg. of body weight is increased many times; discounting differences in temperature (dogfish 15° C.?, frog 20° C.?), this increase implies either a greater quantity of proximal tubular tissue in the frog or greater specific excretory activity. Despite the increase in Tm_{PR}, the ratio Tm_{PR} per 100 cc. of filtrate is reduced as compared with the dogfish. In the frog, glomerular activity is relatively more important than tubular activity.

Although the chicken has a mesonephros, the appearance of the warm-blooded state may account for the remarkable increase in tubular activity. But if Q_{10} = 2 0 per cent (and it may be greater), a difference in temperature of 15 to 39° C. would only account for a 2.5-fold increase, whereas the actual increase as compared with the frog is nearly fourteenfold. The increase is less in the filtration rate, a fact which is not surprising, since filtration is not temperature-sensitive, but one which may in part be attributed to poor glomerular development. Pitts [1823] gives the kidney weight in 2 chickens as 7.15 gm/kg.; this conversion would give a filtration rate of 0.258 cc/gm. KW, a figure to be compared with 0 46 cc. in women and 0.405 cc. in men. It is surprising, in view of the structure of the glomerulus in the chicken, that this figure is so high. The ratio C_T/C_{IN} remains high, showing that tubular perfusion through the renal-portal system accounts for most of the renal blood flow.

For comparison, the data from mammals are reproduced from table XIV. As noted above, glomerular activity is greater in mammals than in the chicken because of better vascularization of the glomeruli With the disappearance of the renal-portal system, the ratio C_T/C_F falls to a level substantially below that observed in the mesonephric forms, and tubular activity, as judged by Tm_{PR} per 100 cc. of filtrate, decreases to a value below that of the frog.

The data, meager as they are, support the interpretation that, with the evolution of warm-blooded forms capable, unlike the bird, of elaborating a hypertonic urine, glomerular activity was preserved and played [illegible] of urine by an extravagant process of [illegible] ively less im- [illegible] fostered the [illegible] disappearance of the renal-portal system, or whether the disappearance of the renal-portal system fostered the increased emphasis on filtration, remains as yet, like so many problems in evolution, an enigma within the story of adaptation and natural selection.

CHAPTER XVIII

Renal Hemodynamics *

THE NATURE OF GLOMERULAR FILTRATION

Any approach to the problem of renal hemodynamics must start from certain premises concerning the nature of the processes of capillary transudation in the kidney. The view accepted by Cushny, which was based upon the contemporary views of Starling and which is the one now accepted by all investigators, is that the separation of the glomerular filtrate is the result of a simple process of ultrafiltration of water and its contained solutes (other than the plasma proteins, lipids, and other macromolecules) through the capillary tuft, the effective filtration pressure being the difference between the hydrostatic pressure within the capillaries on the one hand and the sum of the oncotic pressure plus the hydrostatic pressure in the capsule on the other. This view requires that the glomerular membranes be permeable to all plasma electrolytes and other substances possessing significant osmotic pressure, for otherwise their osmotic pressure would render filtration impossible. The total osmotic pressure of the plasma may be taken as $-0.553/1.85^{\circ}$ C $\times$ 22.4 $\times$ 760 mm. Hg, or 5090 mm. Hg, whereas the pressure in the glomerulus available for filtration does not exceed 60 mm.

* This chapter has been prepared with the assistance of Dr Domingo M. Gomez A more detailed exposition will be presented elsewhere

In many though not all instances, changes in the renal circulation leave the filtration rate essentially unchanged despite wide variations in renal blood flow. This constancy of the filtration rate (under these particular conditions) might be construed as evidence that the properties of the glomerular membranes are such that the rate of filtration is independent of glomerular pressure, a hypothesis wholly contrary to the concept of simple ultrafiltration. We have no direct knowledge of the rate of passage of water *per se across the glomerular membranes, the filtration rate being defined* in terms of reference substances such as inulin or creatinine. It might be argued that the constancy of the inulin clearance issues from the circumstance that the glomerular membranes so condition the passage of inulin molecules that the quantity which enters Bowman's capsule per unit time is constant and independent of the passage of water. This supposition is controverted by the facts, first, that inulin is present in the capsular fluid of the frog and *Necturus* in the same concentration as it is present in plasma water; and, second, that under controlled conditions in all species examined inulin is always excreted in proportion to the plasma *concentration. There is no limiting rate of glomerular excretion* of inulin (as in tubular excretion) and the fact that its excretion is so strictly dependent on plasma concentration requires the simultaneous passage of water in equivalent amounts. When to this evidence there is added the similar evidence on the *simultaneous* excretion of creatinine in the dog, rabbit, etc., it may be said that the data require the simultaneous passage of water and inulin (or creatinine) in the proportion in which they exist in the plasma.

It could still be argued, however, that the glomerular membranes are so constructed as to permit the passage into Bowman's capsule per unit time of a constant volume of water with its contained inulin and all other solutes, the volume so passed being relatively independent of glomerular pressure. (Such a system is roughly imitated in a 'slow' filter, i.e. one in which the resistance is so high that the movement *of fluid is but slightly influenced by* moderate *changes in hydrostatic pressure.) Any membrane* thus conditioning the passage of water independently of pressure can do so only by being relatively impermeable, and its properties must be such that the movement of water is conditioned by inter-

molecular forces such as solubility in heterogeneous phases, surface tension, adsorption, diffusion, etc., or cellular transport involving such forces (secretion), and under these circumstances it can confidently be expected that the passage of various molecular species will be differentially conditioned. The now abundant evidence on the excretion of inulin, creatinine, and a variety of other substances presents no evidence of such differential permeability.

If the positive evidence is adequate to exclude the conditioned passage of inulin specifically, and the conditioned passage of water and solutes generally, then the only alternative is to accept the hypothesis that water with its contained solutes moves through the glomerular membranes in consequence of differences in hydrostatic pressure, not restrained to a significant degree by viscous or frictional forces. This is, of course, the Starling concept of ultrafiltration and the accepted concept of glomerular filtration.

FILTRATION PRESSURE EQUILIBRIUM

The passage of water with its diffusible solutes into Bowman's capsule occurs only in consequence of the fact that the hydrostatic pressure within the glomerular capillaries exceeds the sum of the oncotic pressure plus the capsular pressure. By capsular pressure we designate the pressure existing in Bowman's capsule; it may be accepted that the compressibility of this capsule is such that the capsular pressure is practically identical with the renal interstitial pressure.*

In conformity with the principle of ultrafiltration, we conceive the filtration process to be a reversible one, so that, if the pressure in the glomerular capillaries falls below the sum of the oncotic plus capsular pressure, filtration will be reversed and fluid will be reabsorbed from the capsule into the glomerular capillaries.†

* This generalization, however useful or even necessary in the present discussion, should not be taken to mean that the interstitial pressure is the same everywhere throughout the kidney Gottschalk (pers com) has shown that the injection of saline into one pole of the kidney in sufficient quantity to produce a bleb and a considerable local increase in pressure does not immediately increase the interstitial pressure at the other pole. The kidney as a whole does not behave like a completely fluid system.

† A minimal filtration (isogravimetric) pressure about equal to the oncotic pressure is demonstrable in muscle [147a]

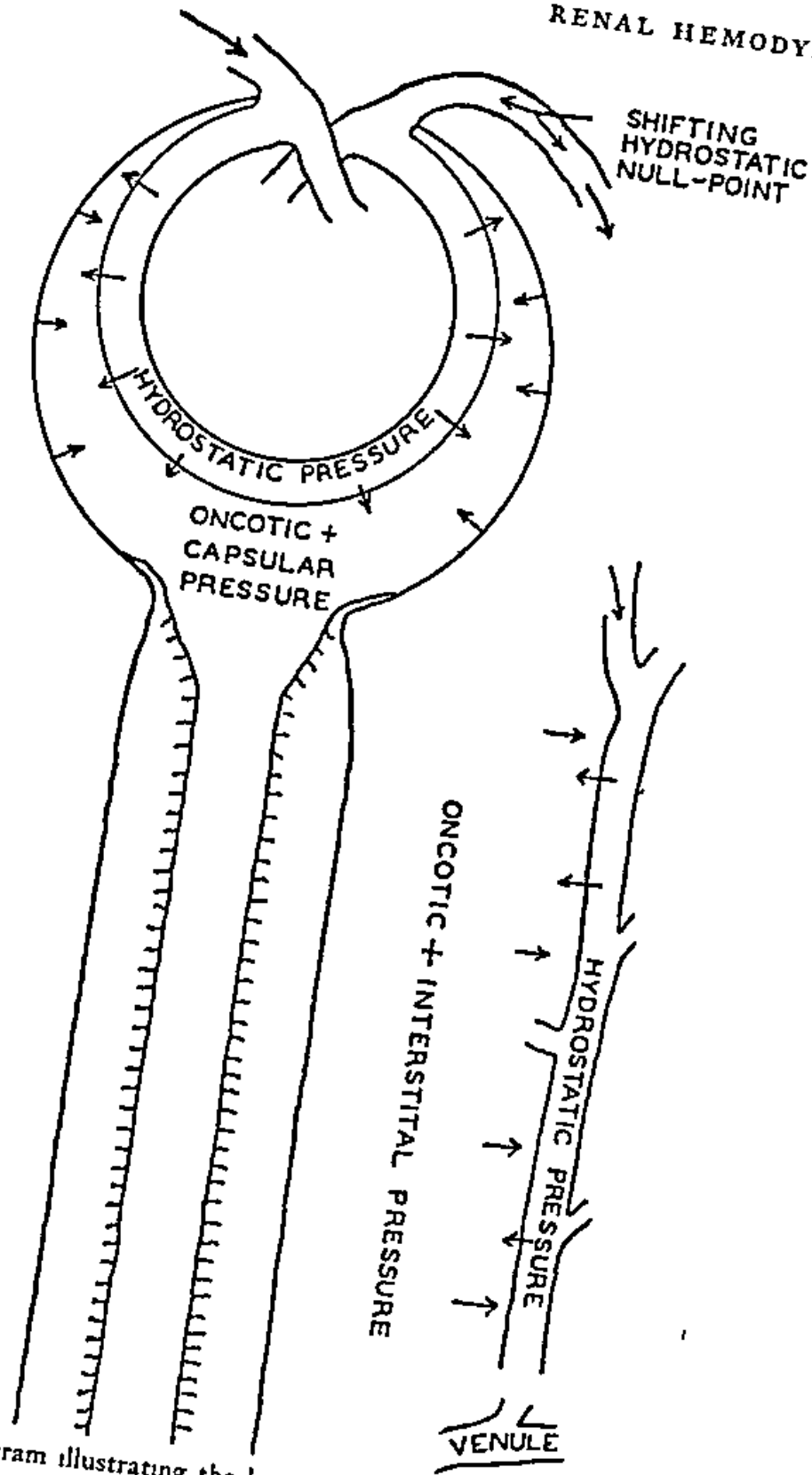


FIGURE 110. Diagram illustrating the hemodynamic factors involved in filtration and reabsorption.

Also in accordance with the principle of ultrafiltration, we conceive that it is because hydrostatic pressure is less than the sum of the oncotic plus interstitial pressure that fluid is reabsorbed from the interstitial space into the peritubular capillaries.

As the blood traverses the glomerular capillaries, the oncotic pressure will rise in consequence of increasing concentration of protein. Similarly, the oncotic pressure will decrease in the peritubular capillaries during fluid reabsorption (fig. 110). Should the opposing pressures tending to effect filtration and reabsorption become equal to each other in either of these capillary beds, transfer of fluid across the membrane would cease and filtration equilibrium would exist. Considerably doubt exists that filtration equilibrium is reached in either the glomerular or peritubular capillaries, but it will be very closely approached in the latter, despite the transfer of a large volume of reabsorbate, because of the large permeability coefficient. From a teleological point of view it is doubtful that filtration equilibrium occurs in the glomeruli, for this would waste the latter portion of the capillary plexus from filtration and, by promoting reabsorption of fluid, would in some measure defeat the filtration process. Again, teleologically, it is doubtful that it would occur in the peritubular capillaries, for this would waste the early portion of these capillaries from reabsorption and, by promoting filtration, would in some measure defeat the reabsorptive process Ideally, the hydrostatic null point or point of equality between opposing pressures should occur in the proximal end of the efferent arteriole with continued fall in pressure distally, thus promoting maximal filtration in the glomeruli and maximal reabsorption in the peritubular capillaries.

FILTRATION PRESSURE

The hydrostatic pressure in the mammalian glomerulus cannot be calculated directly Winton's studies [2249] on the isolated dog kidney indicate that the mean glomerular pressure in this preparation can vary from 30 to 90 per cent and averages about 60 per cent of the mean arterial pressure. Selkurt, Hall, and Spencer [1821] have found that the renal plasma flow and filtration rate are well maintained in anesthetized (pentobarbital) dogs at arterial pressures ranging from 150 down to 100 mm. Hg at lower

both functions decrease, the filtration rate decreasing more rapidly than the renal plasma flow, leading to a marked decrease in filtration fraction. Urine flow ceases at a pressure of about 60 mm. Hg, indicating that filtration stops at this arterial pressure. Because of decrement of pressure in the afferent arterioles, this figure throws no light on the minimal filtration pressure itself except to indicate that it may be of the order of 60 per cent of 60 mm. Hg, or 36 mm. Hg, i.e. somewhat above the oncotic pressure of the plasma (25 mm. Hg), as would be required in theory since some pressure head is required to effect filtration and move fluid down the tubules.

INTERSTITIAL (OR INTRARENAL) PRESSURE

Winton [2248] indirectly estimated the intrarenal pressure in the isolated perfused dog kidney by measurements of the arterial and venous pressures and the ureteral pressure in relation to changes in urine flow, and obtained an average figure of 10 mm. Hg. During some types of diuresis the pressure rose to 20 to 30 mm. Hg. A question may be raised, however, about the applicability of this indirect method, and especially with respect to the use of ureteral rather than pelvic pressures in such calculations.

Gottschalk (pers. com.), using capillary pipettes of approximately 100 μ diameter and noting the pressure required to cause minimal and reversible movement of fluid into the interstitium, btained an average interstitial pressure of 10 mm. Hg in cats, bbits, guinea pigs, and rats. When venous pressure was inreased by progressive compression of the renal vein, the interial pressure remained constant until the renal venous pressure roached the pre-existing intrarenal pressure and then began to

At renal venous pressures above 20 mm. Hg the interstitial sure was at most 1 or 2 mm. more than the renal venous pres-

Reducing renal arterial pressure by compression of the abnal aorta had no consistent effect on interstitial pressure at l pressures of 40 to 120 mm. Hg; below 40 mm., interstitial re began to decrease. Death of the animal, or complete of the renal artery, reduced the interstitial pressure and

the renal venous pressure to the same level, i.e. to 1 to 3 mm. Hg.*

Ferris (pers. com.), in observations made by means of a capillary pipette and a 25 gauge needle with side perforations, obtained values of 14 and 18 mm. Hg in 2 subjects without evidence of renal impairment, and undetermined values greater than 45 mm. Hg in 2 subjects with acute mercury nephrosis and anuria with visual evidence of renal edema Since the renal venous pressure in man averages 11.5 mm. Hg,[1419] it seems reasonable and convenient, for hemodynamic calculations in the normal subject, to take the intrarenal pressure as 10 mm Hg. Where the renal interstitial pressure is increased by an increase in renal venous pressure (cardiac failure, etc) on the basis of Gottschalk's observations it may be taken as equal to the latter. Where renal edema is present the interstitial pressure may be substantially higher than the renal venous pressure and no quantitative statements can be made in advance of measurement.

RENAL VENOUS PRESSURE

Blake, Wegria, Keating, and Ward report that the normal renal venous pressure in the anesthetized (pentobarbital) laparotomized dog averages 7 7 ± 1.5 mm. Hg.[188] Fishman, Stamler, Katz, Miller, Silber, and Rubenstein [660] find that in trained, unanesthetized, resting dogs this figure ranges from 7 to 9 mm. Hg. This pressure, as measured by renal vein catheterization in 17 normal human subjects, averaged 11.7 mm. Hg (10 to 14.6).[1419] The point of zero reference in these studies was determined roentgenologically to average 9 4 cm. above the table top with the subject in the recumbent position.

* Bush, Coffman, Montgomery, and Swan [301] report that the pressure required to force 1 to 2 cu mm. of saline into the dog kidney through a 20 gauge needle with side perforations averaged 72 mm Hg (range 55 to 88 mm.). Similar values were obtained in cats and rabbits This method in the hands of these investigators yielded intramuscular pressures of 4 to 7 mm. Hg. They do not equate this pressure with the interstitial pressure, however, it is probable that it represents tearing or distortion pressure uniquely related to their technique and having nothing to do with interstitial pressure.

Blake *et al.*[188] found that when the renal venous pressure was increased on one side in the anesthetized (pentobarbital) laparotomized dog, elevation of pressure to 27 mm. Hg had no effect on filtration rate, renal blood flow, T_{mG} or T_{mP}. (The increased sodium and water reabsorption observed by them under these conditions has been noted in chapter XXII.) In their studies on unanesthetized dogs with pericardial tamponade, Fishman *et al.* find that renal venous pressure may rise to 20 mm. Hg with reduction in filtration rate or renal blood flow. The absence of hemodynamic effects implies that postglomerular dilatation offsets the increased venous pressure. In contrast to these results, however, are those of Selkurt, Hall, and Spencer,[1824] who by similar methods (laparotomized dogs anesthetized with pentobarbital) found that an increase in renal venous pressure from 7.5 to 22.4 mm. Hg decreased the renal blood flow and filtration rate by an average of 15 per cent, a decrease that can be explained almost entirely by the decrease in pressure gradient across the renal vascular circuit, the arterial-venous pressure difference decreasing by an average of 11.5 per cent The PAH and creatinine clearances showed parallel reductions, indicating that elevated renal venous pressure does not increase glomerular pressure.*

In view of these conflicting results, and especially in view of the possibility of initiating changes in renal vasomotor tone by increasing renal venous pressure, it seems impossible to define the pure hemodynamic effects of the latter at the present time except to affirm the conclusion that the increase in renal venous pressure in chronic congestive failure, whatever its effect on sodium reabsorption, cannot explain the observed reduced filtration rate and renal blood flow.†

* Vasomotor changes in the kidney cannot be ruled out, and it is particularly to be noted that in the experiments of Selkurt *et al* the renal plasma flow throughout the period of observation was steadily declining, falling by as much as 30 per cent in 2 hr or so. This fact in itself implies that renal vasomotor changes were somehow initiated by the conditions of the experiment.

† Maxwell, Breed, and Schwartz[1419] report an average renal venous pressure of 22 mm Hg (12 7 to 30 0) in 9 subjects in congestive heart failure, and, as noted in chapter XXII, calculation shows this to be insufficient to reduce the renal blood flow by more than 14 per cent, far less than is observed in most patients in failure

CALCULATION OF RENAL RESISTANCE

Smith, Chasis, Goldring, and Ranges [1934] attempted to treat the problem of renal resistances hemodynamically. They erroneously started with the assumption that filtration equilibrium is necessarily reached in the glomerulus.

In Lamport's [1201, 1202] subsequent treatment of this problem he also commits himself to the unwarranted assumption above and introduces a minimal factor of 20 mm Hg plus another 20 mm. intracapsular pressure, both opposing flow Lamport deduces that the conditions required for a constant filtration rate when the renal blood flow is changing are represented by inverse changes in afferent and efferent arterioles This does not appear to follow from his own equations and is contrary to hemodynamic principles. The consequences of such inverse changes are illustrated by figure 13 in Gomez' [806] discussion of renal hemodynamics.

Brun, Knudsen, Petersen, and Raaschou [279] have examined the process of filtration in a physical model and translated their observations through hydrodynamic equations to the changes in renal clearances observed in the supine and erect posture. They conclude that the changes in clearance cannot be explained solely by general changes in the pressure and composition of the blood, but must involve changes in efferent arteriolar tone.

The theoretic aspects of renal hemodynamics have subsequently been treated in detail by Gomez [807] as a subordinate phase of general hemodynamics,[806] and the following working equations for the calculation of renal resistances have been derived by him from that analysis.

The application of hemodynamic theory to the calculation of segmental resistances requires certain simplifying assumptions, without which no evaluation whatever can be attempted. These assumptions involve the following considerations:

a. The blood flow is a linear function of pressure only when oth flow and pressure are relatively large, and the calculation of esistances is meaningful only under such conditions. It would eem that one can safely treat flow and pressures down to about e-third and two-thirds of their respective normal values (i.e. o cc. for renal blood flow and 60 mm. Hg for mean arterial essure).

b. The specific coefficient of permeability of a membrane is d fined as the rate of movement of fluid across a unit area per un pressure per unit time (cc. per sq. cm. per mm. Hg per sec.). Th gross permeability coefficient is the product of the specific perme- ability coefficient times the total surface area. In comparing two individuals, or the same individual under different circumstances, it must be assumed that the gross permeabilities of both the glomerular bed and peritubular capillaries remain constant, a an approximate numerical value must be assigned to the form This assumption of constant gross glomerular permeability is n applicable to glomerular disease (glomerulonephritis, nephrosis intercapillary glomerulosclerosis, eclampsia, etc.) and in such in- stances valid hemodynamic comparisons with the normal kidney cannot be made.

c. The interstitial pressure will in theory remain relatively con- stant within certain limits of renal blood flow, but it will be de- pendent on the venous pressure, as specified above. A numerical value must be assigned to the interstitial pressure, an assignment that can be made, so far as the normal kidney is concerned, on the basis of Gottschalk's studies.

d. During filtration, the oncotic pressure of the plasma is in- creased, and this increase may affect or in turn be modified by a shift of water between the red cells and the plasma. This shift is here neglected and the change in oncotic pressure in the glomeruli is related simply to the fraction of plasma water filtered.

The values of total glomerular permeability, interstitial pres- sure, and renal venous pressure that must be assumed for purposes of calculation are within wide limits not critical in influencing the qualitative changes in calculated resistances.

e. For practical purposes the renal circulation may be divided into five functional segments:

1. afferent arterioles
2. glomerular capillaries
3. efferent arterioles
4. peritubular capillaries
5. venules

Since these segments are arranged in series, each segment independently contributes its quota of resistance to the total resistance between the renal artery and vein. In general, variations in the resistance offered by any segment may be conceived as resulting chiefly from variations in the total cross-sectional area of that segment, but they will generally be accompanied by passively induced changes in caliber, and therefore in resistance, of other segments.

Hemodynamic theory does not at the present time permit us to calculate the local resistance of the glomerular capillaries or the peritubular capillaries as individual segments, and their contribution to total renal resistance must therefore be subsumed in efferent and venular resistance, respectively. But because of the large number of capillaries involved in both segments, and the relatively slow movement of blood in each capillary, their absolute contribution to resistance is small in comparison with that of the afferent and efferent arterioles and the venules.

Neither can an exact anatomical locus be ascribed to these segments. Rather this locus must be defined functionally, the afferent resistance as the resistance of the arterial and arteriolar bed and some undefined fraction of the glomerular resistance, the latter having a small value relative to the whole, the efferent resistance as the residual glomerular resistance (again very small) plus the resistance of the efferent arteriole and an undefined fraction of the resistance of the peritubular capillaries (again very small); and the venous resistance as the residual peritubular capillary resistance plus the resistance of the venules and veins down to the vena cava (or renal vein) where the renal venous pressure is measured.

The total renal resistance is equal to the sum of the segmental (series) resistances and, in conventional hemodynamic terms, may be calculated as the effective perfusion pressure divided by the blood flow:

$$(1) \qquad R = \frac{P_m - P_v}{Q} \times 1328 = R_A + R'_E + R_V$$

where R = total renal resistance (dynes. sec. cm.$^{-5}$)
R_A = afferent resistance (dynes. sec. cm.$^{-5}$)
R'_E = net efferent resistance (dynes. sec. cm.$^{-5}$) (to be defined below)
R_V = venular resistance (dynes. sec. cm.$^{-5}$)
P_m = mean arterial pressure (mm. Hg)
P_v = renal venous pressure (mm. Hg)
Q = renal blood flow in cc/sec. (all values of Q and of the filtration rate, q, must be corrected to 1.73 sq. m. before incorporation into the equations, because surface area does not factor all the terms in equations 6, 8, and 10.)

The factor 1328 serves to convert blood pressure units (mm. Hg) into absolute units of resistance and is derived by multiplying the acceleration of gravity, G (980.6 cm. sec.$^{-2}$), by the weight of 1 mm. of Hg (1 3546 at 20° C.), this product yielding dynes/sq. cm. or barys, which when divided by cc/sec. yields dynes. sec. cm.$^{-5}$

Equation 1 directly yields the total renal resistance, R, by its second member through the clinically determinable values, P_v, and Q.

VENULAR RESISTANCE, R_V

In order to convert the third member of this equation into one involving clinically determinable data, the first step is to note that the venular resistance, R_V, is the decrement in pressure between the peritubular capillaries and the renal vein, divided by the renal blood flow. Assuming that filtration equilibrium has been very closely approximated in the peritubular capillaries,* the hydrostatic pressure as it enters the venules may be taken as equal to the oncotic pressure plus the interstitial pressure:

$$R_V = \frac{P_t - P_v}{Q} \times 1328 = \frac{H + h - P_v}{Q} \times 1328 \tag{2}$$

* As must be the case where 85 to 99+ per cent of the water of the glomerular filtrate is reabsorbed by these capillaries

where P_t = the mean hydrostatic pressure at the end of the pe tubular capillaries

P_v = the renal venous pressure (or vena caval pressu near the outlet of the renal vein)

h = the mean oncotic pressure in the peritubular capi laries (to be defined below)

H = the interstitial pressure

P_v, if known, is to be taken as measured, or, in the absence of increased peripheral venous pressure, the normal approximate average value of 10 mm Hg may be used; h may be obtained from the protein concentration of systemic blood by applying the following relationships:

(3)

$$C_E = C_A \frac{Q'}{Q' - q}$$

where C_A = the plasma protein concentration (in gm/100 cc.) in afferent blood

Q' = the renal plasma flow

q = the filtration rate (both in cc/1 73 sq. m.)

C_E = the plasma protein concentration in the efferent glomerular blood

The mean protein concentration, C_m, in both the glomerular and peritubular capillaries may be taken as the arithmetical mean between C_A and C_E:

(4)

$$C_m = \frac{C_E + C_A}{2} = C_A \left(\frac{Q' - \frac{q}{2}}{Q' - q} \right)$$

The mean oncotic pressure is calculated from the following empirical formula

(5)

$$h = A[C_m - 2]$$

where A is a factor having the dimension of pressure. This term has been determined from the relationship between oncotic pressure and plasma protein concentration in normal subjects, as recorded by Wells, Youmans, and Miller,[2184] to have an average value of 5 0.

In respect to H, a choice must be made between the alternati conditions of low and high renal venous pressures: where P_v is les than 10 mm. Hg, H may be taken as constant and equal to 10 mm.; where P_v is equal to or greater than 10 mm., H may be taken as equal to P_v with the important qualification that H may be greater than P_v in renal disease (constrictive perinephritis, etc.) or in the presence of renal edema.

NET EFFERENT RESISTANCE, R'_E

In speaking of the efferent resistance, it will be observed that a quantity, q, of fluid is shunted around the efferent arterioles by glomerular filtration and tubular reabsorption into the peritubular capillaries, this quantity normally amounting to about 10 per cen of the renal blood flow. We must, therefore, distinguish between what would be the true efferent resistance were this shunting absent, and the net efferent resistance as calculated with due allowance for the shunt.

The true efferent resistance, R_E, and the compound total permeability of the glomerular and peritubular capillaries are related in such a manner that R_E is equal to the quotient of the 2 parallel shunts, q and Q − q, divided by $\bar{\lambda}$, the gross permeability of the glomerular capillaries:

(6)

$$R_E = \frac{q}{\bar{\lambda}(Q - q)} \times 1328$$

The approximate value of $\bar{\lambda}$ is 0.0812, this value (which is the inverse of a resistance) being derived from the average filtration rate of 130 cc/min. and the assumed intraglomerular pressure of 60 mm. Hg.* Any error in this assumed value will affect all calculated resistances equally so long as H is fixed and therefore will not distort the calculation of relative resistances.

The net efferent resistance, R'_E, is that presented by the parallel combination of the efferent arteriolar segment and the shunt through the glomerulus and peritubular capillaries. R'_E, R_E, and λ are connected through the conventional relation for parallel re-

*$\bar{\lambda} = \frac{q}{P_g - h - H}$ where P_g is the glomerular pressure, here taken as 60 mm. Hg, q is here taken as 2 167 cc/sec , h as 25, and H as 10 mm. Hg.

sistances by the equation

(7)
$$R'_E = \frac{R_E \times 1328}{\bar{\lambda}R_E + 1328} = \frac{R_E}{\frac{\bar{\lambda}R_E}{1328} + 1}$$

Substituting (6) in (7)

(8)
$$R'_E = R_E \frac{Q - q}{Q}$$

AFFERENT RESISTANCE, R_A

From equation (1)

(9)
$$R_A = R - (R_V + R'_E)$$

Alternatively, replacing R, R_V, and R'_E by their respective values as obtained from the second member of (1), from the third member of (2), and from (8),

(10)
$$R_A = \frac{1328}{Q}\left[P_m - \left(H + h + \frac{q}{\bar{\lambda}}\right)\right]$$

all the terms of which are clinically determinable.*

GLOMERULAR DYNAMICS IN THE NORMAL HUMAN KIDNEY

NORMAL VALUES OF RENAL RESISTANCES

Normal values of renal resistances, calculated from the averaged data on renal clearances recorded on normal subjects by Goldring

* In this derivation, plasma flow is to be taken as equal to the diodrast or PAH clearance uncorrected for E_D or E_{PAH}. In the normal kidney, the fact that E is less than 1.0 may be in great part attributed to shunting of blood around the excretory tissue of the kidney (i.e. through the perirenal fat, capsule, etc.) and this extrarenal circulation may be treated as a shunt, the resistance of which, R_s, is

(11)
$$R_S = E\frac{P_m - P_V}{(1 - E)Q} \times 1328$$

The net parallel resistance, R_W, of the kidney including this shunt is then

(12)
$$R_W = \frac{RR_s}{R + R_s} = E\frac{(P_m - P_V)}{Q} \times 1328$$

et al.[197] by assuming $P_m = 90$ mm. Hg, are given as series I in tal
XVII. Series II of this table represents similar calculations from th

TABLE XVII

Renal Resistances

	Normal subjects		Hypertensive subjects	
	Series I Data from Goldring *et al.*[197]	Series II Data from Bolomey *et al.*[207]	Series III Data from Bolomey *et al.*[207]	Per cent increase relative to series II
R	$\times 10^3$	$\times 10^3$	$\times 10^3$	
R_A	5 31	6 97	17.2	147
R'_E	1 99	3.17	11.3	256
R_V	1 66	1 91	2 98	56
	1.66	1 88	2.98	58

averaged data recorded by Bolomey *et al.*,[207] using the observed average blood pressure of 92 mm. Hg.

Figure III shows the mean pressures to be expected at the end of various renal segments when all critical terms are given arbitrary values.

ESSENTIAL HYPERTENSION

Average clearance data on 26 subjects with essential hypertension ($P_m = 145$ mm. Hg) are given by Bolomey *et al.*[207] The renal resistances calculated from the mean values for the entire series are given in table XVII. It will be seen that, relative to series II, in these hypertensive subjects R is increased by 147 per cent, R_A by 256 per cent, R'_E by 56 per cent, and R_V by 58 per cent.

Were the 'normal' kidney, represented by series II, perfused at a mean pressure of 145 mm. Hg, as in the hypertensive subjects, and the resistances not changed, the filtration rate would be increased from 123 to 178 cc., the renal blood flow from 1052 to 1545 cc., and the filtration fraction from 0.190 to 0.280.

Conversely, were the perfusion pressure of the hypertensive kidney (series III) reduced to the normal value of 92 mm. Hg (as in series II), the filtration rate would decrease from 79.8 to below 38 cc. and the renal blood flow from 670 to below 378 cc., these terminal figures probably being too high because of the passive diminution in the diameter of the vessels at the reduced pressure.

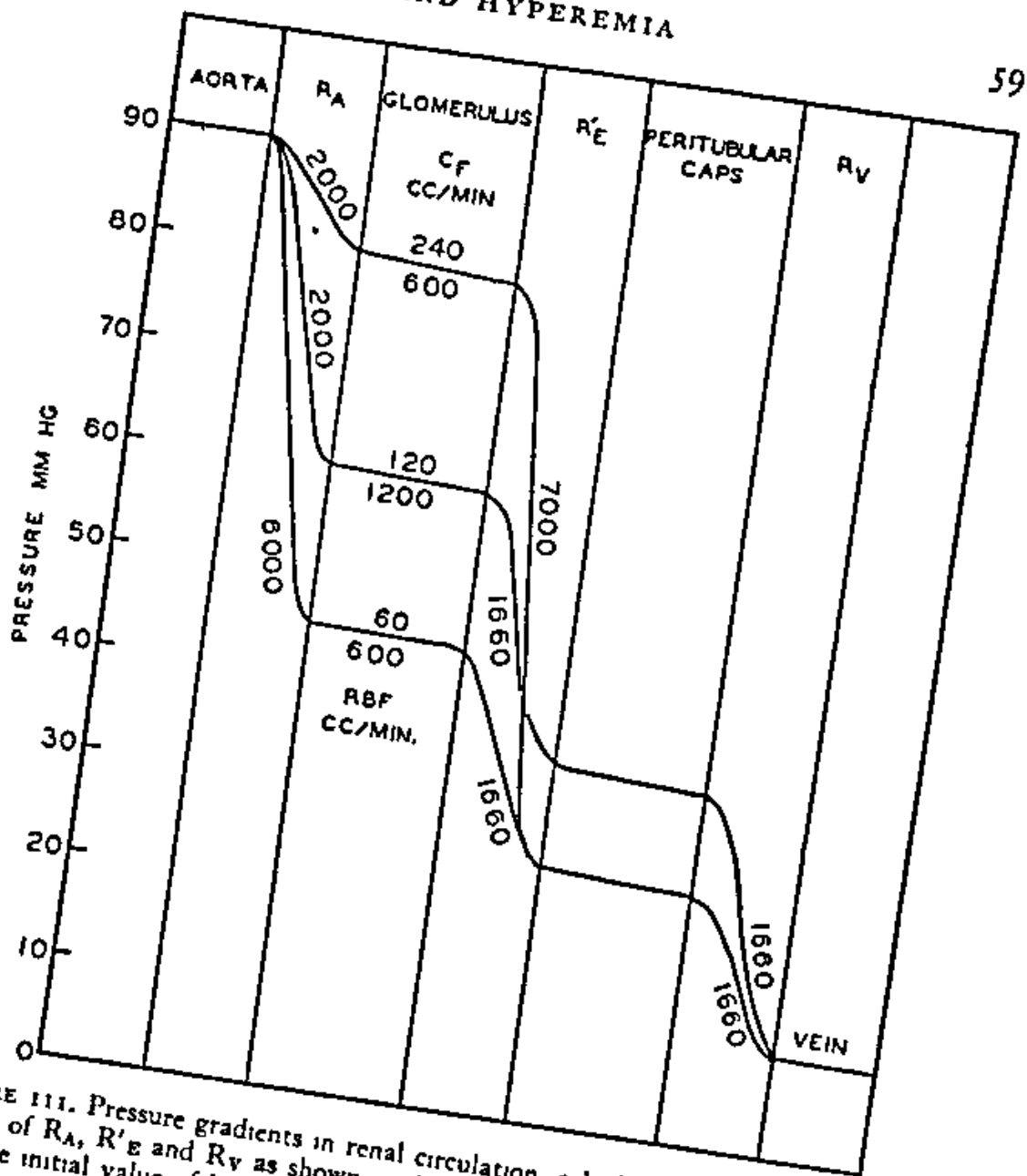


FIGURE 111. Pressure gradients in renal circulation, calculated for the selected values of R_A, R'_E and R_V as shown, and H = 10 mm Hg, C_A = 6 5 gm/100 cc The initial value of h for the mid-curve is 24 mm. Hg, this term varying with the imposed new resistances

RENAL ISCHEMIA AND HYPEREMIA

Numerous data are available on the diodrast and inulin clearances in normal subjects under various conditions of renal blood flow. These data may be divided into three groups: (1) observations made during standard conditions by Goldring *et al.*,[197] which w hall designate as 'basal,' with the reservations concerning the us

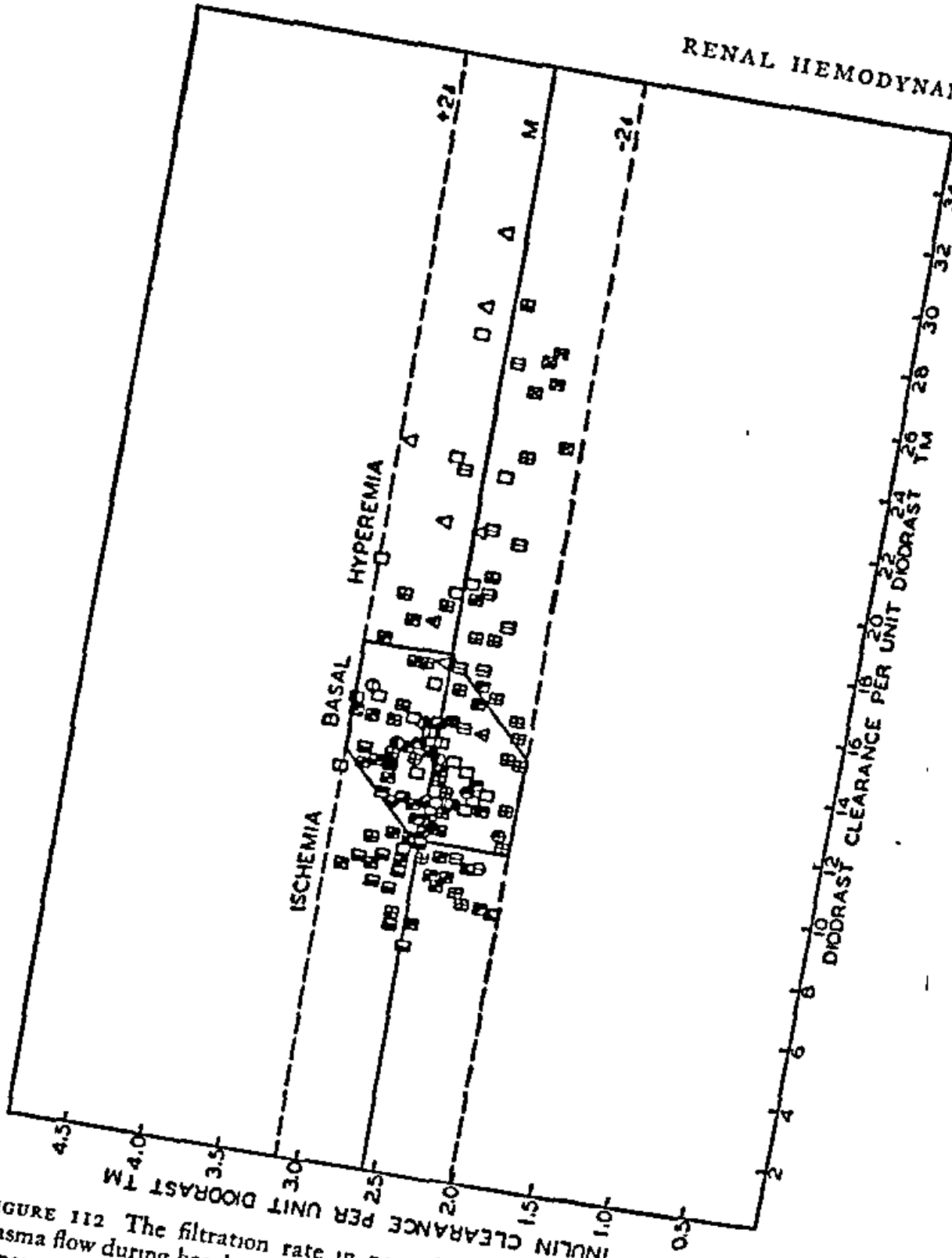


FIGURE 112 The filtration rate in normal subjects in relation to the renal plasma flow during basal conditions, ischemia induced by adrenalin and pyrexial hyperemia.

On the assumption that diodrast Tm, which is a measure of the total tubular excretory tissue in the kidney, is closely proportional to the total renal weight,

of this word stated by the authors; (2) observations made during the reduced renal blood flow induced by adrenalin, neosynephrin, and marked apprehension, and here referred to as 'ischemia'; and (3) observations made during the increased renal blood flow induced by the pyrexial reaction and here designated as 'hyperemia.'

These data are presented in figure 112. Each datum contained in the 'basal' group is the average of 3 or more consecutive clearance periods, each subject being recorded as often as examined. Each datum referable to 'ischemia' or 'hyperemia' is the average of at least 2 successive clearance periods obtained during reduced or increased renal blood flow, each subject thus contributing several data from each occasion on which ischemia or hyperemia was induced. Goldring *et al.* reported, in 35 men and women, the average value of $C_{IN}/Tm_D = 2.56 \pm 0.28$ cc/min.; for purposes of comparison this mean is indicated by a solid line with twice the standard deviation (dashed lines). This mean ratio includes only observations made under 'basal' conditions, and in its calculation each subject enters only once, thus contributing to the mean only his or her average behavior.

It is evident from figure 112 that the ratio C_{IN}/Tm_D at all renal blood flows is adequately contained within the statistical parameters of the 'basal' data. It may therefore be said that the filtration rate remains essentially constant during ischemia and hyperemia induced by the measures specifically stated. (It is not implied that this constancy will obtain if ischemia or hyperemia is induced by measures other than those stated, and indeed such is not the case.)

In consequence of the constancy of the filtration rate, the filtration fraction shows a reciprocal relation to renal blood flow,

---

Each datum represents the average of 2 or more clearance periods, each subject furnishing several data on each examination under ischemia or hyperemia

The hexagon is an arbitrary area which encloses 95 per cent of the basal observations (Smith, Chasis, Goldring, and Ranges [111])

the two variables, C_{IN}/C_D and C_D/Tm_D, necessarily generating a rectangular hyperbole as shown in figure 113.

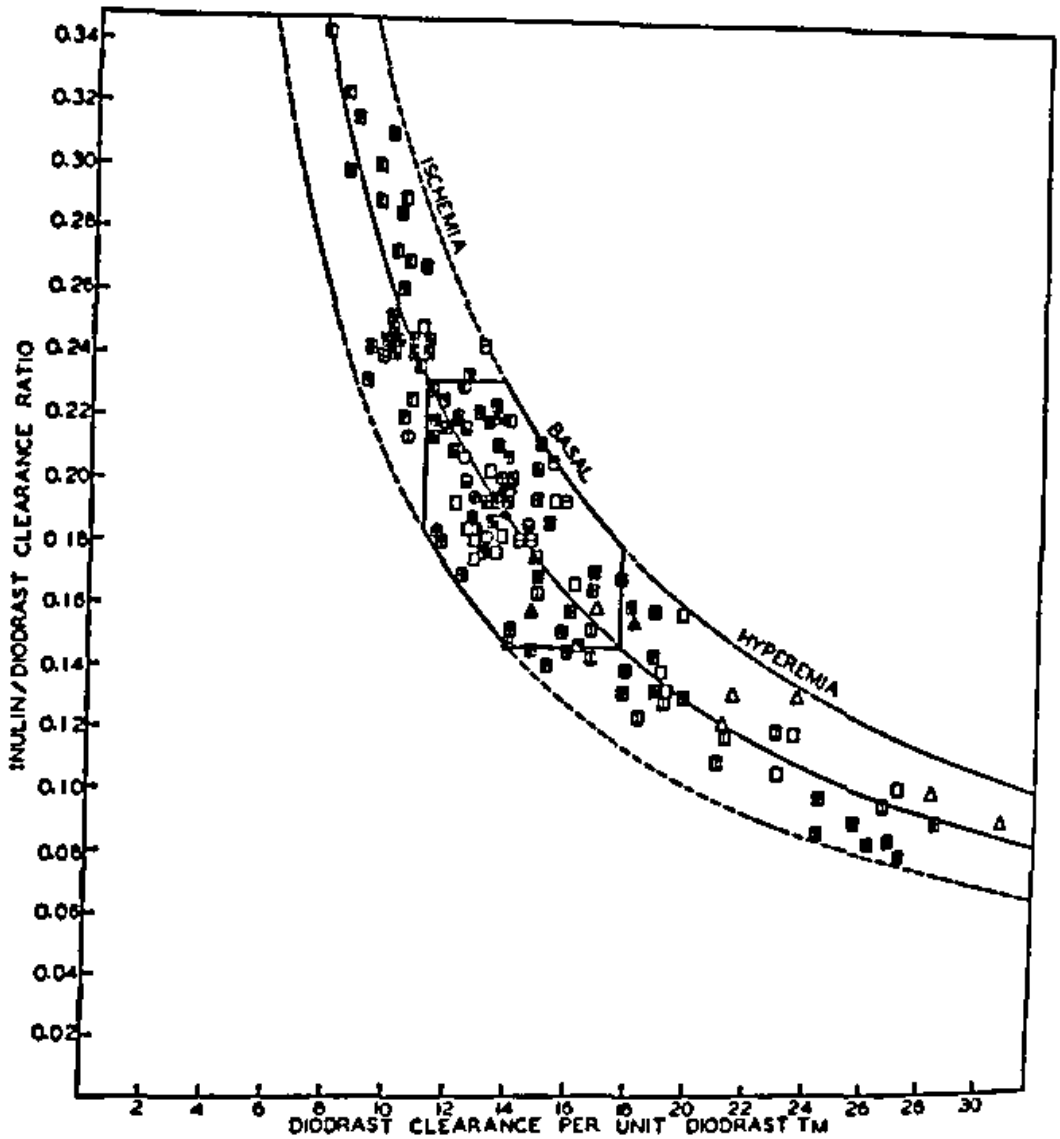


FIGURE 113. The filtration fraction in relation to renal plasma flow per unit Tm_D. The solid curve represents the course of the filtration fraction if the filtration rate remains constant (see fig 114); i.e if $C_{IN}/C_D \times C_D/Tm_D = C_{IN}/Tm_D = 2.56$. The dotted lines represent this mean value $\pm 2\sigma$ The hexagon is an arbitrary area which contains 95 per cent of the normal data obtained under basal conditions, under adrenalin, the filtration fraction rises above the limits of the hexagon, during hyperemia it falls below, but in both instances it remains within the normal parameters (Smith, Chasis, Goldring, and Ranges [1934])

The hemodynamic sequence in the kidney which gives rise to a relationship such as is shown in figures 112 and 113 can best be grasped from figure 114, which represents the changes in filtration

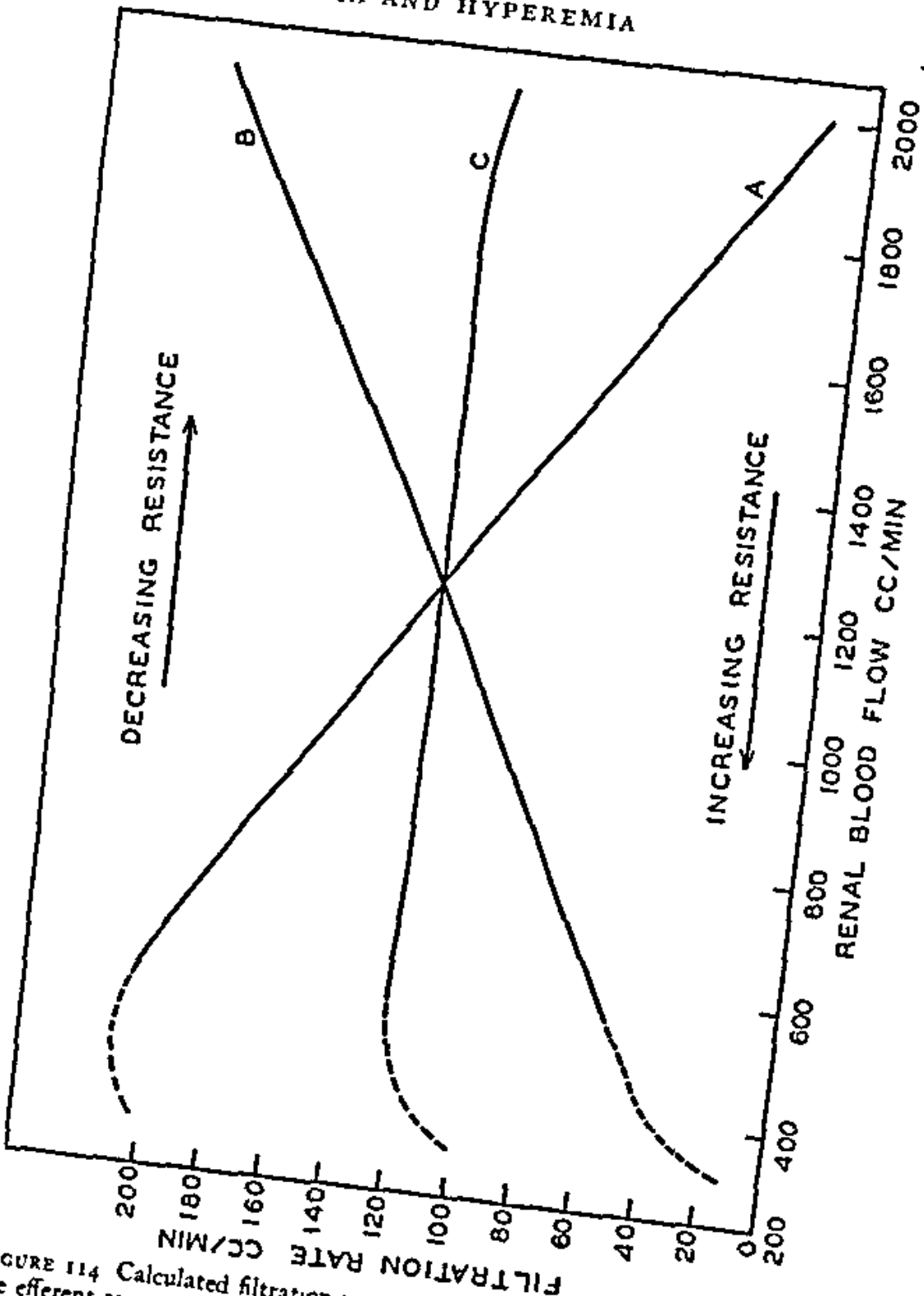


FIGURE 114 Calculated filtration rate in relation to renal blood flow (A) when the efferent resistance alone is changed, (B) when the afferent resistance alone is changed, and (C) when both resistances are changed proportionally. At the normal point of departure the renal characteristics are as follows. $R_A = 1.99 \times$

to be expected from changing only (a) efferent arteriolar resistance, (b) afferent arteriolar resistance, and (c) by equal changes in both segments. In constructing this figure, arbitrary values were taken for the median point, the renal blood flow, filtration rate, R_A, and R'_E, while R_V was taken as constant throughout. When the renal blood is reduced by pure efferent constriction, the filtration rate increases. This is because any increase in R'_E is accompanied by an increase in glomerular pressure and consequently in the filtration fraction. Conversely, when the renal blood flow is reduced by pure afferent constriction the filtration rate decreases. Exactly equal changes in R'_E and R_A result in only a moderate increase in filtration rate as the renal blood flow is decreased from large to small values lying within the physiological range of hyperemia and ischemia, shown in figure 112.

The changes in filtration fraction corresponding to the foregoing changes in resistance are shown in figure 115.

It must be concluded that, contrary to the conclusion of Smith *et al.*,[1934] the functional changes in renal blood flow associated with hyperemia and adrenergic ischemia represent approximately equal changes in R_A and R'_E, disregarding changes in R_V.

Data derived from unpublished studies by Gomez, Maxwell, Fishman, Morales, and Crowder, obtained during the intravenous infusion of adrenalin are given in figure 116. The data shown at A give the segmental resistances in absolute units during the control period. Moderate reduction in renal blood flow was effected by adrenalin at B without reduction of filtration rate. This is perhaps the most frequently observed effect of moderate doses of adrenalin, as shown in figure 77. At this time R_A had increased by 19.2 per cent, R'_E by 37.7 per cent, and R_V by 34.5 per cent. At C, where the renal ischemia was most marked and the filtration rate was somewhat reduced, these increments were 81.6, 49.6, and 109.3 per cent respectively.

Thus the most marked effect of adrenalin at the peak of its

10^3, $R_E = 1.66 \times 10^3$ and $R_V = 1.66 \times 10^3$, $C_F = 120$ and RBF = 1200 cc/min, H = 10 mm. Hg. The initial value of the mean oncotic pressure, h, is 24 mm. Hg, but this value is dependent on the changes in resistance which are imposed on the system, being determined by the derived values of filtration rate and renal plasma flow.

action was upon the venular resistance, the effect on the efferent segment being intermediate in intensity. (It cannot be supposed that this is the invariable action of adrenalin; larger doses might have a qualitatively different effect.) This increase in venular re-

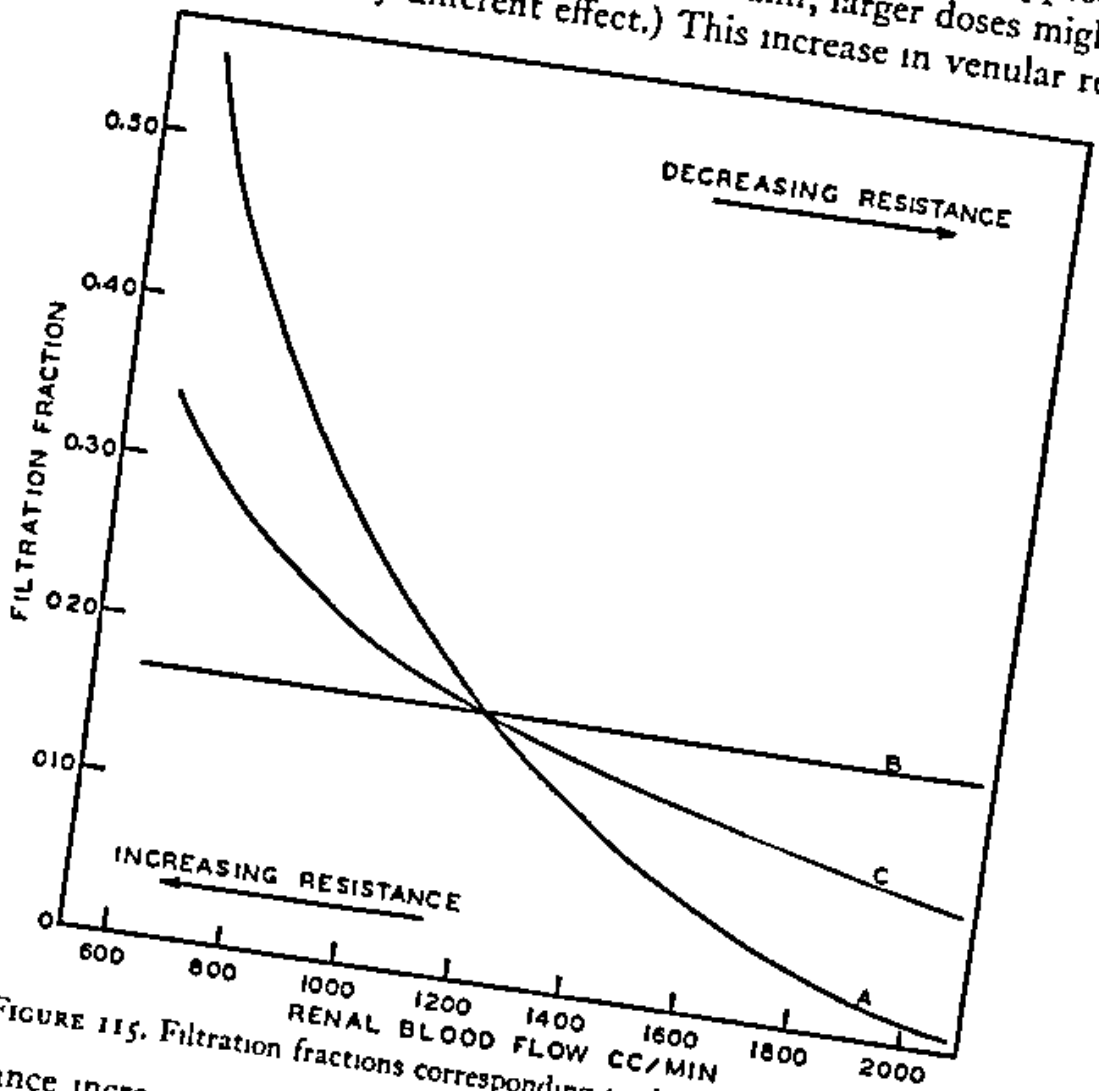


FIGURE 115. Filtration fractions corresponding to the data in figure 114.

sistance increases the pressure in the peritubular capillaries and opposes the reabsorption of water, leading to an increase in the volume of the interstitial fluid. It is this expansion of the interstitial fluid, rather than an increase in volume of the glomeruli, which we conceive to be the explanation of the paradoxical increase in volume of the kidney under the action of adrenalin as first described by Richards and Plant [113]

Figure 117 shows a normal subject examined during pyrexial hyperemia induced by the intravenous administration of 75 mil-

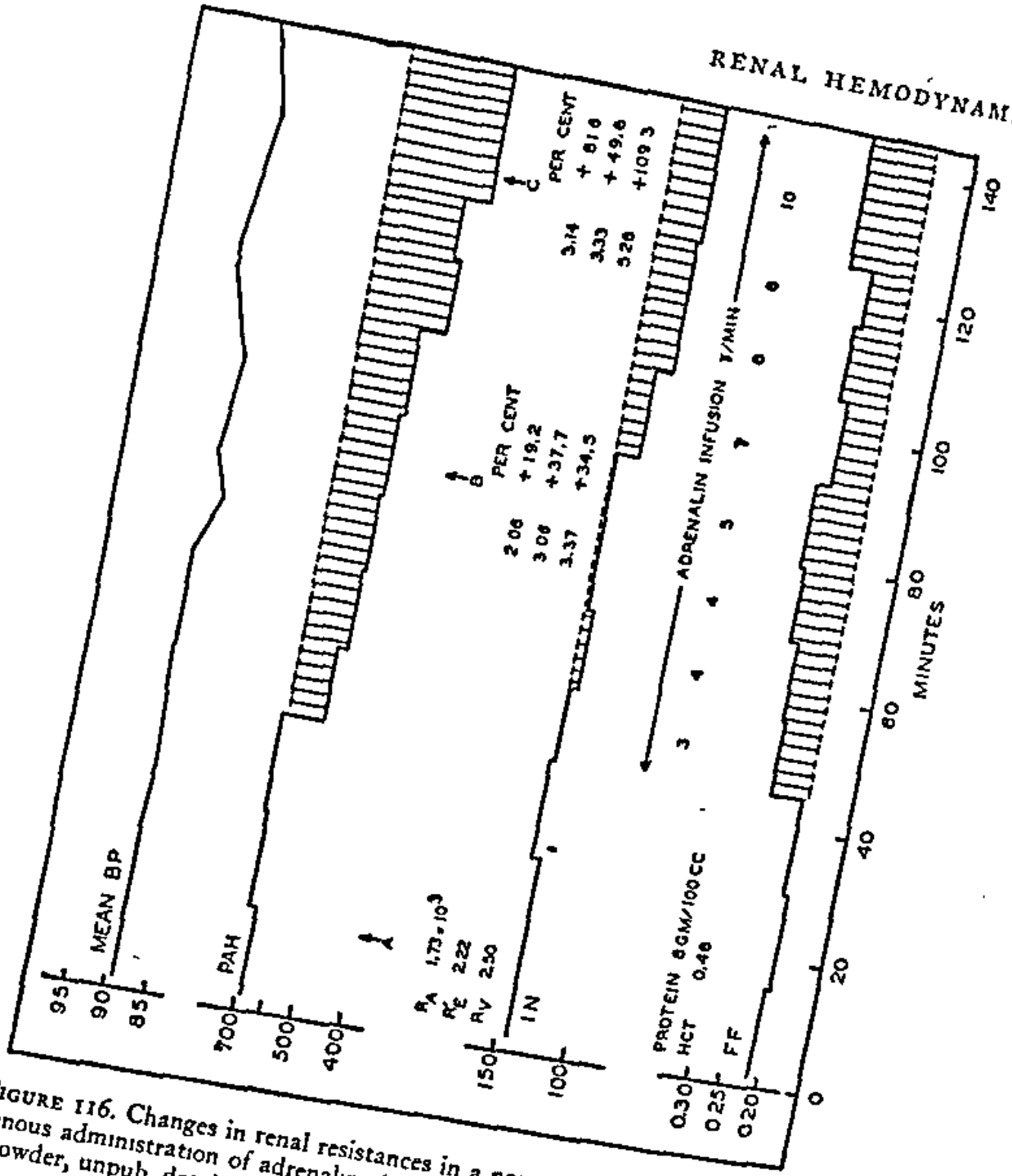


FIGURE 116. Changes in renal resistances in a normal subject during the intravenous administration of adrenalin. (Gomez, Maxwell, Fishman, Morales, and Crowder, unpub. data)

lion triple typhoid vaccine. The patient had been premedicated with amidopyrine, 10 grains every 4 hr. from noon the day before until 8 A.M. on the day of the test (see also figures 83 and 84). As usual, renal hyperemia follows only after a long latent period. At B, about the time at which the chill would have occurred in an un-

premedicated subject, the blood pressure decreased significantly, this period of hypotension being accompanied by a transient reduction in the filtration rate. At B, R_A had decreased by 34.7 per cent, while R'_E and R_V had increased by 102 and 169 per cent, respectively. At C all 3 resistances had decreased by 52.7, 44, and 55 per cent respectively.

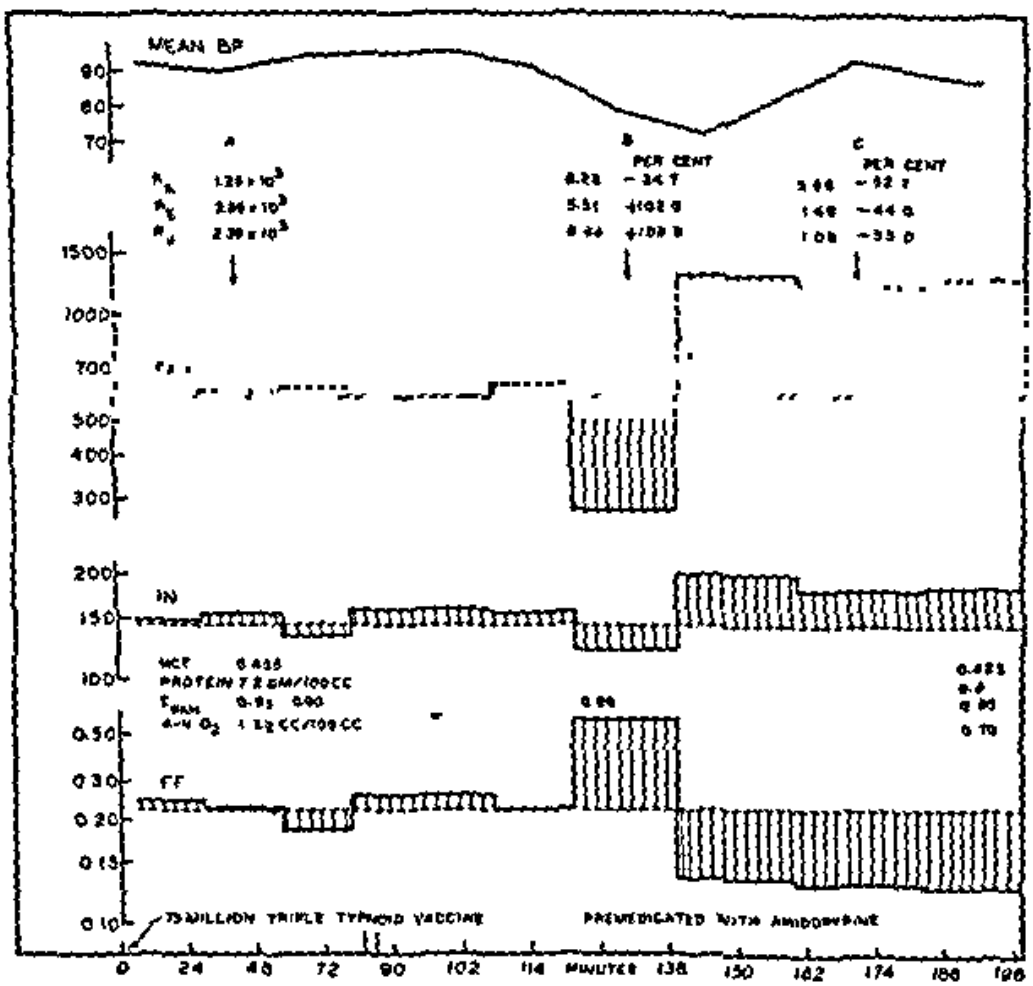


FIGURE 117 Changes in renal resistances in a normal subject during pyrexial hyperemia (Gomez, Maxwell, Fishman, Morales, and Crowder, unpub data)

CONGESTIVE HEART FAILURE

Figure 118 shows observations in a subject in the edematous state of chronic congestive heart failure. As noted in chapter XII, in this condition the renal blood flow and filtration rate are markedly reduced. In this particular patient, all resistances were increased

over normal, R_V somewhat more than R_A and R'_E. Paracentesis of 3700 cc. of ascitic fluid had no effect on renal function, and neither did phlebotomy, despite the fact that the latter caused a decrease in peripheral venous pressure from 30 to 20 mm. Hg.

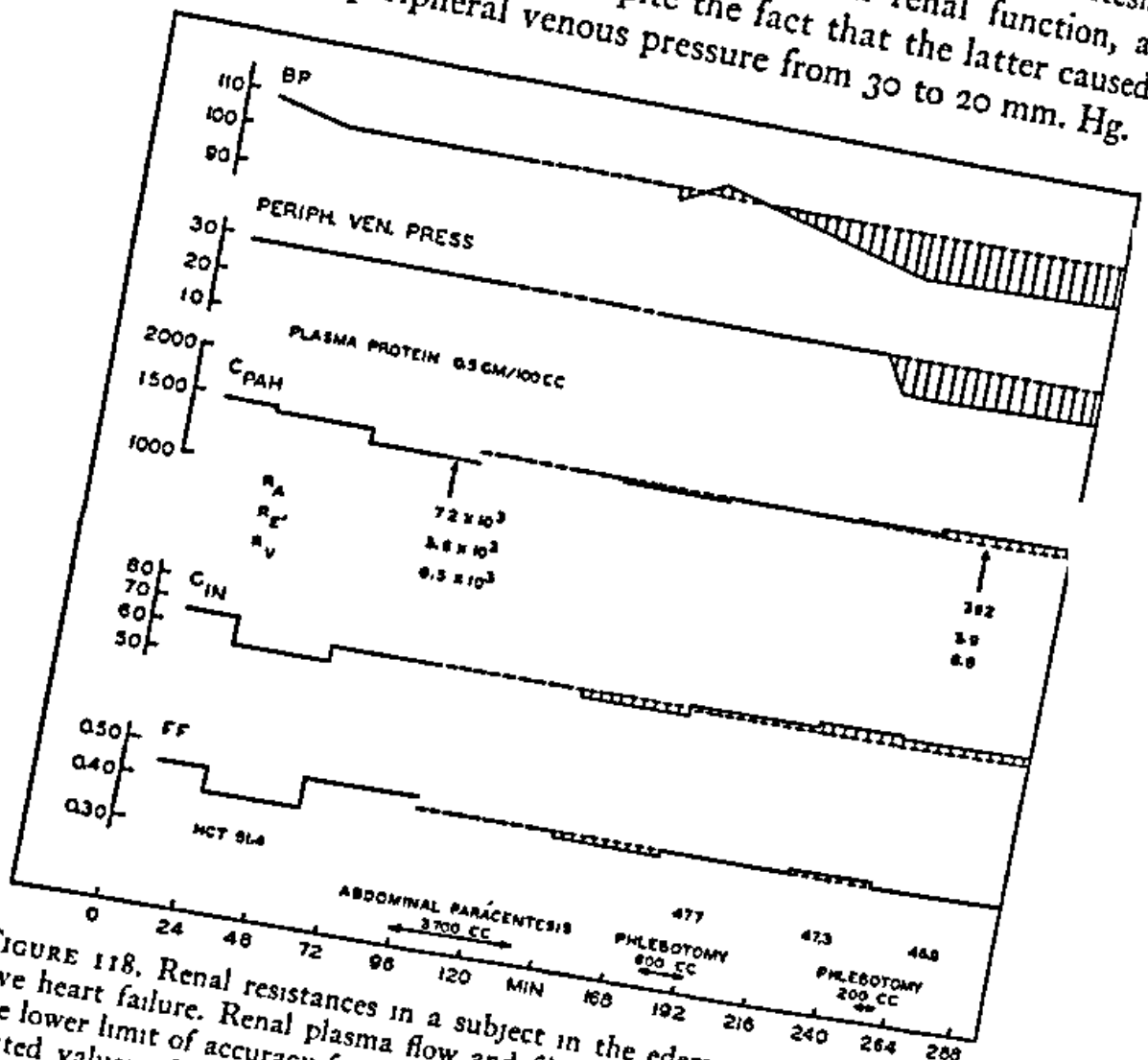


FIGURE 118. Renal resistances in a subject in the edematous state of congestive heart failure. Renal plasma flow and filtration rate in this patient are at the lower limit of accuracy for the use of hemodynamic equations and the estimated values of R may be inaccurate. (Gomez, Maxwell, Fishman, Morales, and Crowder, unpub data)

These studies show that all three vascular segments are involved in spontaneous changes in renal blood flow and in those which accompany adrenalin ischemia of moderate intensity and pyrexial hyperemia.* The present data lead us to infer, and at the moment it can be no more than an inference, that the muscularly active

*It may be recalled that adrenalin ischemia and pyrexial hyperemia are essentially unmodified in the denervated human kidney (ch. XIV).

segments of the renal circulation, the afferent and efferent arterioles and veins, comprise an integrated system which generally operates, in the interests of glomerular-tubular balance, to maintain a constant filtration rate. In view of the evidence of the autonomy of the renal circulation (ch. XIV) this integration appears to be worked out between these vascular segments essentially without extrarenal aid. It will bear repeating that, by the present evidence, the chief consideration in glomerular-tubular balance appears to be the maintenance of salt and water balance. But, apart from implications involving the extracellular fluid (ch. XI), how these changes in the renal vasculature are initiated remains a mystery, and it is therefore impossible at the present time to interpret the changes in pathological states such as essential hypertension and congestive heart failure.

Part IV

CHAPTER XIX

Limitations of Clearance Methods during Disturbed Renal Function

In interpreting the results obtained in the diseased kidney by clearance methods, the limitations of these methods must be clearly kept in mind. These limitations were emphasized by the writer [1010] in an early paper which has apparently not been too widely read.

It will aid in this discussion if certain concepts are given sharp definition, even though these concepts may prove to be oversimplified (fig. 119).

One may speak of a *normal, active nephron* as one in which the glomerulus and tubule are functioning in the formation of glomerular filtrate and in the tubular excretion or reabsorption of some particular solute. The glomeruli and tubules of normal nephrons may become partly or wholly inactive as a result of local ischemia without losing their potentiality for immediate return of function on the restoration of an adequate blood supply.

An *aglomerular tubule* is one in which excretory function and urine formation persist after destruction of the adjoined glomerulus. There is as yet no functional evidence of the existence of aglomerular tubules in the normal or diseased human kidney. It remains to be demonstrated whether or not the mammalian nephron, which normally reabsorbs water, can under any circumstances excrete it, and the tubular excretion of water must be pre-

supposed if the term 'aglomerular nephron' is to have any significance. If water is excreted by the tubules in the mammals, tubules temporarily rendered *inactive* by functional cessation of the attached glomeruli might fall in this category. In the absence of tubular water excretion, such *inactive* nephrons would fall in the category of *inert* tissue.

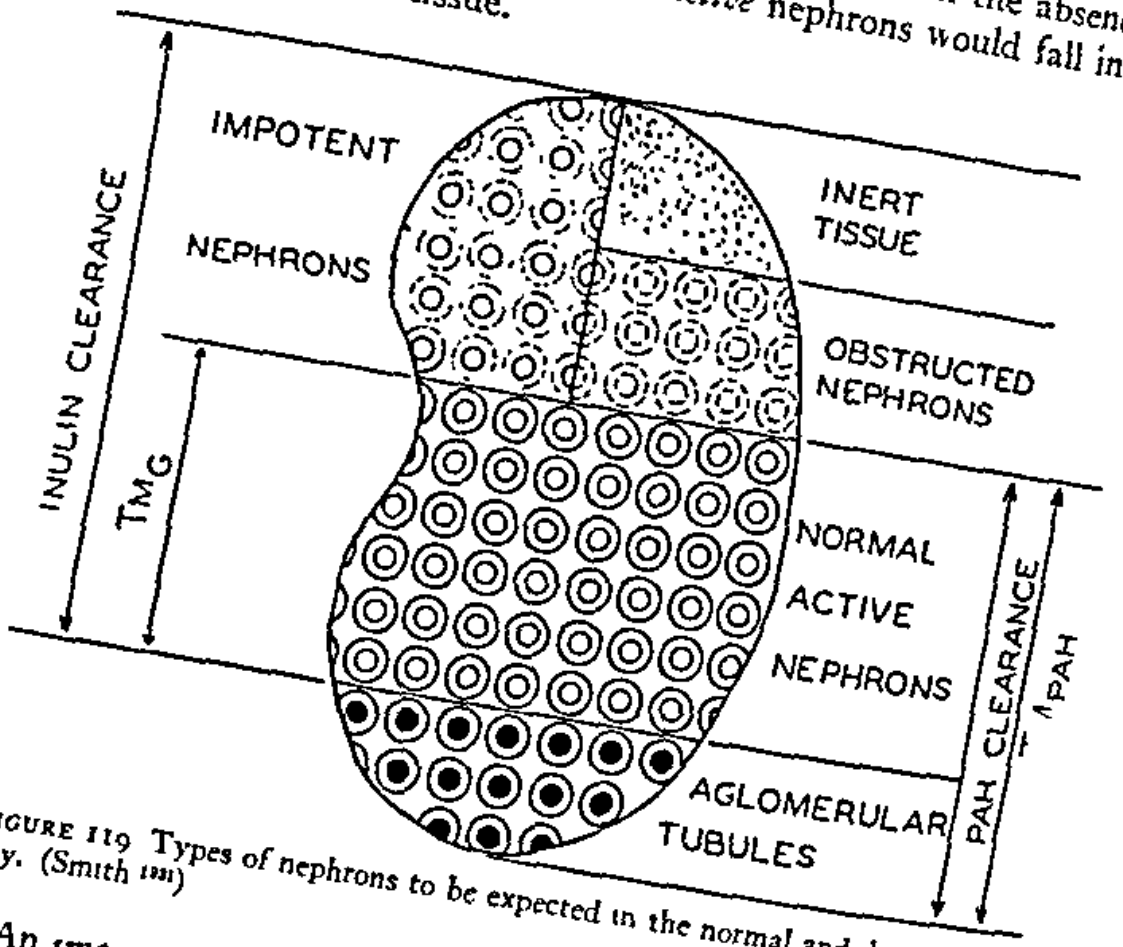


FIGURE 119 Types of nephrons to be expected in the normal and diseased kidney. (Smith 1951)

An *impotent nephron* is conceived as one in which the tubule remains anatomically intact and connected with an active glomerulus and a patent collecting duct, but in which the capacity to reabsorb or excrete one or more substances has been lost. It is possible that the tubular transport of some test substance (diodrast, PAH, etc.) might be lost without the transport of other substances being affected, but in general unfavorable circumstances, such as ischemia, toxic substances, atrophy, etc., may be expected to affect all mechanisms of tubular transport in any one tubule cell in a qualitatively similar manner. Where all tubular reabsorptive activity is lost, the tubule would act as a passive conduit to drain

glomerular filtrate into the urine. The occurrence of large numbers of impotent nephrons is indicated in the early recovery phase following anuria, where a dilute urine, not differing greatly from glomerular filtrate, is excreted. Permeable nephrons, in which glomerular filtrate continues to be formed but all or nearly all of the constituents, including water, escape through injured tubules, would fall into the above category, but would not contribute to the formation of urine.

Obstructed nephrons represent those in which protein casts have obstructed the tubule or collecting ducts. Presumably the earlier portions of such tubules would suffer some increase in permeability or loss of transport power.

Non-excretory renal tissue perfused by blood flowing from the renal artery to the renal vein may be designated as *inert tissue*. This would include the renal capsule, perirenal fat, non-excretory circulatory channels through the renal pelvis and calyces, *impotent nephrons, permeable nephrons and obstructed nephrons*, as defined above, and fibrotic glomeruli and tubular fragments generally.

Since there are two million-odd nephrons in the two kidneys, it is self-evident that no overall method of examination can directly reveal what is occurring in individual nephrons. Impairment in any clearance function may be the result of the partial reduction of function in all nephrons or the complete reduction of function in a few. Conversely, constancy of function does not imply constancy in all contributing nephrons, since function may be increased in some nephrons at a time when it is decreased in others.

Since a variable quantity of water is reabsorbed by the tubule, it is impossible, either in a single nephron or in the total kidneys, to deduce from the urine flow how much water has been filtered from the blood. The rate of filtration can be deduced in either case only by means of an appropriate standard of reference, namely a completely filtrable solute which is neither reabsorbed nor excreted by the tubule; and, in turn, the selection of this standard of reference can be made only by a comparison of clearances of various substances with different diffusion coefficients and potentialities for tubular reabsorption or excretion.

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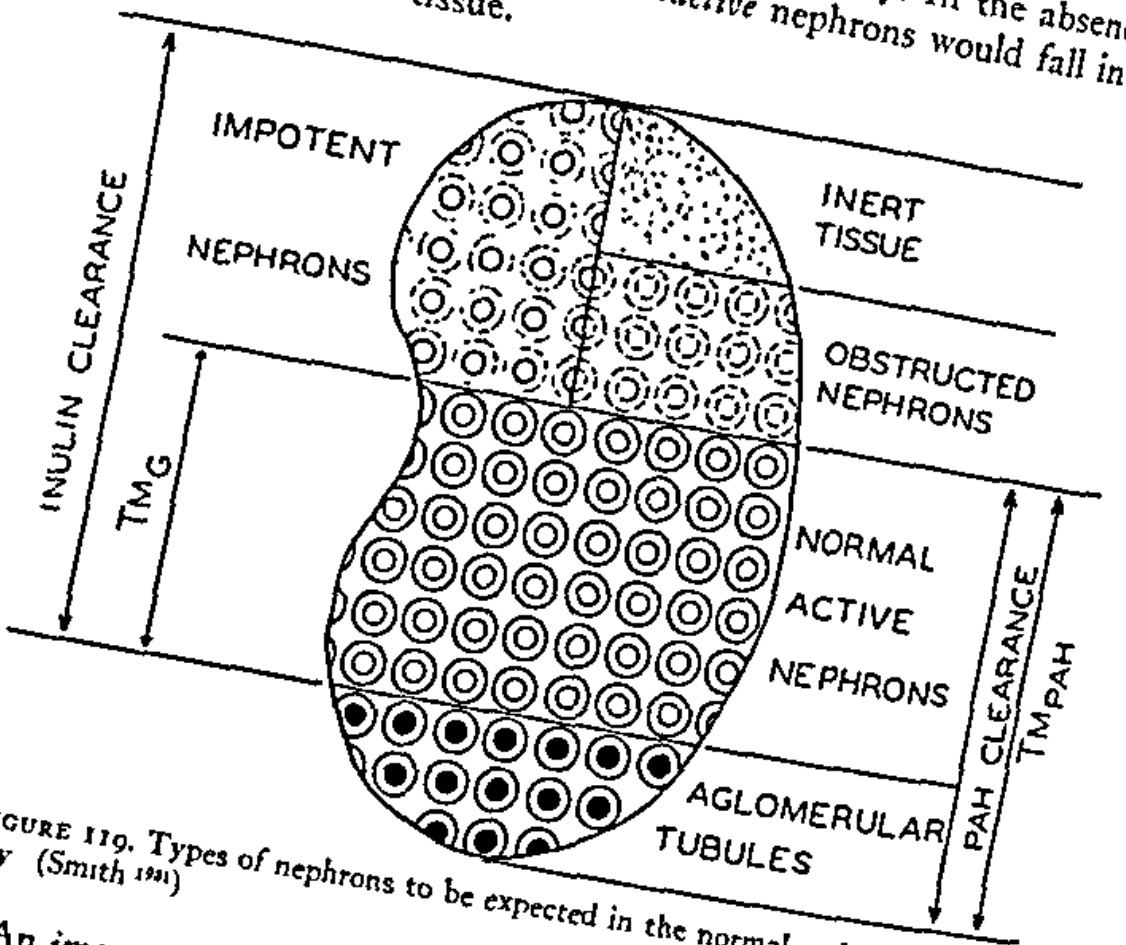

FIGURE 119. Types of nephrons to be expected in the normal and diseased kidney (Smith 1951)

An *impotent nephron* is conceived as one in which the tubule remains anatomically intact and connected with an active glomerulus and a patent collecting duct, but in which the capacity to reabsorb or excrete one or more substances has been lost. It is possible that the tubular transport of some test substance (diodrast, PAH, etc.) might be lost without the transport of other substances being affected, but in general unfavorable circumstances, such as ischemia, toxic substances, atrophy, etc., may be expected to affect all mechanisms of tubular transport in any one tubule cell in a qualitatively similar manner. Where all tubular reabsorptive activity is lost, the tubule would act as a passive conduit to drain

normal nephrons. With regard to diffusion, a concentration gradient will be established between the capillary adjacent to the impotent tubule and some other normal tubule; as long as the plasma concentration of PAH is constant, the actual time required for a PAH molecule to move the length of this gradient may be neglected and the radius of effective diffusion may be conceived to be limited only by a physical interruption of the diffusion freeway. The PAH cleared by a particular tubule may have diffused out of a remote capillary, and the concentration of PAH in that capillary will continue to decrease as the blood moves distally.

With regard to the circulation of interstitial fluid, it will be noted that, out of 127 cc. of filtrate formed each minute, the greater fraction is reabsorbed by the tubules and must pass across the interstitial space to the capillary bed before it re-enters the blood. It is scarcely probable that this circulation of interstitial fluid occurs along the shortest possible point-to-point route; on the contrary, there must be a considerable streaming between or along the tubules, which is aided by the arterial pulse. This streaming will not only accelerate the movement of PAH from capillary to excretory tubule, but it may also increase the radius of clearance considerably beyond that which diffusion alone would permit. Although diffusion and circulation of renal interstitial fluid must play an important role in normal renal function, they are possibly of greater significance in the diseased kidney.

It is conceivable that loss of excretory activity may occur in large areas affecting many tubules, in short stretches of single tubules, or even in single tubule cells, and, except for the first circumstance, interstitial circulation may be important in maintaining a high extraction ratio. This appears to be the case, for example, in essential hypertension, where E_{PAH} remains normal despite considerable destruction of excretory tissue as measured by Tm_{PAH}

Any circumstance that restricts the circulation of interstitial fluid (increased intrarenal pressure, edema, perinephritis, etc.) would be equivalent to a reduction in actual blood flow to such areas in the kidney as might be dependent on this circulation rather than on a direct blood supply for their perfusion. But in

In the diseased kidney, an increase in permeability of the tubule may permit the escape of water from the tubular urine without permitting the escape of inulin; and, conversely, a decrease in permeability of the glomerular membranes may retard the filtration of inulin without proportionally retarding the filtration of water; in either case, the differential movement of water cannot be detected by changes in C_{IN}, although, if decreased glomerular permeability can be ruled out, it may conceivably be deduced by the comparison of the inulin clearance with the clearance of some smaller molecule. The parallel behavior of urea and inulin in all stages of chronic diffuse glomerulonephritis indicates that the reduced excretion of both substances is primarily attributable to the obliteration of glomeruli rather than increased back diffusion of urea.[363] In acute nephritis, however, the urea/inulin clearance ratio may be abnormally low, indicating increased permeability to urea and possibly some increased permeability to inulin.

Lastly, it is conceivable that filtration may continue in a glomerulus after the attached tubule has become separated from its collecting duct, or that the tubule may become so permeable that all the constituents in the glomerular filtrate, including inulin, escape into the interstitial fluid rather than the urine. The inulin clearance represents only such inulin as is passed into the bladder and will reveal nothing of these circumstances. Whatever significance the complete local reabsorption of glomerular filtrate may have in renal pathology, it remains beyond the possibility of examination as long as only the total urine is available for analysis.

The PAH (or diodrast) clearance has been defined as the virtual volume of plasma completely cleared of PAH per unit of time. This virtual volume is less than the actual renal plasma flow through the kidney as a whole, because some blood passes from renal artery to renal vein (normally about 9 per cent) by way of inert tissue. Inasmuch as the PAH clearance approaches in magnitude the total renal plasma flow, it affords a method of measuring the latter, subject only to the qualification that the extraction ratio (normally 91 per cent) remains constant.

If a nephron loses its excretory power, the blood which once was cleared by that nephron may, through diffusion of PAH or circulation of interstitial fluid, continue to be cleared by neighboring

this is measured at high plasma concentrations. These same considerations apply to blood exclusively perfusing inert tissue; * if particular PAH molecules are not brought into effective juxtaposition with functional excretory tissue for clearance at a low plasma concentration, in general † they will not be made available for clearance simply in consequence of increasing the plasma concentration; i.e. any tissue incapable of excreting PAH at low plasma concentration will not acquire excretory capacity because of an increased PAH concentration In general, therefore, where the plasma concentration is the only changing factor, inert tissue is excluded from both the PAH clearance and Tm_{PAH}; hence, in the measurement of these two values, the same vascular and interstitial channels are involved, and the two values refer to the same nephrons or lesser units of excretory activity. Whether Tm_{PAH} is conceived in terms of entire nephrons, individual cells, or hypothetical excretory units of minimal dimensions is immaterial; the

* The terms 'exclusively perfusing' exclude diffusion through and circulation of the interstitial fluid, while the terms 'inert tissue' exclude normal tubular tissue which is inactive simply because of ischemia or because it is presented only with blood that has previously been cleared

† It is possible that a decrease in permeability of the capillaries, interstitial tissue, or tubule cell, or some change in the tubular excretory mechanism itself, could retard the movement of PAH from blood to tubular urine, since the blood is available for clearance in the peritubular capillary for only a brief period, this retardation would lower the fraction of the PAH removed during its passage down this capillary But, whether the retarding factor is a positive barrier (i e relatively impermeable connective tissue) or a negative fault (e g. failure of the tubule cell to handle all molecules presented to it), it is reasonable to expect that the retardation would operate on any and all molecules with statistical indifference, with the result that the clearance probabilities for any particular molecule would not be increased by increasing the number of molecules

Exceptions to this statement are conceivable, one might imagine that at a low concentration so large a fraction of PAH was absorbed on the plasma protein that escape from the capillary by diffusion was greatly retarded and the extraction ratio correspondingly reduced, if, at some higher concentration the plasma proteins became saturated, the diffusion of PAH from the capillary, and consequently the extraction ratio, would be increased Since protein binding is a function of plasma concentration, this particular situation, chosen for illustration only, is not to be expected in practice. Whether or not, as a result of disease, a change in the kinetics of the tubular excretory process could have this consequence is undetermined, but it would seem that the problem can be examined by the progressive elevation of the plasma PAH level. Such titrations as have been recorded to date have supplied no evidence of this situation

general it need not be expected that the extraction ratio will necessarily decrease *pari passu* with focal injury of tubular tissue.

The increased volume of plasma that is made available for clearance by normal tubules in consequence of the formation of impotent nephrons will appear in clearance tests as an apparent hyperemia of the residual functional tissue (increase in C_{PAH} relative to Tm_{PAH}); but, unlike the hyperemia resulting from dilatation of the renal arterioles or increased perfusion pressure, this apparent hyperemia may not afford the normal tubules a proportionately increased supply of oxygen, etc., and it seems advisable to distinguish it from true hyperemia (vascular dilatation) by qualifying it as a vicarious clearance. Failing vicarious clearance, the destruction of renal parenchyma without parallel destruction of the vascular bed will tend to reduce the extraction ratio of PAH, and this ratio may, in the diseased kidney, have any value between the normal value and zero. In considering the diseased kidney as a whole, the PAH clearance will have no certain relation to the total plasma flow unless it is corrected by the extraction ratio.

This circumstance does not, however, impair the usefulness of the clearance method; on the contrary, under these conditions the clearance method acquires unique physiological significance. It will aid the reader to visualize the argument if, as an extreme example, it is imagined that an inert tube is inserted between the renal artery and the renal vein of a normal kidney, so that some large fraction of the renal arterial blood passes directly to the renal vein by way of this tube. Since the clearance method depends upon the presence of living excretory tissue to remove PAH from the blood and excrete it in the urine, in the absence of knowledge of the extraction ratio, this method will not reveal how much blood passes from renal artery to renal vein through the inert tube. Nor will the tube begin to excrete PAH when the plasma concentration is raised; i.e. it will not only fail to contribute to the PAH clearance such PAH as is carried by the blood passing through it at low concentrations, but it will also fail to contribute to Tm_{PAH} when

* This circumstance was recognized in our original description of the diodrast clearance method 1918 and was the basis of the definition of this clearance as the *effective* renal blood, i.e. the *virtual* volume of blood that is completely cleared of diodrast.

CHAPTER XX

Primary Disturbances of Salt and Water Balance

OSMOTIC DIURESIS

All vertebrates can excrete a urine that varies from marked hypotonicity to isotonicity with the blood, whereas only mammals,[1923] and to a lesser extent birds,[1141] can elaborate a hypertonic urine. Thermodynamic work is performed in the elaboration of a dilute urine by abstracting urinary solutes from water, and in the elaboration of a hypertonic urine by abstracting water from urinary solutes In both cases the energy is presumably derived entirely from the metabolism of the tubule cells

Among the mammals, the active (distal) reabsorption of water can produce a urine with considerable osmotic pressure. When the distal load of water is small, the extent to which the distal urine can be concentrated is apparently limited by the total osmotic pressure of the tubular urine, the osmotically active constituents that are not reabsorbed will prevent the complete reabsorption of water and thus place a lower limit upon the rate of urine formation Normally the chief osmotically active constituent of the urine is urea, and it is perhaps to the advantage of the organism that at very low urine flows a considerable fraction of the filtered urine is reabsorbed, since in extreme dehydration this circumstance permits water excretion to decrease to lower levels than it otherwise could.

ratio C_{PAH}/Tm_{PAH} expresses the virtual quantity of plasma completely cleared of PAH per unit quantity of the excretory tissue which is effecting the clearance. Hence C_{PAH} and Tm_{PAH} have the same significance in the diseased as in the normal kidney, in which, as emphasized above, there is already some inert tissue and some uncleared blood; if in disease a larger proportion of blood perfuse inert tissue and escapes uncleared, the significance of this ratio remains unchanged.

Thus, a reduction in the overall extraction ratio of PAH in the diseased kidney does not seriously impair the usefulness of the clearance method. On the contrary, this method is the only one capable of determining the volume of blood cleared by such functional excretory units as are inextricably mixed with scar tissue, tubular detritus, connective tissue, etc., a datum upon which no information could be gained by the measurement of the total renal blood flow. When the PAH clearance is referred to the total quantity of available functional tissue by utilization of the ratio C_{PAH}/Tm_{PAH}, a datum is obtained that in most instances will be qualitatively and quantitatively comparable with observations made on the normal kidneys. Even in normal subjects, C_{PAH} should be related to Tm_{PAH} in order to take into account the varying quantities of excretory tissue that may be expected to occur in different individuals.

Although the PAH clearance *per se* cannot afford a reliable index of the total renal plasma flow in the diseased kidney, because of the possible reduction in the extraction ratio, if the extraction ratio is known, the total renal plasma flow can be calculated by dividing the clearance by the extraction ratio (i.e. C_{PAH}/E_{PAH}). This remains reliable in principle so long as both terms can be accurately measured, but in practice a large error is involved when the extraction ratio is small because this term must be determined by difference. When the extraction ratio is zero, the calculation of course becomes mathematically absurd.

tinguished, and we shall first consider the circumstances associated with (b).

Evidence has been presented in chapter XI that, as the load of water delivered from the proximal system to the distal tubule is increased, distal reabsorption remaining fixed in rate, a progressively smaller fraction of this water is reabsorbed and the osmotic pressure of the bladder urine approaches that of the proximal urine (or plasma).[2171] The load of water delivered to the distal tubule will be conditioned not only by proximal water reabsorption but, proximal reabsorption remaining constant so far as sodium and water are concerned, by the filtration rate. Thus, during maximal ADH activity the urine flow may be expected to be in some measure sensitive to the filtration rate. Shannon's [1861,1862] data show that (a) in a normal dog during the post-diuretic phase, the urine flow returns to oliguric levels only when the filtration rate (and distal load of water) decreases, and independently of the urine chloride concentration and osmotic pressure; (b) when a diabetes insipidus dog that is receiving large amounts of ADH (20 to 200 milliunits/hr.) is given water, the urine flow increases with the filtration rate but without concomitant increase in urinary sodium, chloride, or osmotic pressure; (c) when a diabetes insipidus dog is given saline, the urine flow increases with increasing filtration rate, again independently of the concentration of sodium in the urine. The facts all conform with the foregoing interpretation.

The fact that during osmotic diuresis the urine is relatively dilute has been recorded by several investigators. Shannon [1854] observed that, during glucose diuresis in the dog, the glucose concentration in the urine was less than 5 per cent ($\Delta = -0.517°$ C.), although the dog kidney during physiological oliguria can elaborate a urine with $\Delta = -3.0°$ C. Δ in the urine of the rabbit maintained on a diet of oats, bran, and cabbage averaged $-2.543 \pm 0.536°$ C., with an extreme value of $-3.556°$ C.,[933] and yet during sucrose diuresis combined with ADH the maximal value is about 0.8° C.[1504] During dehydration Δ in the urine of the rat may reach $-4.5°$ C., but during sodium chloride or urea diuresis this figure decreases to $-2.7°$ C. or less. This phenomenon does not occur in the newborn

The expression 'osmotic diuresis' has been used to designate the increased urine flow evoked by the intravenous administration of hypertonic sodium chloride, sodium sulphate, urea, sucrose, mannitol, etc., during marked glucosuria and under other similar conditions where the urine is loaded with an osmotically active constituent. However, the expression should not be interpreted as indicating that the urine under these conditions is maximally concentrated; on the contrary, with the progressive development of diuresis the osmotic pressure of the urine decreases, approaching that of the plasma as a limiting value. During all osmotic diuresis the urine is more dilute than during oliguria, when the excretion of all substances is minimal. The mechanism of osmotic diuresis must be sought primarily in the proximal system, where the osmotic agent reduces water reabsorption by its osmotic action,* and, by dilution of the proximal urine, retards the reabsorption of sodium which now adds its osmotic force to that of the primary agent in opposing the reabsorption of water.† Consequently, the quantity of water delivered to the distal tubule exceeds its reabsorptive capacity and the excess is excreted in the urine.

Under normal conditions of hydropenia, the osmotic pressure of the urine is determined by the relative quantities of water and solute (chiefly sodium chloride) reabsorbed by the distal tubule. Activation of the distal tubule by ADH leads to maximal water reabsorption and consequently to maximal concentration of the urine. Water continues to be excreted in small amounts either (a) because of the local restraint offered by the osmotic pressure of urea and other urinary constituents (limiting osmotic pressure of the urine in the strict sense), or (b) because the load of water delivered from the thin limb into the distal tubule exceeds by some small amount the reabsorptive capacity of the latter (osmotic diuresis). Despite difficulties, (a) and (b) can probably be dis-

* Shannon 1934 was apparently the first to state explicitly that any unreabsorbed, osmotically active agent in the glomerular filtrate would retard the reabsorption of water in the proximal tubule.

† Stehle and Melville 1936 have used glucose and mercury bichloride diuresis in an attempt to obtain urine flows in the dog equal to the rate of filtration. They made no attempt, however, to measure the filtration rate and their estimated filtration fraction of 13 per cent is only about half of the known value.

The same relations are displayed more extensively in the data of Rapoport, Brodsky, West, and Mackler,[1678,1680] who studied the osmotic pressure of the urine in boys under conditions of hydropenia and after the administration of urea, glucose, creatinine, sorbose, mannitol, xylose, sucrose, sorbitol, sodium chloride, sodium sulphate, or sodium p-aminohippurate. From oliguria to extreme osmotic diuresis, the rate of urine flow bears a fairly uniform curvilinear relation to the urinary load of solutes, expressed as mosm/min. The authors apply to this relationship an empirical exponential equation based upon the facts, first, that the urine concentration decreases as the load (UV) increases, and, second, that the urine concentration decreases toward that of the plasma as an asymptote. There are, however, an infinite number of pathways by which the asymptote may be approached, and the selection of the simplest exponential function, as made by these authors, is arbitrary and justifiable only on the grounds of convenience. The facts that the equation so constructed permits the prediction of loads representing maximal thermodynamic 'work,' and that low 'work' coincides with low flows, give their equation no physiological significance since these deductions would issue from any other equation of an asymptotic character.

The fact that the urine concentration decreases as the load (UV) increases may be related, in the present view, to the fact that as proximal diuresis increases and floods the distal system, the operations of the latter in reabsorbing water, being limited in rate, become of diminishing importance in changing the composition of the proximal urine, and with large flows the osmotic pressure of the bladder urine must approach that of the proximal urine, which under these conditions is itself isosmotic with the plasma. Any calculation of the precise osmotic pressure to be expected in the urine at various stages of osmotic diuresis must take into account the load of solute and water delivered to the distal system and the limitations in the reabsorption of solute and water by the latter. Such a calculation cannot profitably be made until the operations of the distal system are better understood.

Many older observations may be reinterpreted in the light of the facts above. Thus the observations of Davies, Haldane, and Peskett[493] that the maximal urinary concentration of chloride or

animal (rats and human infants) because during oliguria the urine has an osmotic pressure scarcely more than that of the plasma.[182, 959, 987, 1294, 1296, 1308]

Adolph [27] found that during starvation and thirst the maximal concentration of the urine in man was about 1.2 osm. but the maximal concentration of chloride during thirst, when sodium chloride was ingested, was 0.662 osm., and 0.782 when urea was ingested. Similarly, Black, McCance, and Young [182, 1308] and McCance [1294] found that when the intake of sodium chloride was reduced below the normal level in men enduring water deprivation for 3 to 4 days (or when urea was administered), the average osmotic pressure of the urine remained so nearly constant that they regarded it as maximal and considered the oliguria to be limited by this osmotic pressure. However, when sodium chloride was administered, the chloride content of the urine rose to its recognized maximum of about 0.34 M/liter and the urine volume was increased, the osmotic pressure decreasing below the maximal value observed on a low sodium chloride intake.

McCance and his coworkers [182, 1294, 1308] initially believed that the total amount of osmotically active material claiming excretion determines the minimal urine flow only if the excretion of sodium chloride does not exceed 20 mg/min. (29 gm/day), but, after the administration of sodium chloride, when the concentration of the salt in the urine rises to its maximum, the sodium chloride concentration alone may set the lower limit to water output. Further studies,[987] however, led McCance to abandon this view. When urinary concentrations under conditions of dehydration were compared with those observed after the oral administration of sodium chloride, or after sodium chloride combined with the intravenous administration of sucrose, it was found that the maximal osmotic pressure was reached only at low urine flows. As diuresis increased, the osmotic pressure decreased in a manner suggesting a limitation involving 'a constant amount of osmotic work per unit time.' It is more in keeping with all the facts, however, to believe that the urine flow is independent of the nature of the solute, and that the curve relating urine flow to osmotic pressure merely reflects the reabsorption of an approximately constant amount of water from the isotonic proximal urine.

ing degrees of osmotic diuresis. Actually, the more urea or sodium chloride given, the lower the osmotic concentration of the resulting urine. The limiting osmotic concentration of the urine can, in the present view, be determined only during oliguria, under conditions where the load of water delivered to the distal tubule is less than the maximal rate of reabsorption, and where the only factor limiting the reabsorption of water is the osmotic gradient between the urine and plasma. These conditions have rarely been fulfilled, and indeed it is difficult to see how they can be realized if the concentration of any solute destined for excretion is elevated significantly in the glomerular filtrate.

MAXIMAL SPECIFIC GRAVITY

At best, the specific gravity of the urine is only a blunt index of the degree of concentration because various solutes contribute so differently to the specific gravity. Addis and Shevky,[9,21] in the development of the concentration test named after them, made 94 observations on 75 normal persons, most of whom were medical students, and obtained an average maximal specific gravity of 1.032 ± 0.00281 in a short-period sample collected after 24 hr. of abstinence from water or liquid food. All measurements were above 1.026, and in 95 per cent of the subjects on ordinary diets the specific gravity was 1.028 or above. A specific gravity below 1.026 under the conditions of the Addis-Shevky test may be considered abnormal. In a similar study of Lashmet and Newburg,[1214] all normal subjects concentrated urine to 1.026 or above. The specific gravity of 24 hr. urine samples from 10 normal subjects living under moderate climatic conditions and with no dietary restrictions varied from 1.0079 to 1.0265 because of variable water intake, but after water deprivation for 12 hr. the figure rose to the range of 1.028 to 1.033. The contribution of the various solutes to the specific gravity of these urines was examined by Miller, Price, and Longley.[1454] Statistical analysis reveals that the specific gravity of acid urines collected at random is higher (1.020 ± 0.0047) than that of alkaline urines (1.013 ± 0.0048).[2590] The contribution that individual substances make to the specific gravity of the urine on an equimolecular basis has also been reported by Price *et al.*[1660]

bicarbonate, or of mixtures of the two, in man is about 0.33 M/liter (0.561 osm.), appear to be related to osmotic diuresis. Had the salt been given in larger doses, a lower concentration would have resulted. The fact that a higher electrolyte content (0.50 M/liter) can be obtained if phosphate is mixed with chloride or bicarbonate may be owing to differences in the ionic activity of phosphate salts. Similarly, Gilman and Kidd [781] found that after the ingestion of 1.5 to 24 per cent solutions of sodium chloride in dogs the highest concentration of chloride attained in the urine was approximately 0.31 M (0.527 osm.) and appeared to be little influenced by the rate of urine flow, but, in the light of our present knowledge of osmotic diuresis, a higher concentration would have been expected at lower filtration rates and lower salt loads. In their experiments the maximal concentration of urea was 1.33 osm.

Gamble and his coworkers [741, 742] found that rats which were allowed water *ad libitum* and to which various salts and non-electrolytes (sodium, potassium, chloride, bicarbonate, phosphate, sulphate, glucose, galactose, and creatinine) were administered orally excreted urine of essentially constant osmotic pressure whereas if urea was the predominant constituent of the urine more concentrated urine was formed. But the interpretation of these experiments is rendered difficult, first, by the fact that the kidney was not under stress to reabsorb water, and second, by the fact that the water intake may be governed by the mechanism of thirst without reference to the ability of the kidney to excrete a more or less concentrated urine, and third, by differences in the filtration rate. The rat can excrete a more concentrated urine than was observed in any of the foregoing experiments, and it is open to question if that limit is ever reached with water *ad libitum*.

THE LIMITING CONCENTRATION OF THE URINE

The view generally prevalent heretofore, that during osmotic diuresis the urine is maximally concentrated in the sense of having a maximal U/P ratio with respect to urea, sodium chloride, or some other substance, has, for reasons now clear, led only to confusion. To carry out such studies, investigators have administered solutes in varying amounts and thus inadvertently induced vary-

by Rapoport, Brodsky, West, and Mackler,[1610] 1.30 (range 1.2 to 1.4 osm.). More recently, Rapoport, Brodsky, and West [1615] examined the urine of 15 boys, 8 to 15 years of age (26 collection periods of 30 min. each), who were fasting and had received no water for 16 hr. The average urine flow was 0.49 ± 0.03 cc/min. (705 cc/day) per 1.73 sq. m. The average urine osmolarity was 1.182 ± 0.018 osm and the plasma osmolarity 0.304, giving an osmotic U/P ratio of 3.89. With the reservation that allowance must be made for individual variation, we may take the maximal osmotic pressure of the urine in man as 1.4 osm. ($\Delta = 2.50$); setting the concentration of the plasma at 0.33 osm., the maximal osmotic U/P ratio would be 4.2. The osmotic pressure of the urine in a normal dog at various rates of urine flow is illustrated in figure 120.

Data on other species are given in chapter XVII.

RENAL OSMOTIC WORK

Since von Rhorer's calculation in 1905 of the 'osmotic work' required in the urinary concentration of a single component, this problem has been treated by several investigators. More detailed analyses have been undertaken by Borsook and Winegarden [211] and Newburgh [1503, 1508, 1510] The osmotic work of the kidney, thermodynamically conceived, is done in converting the glomerular filtrate into urine The theoretical minimal work is thermodynamically independent of all intermediate steps in the process of urine formation and may be calculated from the rate of urine formation and the U/P ratios of the various urinary constituents, exclusive of substances synthetized by the kidneys, such as ammonia.

The calculation of renal osmotic work in terms of the composition of the final urine, however, necessarily ignores all intermediate steps in urine formation. For example, in the formation of the glomerular filtrate, energy is expended endothermically upon the plasma in concentrating the plasma proteins, this energy being supplied by the heart through the arterial pressure. The greater part of the water of the glomerular filtrate is reabsorbed from the interstitial fluid (after transfer to that point by the tubules) by the osmotic pressure of the postglomerular plasma, an exothermic

Hayman, Shumway, Dumke, and Miller [941] report specific grav ities in the urine of female dogs as high as 1.069, with a mode at 1.040 to 1.049, all the urine excreted during 24 hr. of dehydration being used. White and Heinbecker [2108] report the maximal figure in dogs dehydrated for 24 hr. as 1.068, to be compared with 1.039

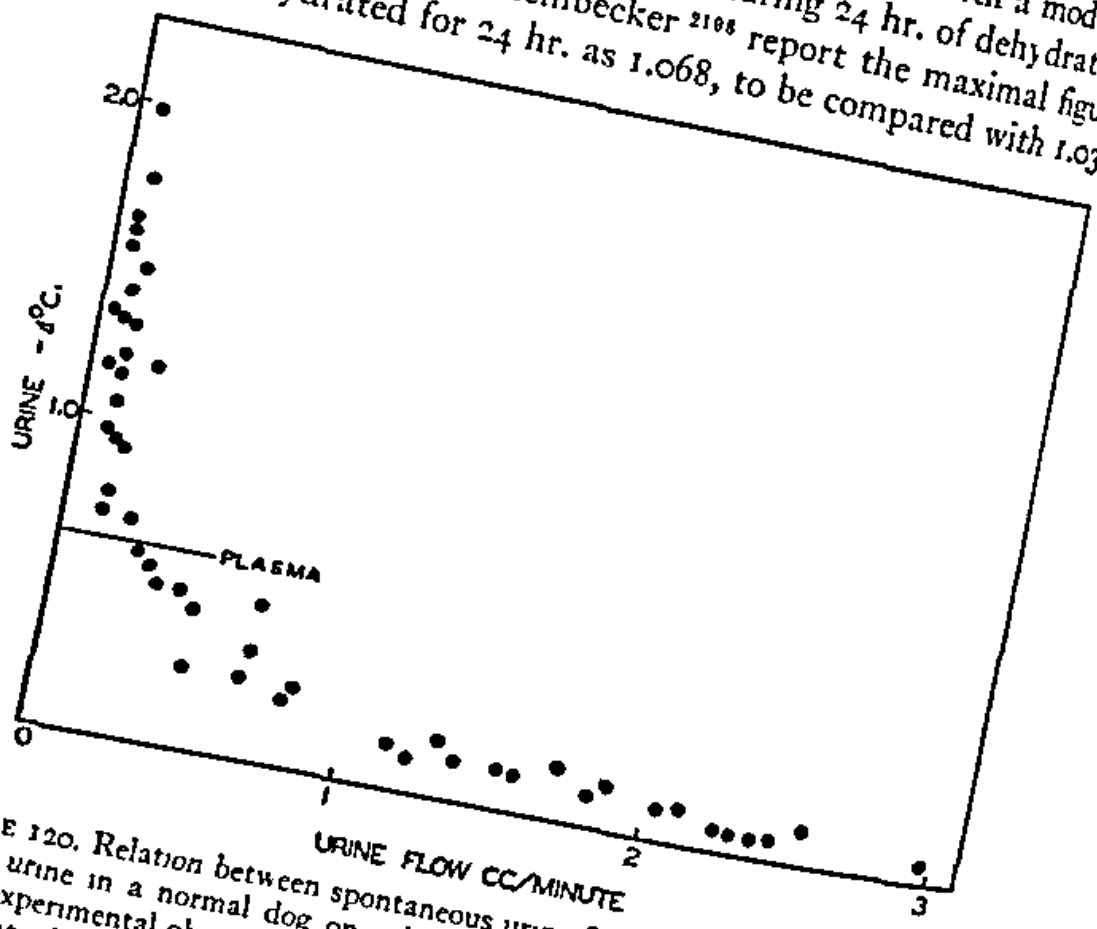

FIGURE 120. Relation between spontaneous urine flow and the osmotic pressure of the urine in a normal dog on a low protein diet. Each point represents a single experimental observation. The line drawn horizontally at $-\Delta = 0.60°$ C. represents the mean of a series of plasma observations obtained during moderate dehydration. These relationships are not fixed in any animal but will vary depending upon variations in filtration rate, food and salt intake. (Shannon [1660])

in diabetes insipidus dogs and 1.040 after total hypophysectomy. The maximal specific gravity in the white rat appears to be about 1.056 (2.0 osm).[959]

MAXIMAL OSMOTIC CONCENTRATION IN MAN

During hydropenia and in the absence of osmotic diuresis, the concentration of the spontaneous urine in man may reach 1.4 osm. The maximal figure indicated by Adolph [27] is about 1.2 osm.; by McCance,[1294] 1.4 osm.; by Gamble and Butler,[737, 739] 1.4 osm.; and

by Rapoport, Brodsky, West, and Mackler,[1810] 1.30 (range 1.2 to 1.4 osm.). More recently, Rapoport, Brodsky, and West [1678] examined the urine of 15 boys, 8 to 15 years of age (26 collection periods of 30 min. each), who were fasting and had received no water for 16 hr. The average urine flow was 0.49 ± 0.03 cc/min. (705 cc/day) per 1.73 sq. m. The average urine osmolarity was 1.182 ± 0.018 osm. and the plasma osmolarity 0.304, giving an osmotic U/P ratio of 3.89. With the reservation that allowance must be made for individual variation, we may take the maximal osmotic pressure of the urine in man as 1.4 osm. ($\Delta = 2.50$); setting the concentration of the plasma at 0.33 osm., the maximal osmotic U/P ratio would be 4.2. The osmotic pressure of the urine in a normal dog at various rates of urine flow is illustrated in figure 120.

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process in which the plasma proteins are rediluted approximately to their original state. Thus, apart from the separation of a small quantity of water from the plasma as urine water, the net work done upon the plasma proteins is nil. Yet a significant and calculable quantity of cardiac energy has been expended in this cycle, as shown by the decrease in pressure between the glomeruli and the renal vein. The same consideration applies to nearly all the normal constituents of the urine. Some 1100 gm. of sodium chloride, 425 gm. of sodium bicarbonate, 150 gm/day of glucose are filtered, to be reabsorbed almost wholly by the tubules. It has been demonstrated that the reabsorption of all three substances involves an active process requiring the expenditure of energy by the tubules. That water is also ultimately reabsorbed, possibly in great part by passive diffusion, does not abolish the requirement for this energy expenditure. Physiologically, the work represented by the composition of final urine is an almost negligible fraction of the work it is known that the kidney must do in order to make that urine, and the calculation of the so-called minimal thermodynamic work has no more significance. As Borsook and Winegarden [214] pointed out, the work so calculated represents only about 1 per cent of the probable metabolism of the kidney as calculated from the oxygen consumption. This is not to say that the efficiency of the kidney is only 1 per cent; the kidney's efficiency may be very high indeed—it is the thermodynamic approach in terms of final urine that is only 1 per cent efficient.*

For the reasons given above, no great significance can be attached to critical urine volumes representing alleged 'minimal work' [1508, 1510, 1678, 1680] or, in the absence of an accurate fractionation of proximal and distal reabsorption, to estimates of thermodynamic work in these segments.[1681] Minimal thermodynamic work would be done by the kidney only if it excreted 187 liter/day of glomerular filtrate, for then all the energy would be supplied by the heart and the renal work would be zero.

The belief has been expressed from time to time that a high protein diet is injurious to the kidney in renal disease.[14] This question cannot be debated here, but without prejudice to the answer clinically it may be said that the use of a low protein diet cannot be de-

* Mudge *et al.*[1488] have noted the physiological inadequacy of such calculations.

fended on the grounds that it reduces renal work by reducing the quantity of urea requiring excretion. The work so saved represents but a very small fraction of the total work of the kidney, which is not appreciably increased, as judged by the oxygen consumption, by urea or other osmotic diuretics (ch. XXVII).

It is impossible at this time to analyze the significance of the changes in urine composition effected by changes in perfusion pressure, or during urea and Ringer solution diuresis in the perfused kidney, as studied in the painstaking experiments of Eggleton, Pappenheimer, and Winton.[585]

WATER DEPRIVATION AND PHYSIOLOGICAL OLIGURIA

Two types of dehydration may be distinguished That resulting from simple water deprivation is characterized by thirst and oliguria; unless extreme, it does not lead to impairment of the circulation and is completely relieved by the administration of water Dehydration resulting from abnormal salt loss is accompanied in the early stages by reduction of extracellular fluid and plasma volume, and by circulatory insufficiency. It is not necessarily accompanied by thirst and cannot be relieved by the administration of water alone, but requires salt as well as water for correction.[1386 1387, 1499]

It has been noted in chapter III that, although the filtration rate in both the dog and man tends to decrease during dehydration and to increase during excessive hydration, these changes do not appear to be an intrinsic part of the mechanism of water diuresis. Black, McCance, and Young [182] found that dehydration for 3 to 4 days, uncomplicated by starvation but sufficiently severe to make the subjects lose 4 to 7 per cent of the body weight, reduced the filtration rate slightly in 3 subjects (−12 to 28 per cent) and made no difference in a fourth. The renal plasma flow increased in 3 and decreased slightly in 1. At variance with these observations, Kenny [1113] reports that when no free fluid is taken for 2 or 3 days, dehydration leads to hemoconcentration of about 7 or 8 per cent, referable to loss of plasma water without change in the circulating red cell volume. He finds that the filtration rate decreased by 26, 37, and 28 per cent in 3 normal subjects, and the renal plasma flow by 41, 37, and 33 per cent, respectively. The filtration fraction in-

creased markedly in the first and third subjects, but not in the second.

During water deprivation, concentrated urine continues to be formed at a minimal rate—the 'urine obligatoire' of Ambard and Papin.[48] Under conditions avoiding osmotic diuresis, this minimal urine flow is presumably determined by the solutes requiring excretion and by the limiting osmotic concentration of the urine.

The fate of various urinary constituents at low urine flows presents some uncertainties. Chesley [366] reports that when the urine flow falls below 0.35 cc/min., the urea U/B ratio becomes fixed at an average figure of 91.5, and hence the clearance becomes directly proportional to V. Consequently he proposes that in oliguria, 'minimal' urea clearances be calculated in an arbitrary manner comparable to the standard clearance, i.e. by using the observed U/P ratio and assuming $V = 0.35$ cc., disregarding the actual value of V. The average normal minimal clearance so calculated is 32 cc/min. McCance [1294] has pointed out, however, that within the range of Chesley's 'minimal' clearances the urea concentration of the urine can be raised by lowering the sodium chloride output, and hence the constant U/P ratio observed by Chesley may occur only under circumstances where the sodium chloride output, and hence total osmotic pressure, happened to be relatively constant. More generally, under conditions avoiding osmotic diuresis, were only one solute present in the urine, this solute would condition the excretion of water in accordance with the maximal osmotic concentration of the urine; U would be constant, and UV would roughly increase or decrease with P by virtue of changes in V. With the several solutes present in the urine in relatively constant proportions, one would obtain the relationship described by Chesley. In further studies, Chesley [367] reports that when the urine flow falls below 0.35 to 0.5 cc/min., not only urea but phosphate, total nitrogen, and total solids become maximally concentrated. Further reduction in urine flow does not increase the concentration. The plasma clearance of endogenous creatinine shows a linear relation to urine flow, and he suggests that in this oliguric range the filtration rate is reduced and varies directly with urine flow. Under these conditions a constant proportion of filtered water appears to be reabsorbed. Assuming that the endogenous

creatinine clearance reliably reflects the filtration rate, it would follow from the fact that the filtration rate so estimated does increase or decrease with urine flow, that the load of all filtrable substances—urea, chloride, phosphate, total non-protein nitrogen, etc.—also varies with the urine flow because this load varies with the filtration rate; if in various experiments the fraction of the substances reabsorbed by the tubules does not vary greatly, then the residuum (UV) in each case will show direct propotionality to urine flow; i e UV/V will be constant and therefore U will be constant for each substance, as Chesley finds. The essential question is why the filtration rate should vary directly with urine flow. The simplest explanation is that the system operates in reverse; increasing degrees of dehydration lead to greater reduction in filtration rate, and this in turn, by reducing the filtered load of solutes, permits reduction in urine flow in accordance with the limits set by maximal osmotic pressure.

LIFE IN THE DESERT

An interesting series of studies on the physiology of man in the desert was carried out by Adolph and his associates during the war.[32] Observations were made on volunteers in controlled hot rooms as well as under natural desert conditions. Only a few of many interesting points can be recorded here.

At high temperatures, the greater part of the water lost from the body is in the form of sweat. Sweating is, of course, highly variable, depending on temperature, humidity, and physical activity. At a dry-bulb temperature of 100° F., water loss from sweating (including respiratory loss) ranges from 7.2 liter/day when the subject is sitting clothed in good shade, to more than 24 0 liter/day when walking clothed in the sun and carrying a 15 kg. pack, and to 28 0 liter/day when walking nude in the sun without a pack. In contrast, the loss of water in the urine is less variable and comparatively small, being determined by the relatively fixed quantity of urinary solutes.

The mean rate of urine formation among men living in the desert in a warm month was 935 cc/day, as compared with 5905 cc. of fluid ingested. The specific gravity fell largely between the limits of 1.020 and 1.038 and averaged 1.027. It is rare for the

specific gravity of the urine in man to rise above 1.040, the maximal value under the conditions studied being about 1.038, and the mean value at water deficits ranging from 2 to 10 per cent of the initial body weight being 1.033.

Since the urinary water is obligated by urinary solutes, the excretion of urine is reduced only in proportion as the quantity of these substances is reduced. Water cannot be saved by attempting to reduce the urine flow by allowing oneself to become dehydrated. Reduction of urinary solutes, on the other hand, can be accomplished to only a limited extent by modifying the food intake. If nitrogenous intake is much reduced, total food intake is likely to be inadequate, and food reduction of any sort is not recommended in ordinary desert life. Ideally, salt intake might be reduced but, practically, the amount of sweat varies so much from day to day that reduction in salt intake incurs the danger of salt deficiency. In any case, where sweating is profuse the loss of water in the urine is much less important than that lost in sweat.

Under conditions of excessive sweating, and when supplied with water *ad libitum*, men drink only enough to compensate for the minimal urinary and sweat losses; the urine volume is less than the average for men in temperate climates, indicating that men who drink all the water they want remain somewhat dehydrated, presumably because a small water deficit is necessary to stimulate the drinking of the large quantities of water required to compensate for the great loss of sweat. It is in line with this interpretation that men who were deprived of water for 8 to 12 hr. in the hot room excreted the same amount of urine (714 cc.) as those who drank *ad libitum* (709 cc.), i.e. they drank only enough to meet the minimal requirement of total water loss. Some 700 to 900 cc/day of urinary water is usually obligated by excretory products. An output of 500 cc/day is minimal except in near-starvation or when the filtration rate is reduced by severe circulatory disturbances.

The chief expenditure of salt is in the sweat rather than in the urine, despite the fact that acclimatization leads to a reduction in the salt content of the sweat.[464] A few men accumulate considerable crusts of salt upon the skin during a single day's exposure and they characteristically eat excessive quantities, but in all men the salt loss is considerable. Whereas an average of 116 mEq. of

sodium chloride (6.8 gm.) was excreted in the urine at a concentration of 125 mEq/liter, it is estimated that probably 3 or 4 times this amount was metabolized. Taking the average salt content of the body as 165 gm., 10 to 15 per cent of this salt is turned over within 24 hr. No significant change occurs in the chloride content of the plasma either under variable desert conditions or as between individuals freshly arrived or returning to temperate climates. Where men become salt deficient, this deficiency is not necessarily reflected in the chloride content of the plasma, but only by diminished physical performance.[2031]

It is believed that men who suffer near-lethal dehydration cease to form urine, if true, this anuria may reflect circulatory failure which occurs only *in extremis*. Under the field conditions studied by Adolph and his collaborators anuria was not observed. They found no evidence that renal function is impaired by exposure to heat, by moderate dehydration, or by both.

These investigators found that the urea clearance at urine flows ranging from 10 to 50 cc/hr. is practically a linear function of urine flow, as pointed out by Chesley.[316]

Adolph and his colleagues estimate that, at maximal daily shade temperatures of 120°, 110°, 100°, 90°, 80°, and 70° F., a man with no water available can survive 2, 3, 5, 7, 9, and 10 days, respectively, if he is engaging in no exercise at all. If he is walking at night until exhausted and resting thereafter, expected survival is cut to 1, 2, 3, 5, 7, and 7 5 days These figures are, of course, estimates only, because there are no reliable data on the survival or death of men without water on the desert.

The foregoing considerations also apply to survival at sea, except that the length of time required for water deficiency to attain a critical value will depend on air temperature, humidity, wind velocity, protection by clothing or shade, sunburn, and food intake, as well as work in paddling.

The drinking of urine by dehydrated men accomplishes nothing since it affords no free water, nor is drinking sea water advantageous. Taking the maximal osmolar concentration of the urine as 1.4 osm/liter and the concentration of sea water as 1.0 osm/liter, a small part of the water in the latter is theoretically available for the excretion of other urinary constituents. But 500 cc/day of sea

water is about all that can be tolerated, even for a few days, by thirsting men without gastrointestinal disturbances; this would yield at best 143 cc. of free water, and probably less than that amount in many individuals, a quantity too small to maintain a subject in water balance under ideal conditions, much less during exposure to wind and sun. Consumption of larger amounts would lead to diarrhea and more rapid dehydration and only accelerate catastrophe.[737,1185] Rats survive slightly longer, while losing the same amount of body water, when allowed to drink sea water than when denied all water. But in some individuals the concentration of chloride in the urine (0.60 M) exceeded that in the ingested sea water (0.52 M), a situation that does not obtain in man, the dog, or marine mammals.[10] The only use to which urine and sea water can be put by man is that he can permit them to evaporate from the clothing, thereby cooling the body, as a substitute for a certain amount of sweat. The minimal urine volume is about 10 cc/gm. of protein metabolized; eating raw fish will not ameliorate dehydration since all the water is required to excrete the protein metabolites.[2235]

As Adolph says, there is no cheap substitute for water except to minimize the requirement and conserve whatever is available.

The pathological disturbances characteristic of water or salt deprivation are designated by Adolph as heat stroke, heat exhaustion, dehydration exhaustion, and heat cramp. Heat stroke is accompanied by severe irritability, prostration, and delirium; sweating often diminishes or ceases and the cooling of the body becomes critically deficient, leading to dangerous hyperpyrexia. Heat exhaustion appears more moderately as faintness, vertigo, nausea, vomiting, tachycardia, circulatory inadequacy, and collapse, and appears to be avoided by acclimatization as well as by rest. Dehydration exhaustion is accompanied by vague discomfort and a sense of heat oppression, restlessness, sleepiness, weakness, susceptibility to easy fatigue, hyperpyrexia, tachycardia, tingling of limbs, dyspnea, and circulatory failure. Heat cramps is a syndrome marked by painful spasms of the voluntary muscles following prolonged muscular activity and profuse sweating at high environmental temperatures. The disturbance has been attributed by some investigators solely to loss of salt and hypo-

natremia, but it appears that other factors are involved.[2051,2216] The depletion of plasma electrolytes is accompanied by the excretion of water, leading to reduction in body fluids and hemoconcentration. The first three disorders are relieved in the early stages by fluids given by mouth or vein and are postponed by rest. It is generally accepted, however, that the ingestion of moderate amounts of salt is both of prophylactic and therapeutic value in heat cramps, whereas drinking water may aggravate the symptoms because of the rapid osmotic dilution of the blood and tissues.[1386 1387,2040]

Gamble and Butler,[739] in studies on normal volunteers who underwent prolonged fasting with short periods of thirsting, found that the average maximal concentration of the urine is 1 4 osm. as measured by freezing point depression ($\Delta = 2.6°$ C.). During fasting and dehydration, water is made available by oxidation of body protein, fat, and glycogen and by incidental release from intracellular and extracellular water as tissue is destroyed. Water loss is represented by insensible evaporation (and sweat, if present) and the obligatory urine expenditure at the osmotic ceiling. The minimal renal water required to maintain water equilibrium is represented by the difference between available water and irreducible loss This figure worked out, in a subject taking 1200 cc/day of water, to be 521 cc.; i.e. he would have remained in water balance on this amount. The addition of 100 gm/day of glucose, by sparing protein, reduced total solute output and hence the renal water requirement to 223 cc/day.

Solute output from an ordinary diet averages 1.2 osm/day, but, with a low protein, low salt, and high carbohydrate diet the output may fall to 200 mosm. The minimal water required for renal excretion under these extreme conditions would be 857 and 143 cc, respectively.

SODIUM CHLORIDE INTOXICATION

Dogs may be killed by the injection of a sufficient quantity of sodium chloride, without change in body water. The increased osmotic pressure of the plasma and interstitial fluid draws water from the tissues and causes intracellular dehydration Death usually results from respiratory failure. There appears to be no critical lethal concentration of sodium or chloride *per se*.[2236]

POTASSIUM INTOXICATION

Elevation of the serum potassium concentration to 12 mEq/liter or more in dogs leads to death from heart block. Potassium intoxication appears to be the *immediate cause of death after bi*lateral nephrectomy, and in some instances in man it appears to play an important role in death from protracted anuria. Elevated potassium concentration is not the cause of death in chronic glomerulonephritis, the concentration being substantially less than the critical value estimated for man and there being no signs of heart block. This circumstance apparently issues from a relative increase in the potassium clearance in advanced renal disease. However, the administration of potassium salts or potassium-rich food in protracted anuria is dangerous and definitely contraindicated.

EXPERIMENTAL SALT DEFICIENCY

The acute reduction of the salt content of the body in normal man produces a syndrome resembling that caused by adrenal cortical deficiency. This reduction can be accomplished by a low salt diet combined with diuresis and sweating. In studies of experimental salt deficiency by McCance and his coworkers [1289, 1291, 1293, 1299, 1300] one subject lost 30 per cent of his body chloride in a few days. His plasma sodium fell from 154 to 139 mEq/liter and the plasma chloride, from 100 to 80 mEq. An equivalent loss in weight occurred, probably attributable largely to reduction of the volume of the extracellular fluid, despite the fact that water was taken *ad libitum*. There were profound muscular weakness, excessive fatigue, mental apathy and confusion, anorexia, nausea, and loss of the sense of taste. There was no acute thirst, despite the loss of body fluid. Slight muscular activity produced cramps, and any muscle suddenly brought into action was liable to spasm, even the muscles of the chest and cheeks.

The total picture in salt deficiency is that the body is forced to compromise between the maintenance of the total base (osmotic pressure) of the plasma and the maintenance of extracellular fluid and blood volume; the former takes precedence over the latter and reduction of extracellular fluid and blood volume, with an in-

crease in hemoglobin and plasma protein, occurs before there is marked depletion of total base

In McCance's studies the filtration rate was reduced by 14 to 36 per cent, a change of possibly critical magnitude in respect to glomerular-tubular balance. The urea clearance was decreased out of proportion to the filtration rate, probably because of oliguria, and because of the reduction in the urea clearance the blood urea rose on a constant protein diet

The extracellular fluid was reduced from 28 to 38 per cent, a reduction large enough to account for the loss in weight. There was possibly some loss of cellular electrolyte and nitrogen and a gain in cellular water owing to the reduction in plasma osmotic pressure.* [1292]

The saliva showed a decreased sodium concentration, increased potassium concentration, and no change in chloride. There was a variable reduction or little change in the free and total hydrochloric acid and in the total chloride of gastric juice. Both sodium and chloride concentration decreased in the cerebrospinal fluid A considerable but variable fall occurred in the concentration of sodium chloride in the sweat. It was shown that adaptation to repeated sweating did not contribute to this result.

The renal responses in salt deficiency are markedly changed from the normal Where normally the ingestion of a large quantity of water leads immediately to marked diuresis, in salt depletion the excretion of water may be delayed 12 hr. Whatever the explanation of this delay, it recalls the similar blunting of diuresis in adrenal insufficiency. A second notable feature is the failure of the kidney to excrete bicarbonate during alkalosis induced by overventilation During and after overventilation, the alkalinity of the urine failed to increase, and indeed in several instances decreased (from pH 6 3 to 5.6, and from 5 3 to 5 0). It is as though, in the face of reduction of plasma sodium concentration, the conservation of sodium takes precedence over the maintenance of acid-base balance, and sodium cannot be spared for the excretion of bicarbonate. This phenomenon is also observed in alkalosis induced by

* Salt deficiency in the rabbit produces the same signs of body fluid and renal disorganization as in man.[1221]

prolonged vomiting and in other circumstances that deplete the plasma sodium or reduce the filtration rate. Instances are on record where the urine was acid despite the fact that the plasma bicarbonate was 90 volumes per cent or more. In all such cases, the administration of sodium chloride, by restoring the plasma sodium, promptly leads to renewed excretion of bicarbonate.[2100]

A third notable difference between the normal subject and one suffering from salt deficiency is that overventilation in the latter produces a marked fall in the urea clearance and in the excretion of endogenous creatinine, presumably owing to a comparable decrease in filtration rate. As a result, in part at least, of this decrease in filtration rate, the diuresis and increased sodium and potassium excretion normally induced by overventilation fail to appear and are replaced by a decrease in urine flow and electrolyte clearances. That the reduction in filtration rate is directly attributable to the alkalosis and not to muscular movements involved in overventilation is shown by the fact that the reduction is prevented if the subject breathes a carbon dioxide-air mixture while overventilating.

Chasis, Goldring, Breed, Schreiner, and Bolomey [255] examined the effects of a low salt-rice diet on hospitalized patients with essential hypertension. The filtration rate decreased in 9 out of 10 patients by the end of the second week, the lowest values reached ranging from 42.4 to 83.5 per cent (average 65.3) of the control level. The PAH clearance decreased in 8 out of 10 patients, the lowest values reached ranging from 61.8 to 92.9 per cent (average 79.5) of the control. Tm_{PAH} decreased in 6 out of 10 patients, the lowest values reached ranging from 72.7 to 91.4 per cent (average 81) of the control. The filtration fraction decreased in 6 out of 10 patients, and in 1 it increased. Addition of salt (30 gm/day) to the rice diet caused the filtration rate to return to or approximately to the control level in all 5 patients in whom it was tried, while the PAH clearance returned to the control level in the 2 patients in whom it had been significantly lowered. Tm_{PAH}, however, showed a further decrease in 4 out of 5 patients to whom salt was administered on the rice diet, and in 1 the depressed value remained unchanged. On return to the ward diet, Tm_{PAH} returned to the control value in 2 patients and approximated it in 1.

Weston, Hellman, Escher, and Leiter [2180] also report a reduction in filtration rate and renal plasma flow in hypertensive subjects on a low salt diet. In their observations limitation of protein also led to a reduction in Tm_{PAH}. It appears that a low salt-rice diet decreases filtration rate and renal plasma flow by virtue of the low salt content, the reduction in Tm_{PAH} being related to low protein intake or features of the diet other than salt There is no reason to believe that the reduction in renal function observed in these hypertensive subjects is materially different than would be expected in normal subjects under the same conditions. However, it should be noted that hypertensive subjects are reported to withstand salt deprivation, so far as weight loss is concerned, better than do normal subjects.[1589]

SIMPLE ALKALOSIS OF OVERVENTILATION

Overventilation for periods of 30 to 45 min. in normal subjects increases the alkalinity of the urine, the pH changing between the extremes of 5 1 and 7.6 to 8.0 It also produces a substantial diuresis The mechanism of alkalinization of the urine is not clear. Under these conditions both plasma pCO_2 and bicarbonate are reduced, and increased bicarbonate excretion cannot be explained in terms of the load of bicarbonate delivered to the distal tubule. It is conceivable that the reduced plasma pCO_2 leads to decreased H^+ secretion in the distal tubule, but there is no experimental evidence to support this interpretation.

In the experiments of McCance and Widdowson [1299] on overventilation in normal subjects, the urea clearance was variably decreased, but, since there was no change in the excretion of creatinine, the change in filtration rate was probably not significant. The rate of excretion of sodium was increased by 50 to 200 per cent, that of potassium by 300 to 500 per cent, changes probably referable to altered reabsorption of cations in association with the excretion of bicarbonate in the distal tubule rather than to altered reabsorption in the proximal tubule.

BICARBONATE ALKALOSIS

Contrary to the earlier belief [1526,1991,2290] that the administration of sodium bicarbonate over prolonged periods, as in the treatment of

prolonged vomiting and in other circumstances that deplete the plasma sodium or reduce the filtration rate. Instances are on record where the urine was acid despite the fact that the plasma bicarbonate was 90 volumes per cent or more. In all such cases, the administration of sodium chloride, by restoring the plasma sodium, promptly leads to renewed excretion of bicarbonate.[2100]

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was above a liter per day during the acute episode, indicating that the patient had suffered some loss of concentrating power. The severe reduction in Tm_D indicates tubular injury, which the authors attribute to renal ischemia, though it may have reflected a direct injury of the tubules with reduction in E_D.

In interpreting these results it should be recognized, on the one hand, that the dog responds to very large doses of sodium chloride by rapid excretion while man excretes excess salt very sluggishly (ch xi). If this response to sodium chloride is pertinent to the handling of large doses of bicarbonate, it is wholly unsafe to reason from experiments on dog to man. On the other hand, bicarbonate is frequently administered clinically where there has been prolonged vomiting with dehydration, which itself has an adverse effect upon the kidney; in so far as the bicarbonate ion will entail the obligatory excretion of additional sodium, this salt may only aggravate a vicious cycle In any case, the data strongly indicate that in man bicarbonate is too dangerous a drug for unrestricted use in self-medication.

WATER INTOXICATION

Water intoxication can be induced by the administration of water at rates more rapid than the kidneys can excrete it, or by stimulating the tubular reabsorption of water by the injection of the antidiuretic hormone in conjunction with water administration. The first symptoms involve the central nervous system, which probably suffers excessive hydration Following protracted convulsions, death occurs from cardiac failure.[1749] Alkalosis and loss of chloride by vomiting or accumulation of gastric juice in the stomach appear to play an important part in the reaction.[1954]

In order to produce water intoxication in dogs retention must exceed 60 cc/kg of body weight, the critical value appears to be from 60 to 70 cc Immediate recovery is effected by the intravenous injection of 10 per cent sodium chloride, whereas urea is relatively ineffective, implying that the disturbance is fundamentally one of superhydration of the body tissues.[908] Instances of water intoxication in man are now relatively rare.[973]

peptic ulcer, leads to renal injury, Kirsner and his coworkers [1122, 1123] could find no pathological evidence for this view by administering bicarbonate to dogs, or from observations on subjects habituated to bicarbonate. Tager and Klinghoffer [2038] report a subject in whom administration of 32,000 gm. of sodium bicarbonate in 20 months produced no marked alteration in plasma electrolytes and no decrease in the urea clearance.

However, McCance and Widdowson [1301] reported a marked reduction of the inulin clearance in a subject with uncompensated alkalosis induced by the prolonged administration of sodium bicarbonate.

As a control on the use of alkali in the therapy of black-water fever, incompatible blood transfusion, and crush syndrome, workers in the Army Malaria Research Unit (Oxford) [82] administered 60 grains of sodium bicarbonate and 60 grains of sodium citrate in 1 ounce of water to 2 normal subjects every 2 hr. for 3 days, and to a third subject every 2 hr. for 1 day only. In 1 subject after 24 hr. on this régime the filtration rate had increased from 179 to 277 cc., in a second subject after 76 hr., from 185 to 163, to 198 cc., and in a third after 68 hr., from 113 to 126, to 260 cc. These remarkable increases in filtration rate were not accompanied by a significant change in the renal plasma flow, so that the filtration fraction increased from 27 to 41, from 23 to 34, and from 23 to 46.8 per cent, i.e. to practically maximal values. In the first subject the urea clearance followed the inulin clearance, but in the second it fell markedly (from 84 to 19.3 cc.) with a rise in blood urea from 19 to 62 mg/100 cc., while in the third it remained unchanged. The decrease in urea clearance the authors attribute to tubular injury, and for this and other reasons consider that large doses of alkali should not be administered in conditions where renal failure may supervene.

Sanderson [1767] also examined a patient in alkalosis (plasma CO_2, 130 vol/100 cc.) and dehydration of vomiting following prolonged ingestion of bicarbonate. The inulin clearance was 22 cc., the diodrast clearance, 231 cc., and T_{mD}, 17 mg. of iodine (normal 40 to 50). Following cessation of bicarbonate ingestion and therapy with intravenous saline, partial recovery of renal function ensued, these values 6 weeks later being 54, 353, and 38. The urine flow

and 362 cc., diodrast clearance 631 and 525 cc., renal blood flow 970 and 858 cc., filtration fraction 0.196 and 0.208; Tm_D was measured in only 3 patients before and after delivery, 2 showing an increase and 1 a decrease in this value, but in 8 pregnant women this value averaged 45 6 mg. of iodine. C_D/Tm_D averaged 13.7 and 13.3, and C_{IN}/Tm_D averaged 2 67 and 2.28 antepartum and postpartum. The data on pregnant women are so close to normal and to the postpartum figures that the authors conclude that uncomplicated pregnancy has no effect on renal function.

Dill, Isenhour, Cadden, and Schaffer [822] report on 8 pregnant women in the thirty-second to fortieth week of pregnancy. The average inulin clearance was 116 ± 16.9; diodrast clearance, 637 ± 145; renal blood flow, 950 ± 237 cc/min.; filtration fraction, 0 176. Postpartum, these figures were 139 ± 16.1, 630 ± 90.7, 980 ± 186, and 0.234, the change in the filtration fraction being referable to the increase in filtration rate. The figures are so close to each other and to those for non-pregnant controls that they indicate again that pregnancy does not influence renal function

PRE-ECLAMPSIA AND ECLAMPSIA

(SPECIFIC TOXEMIAS OF PREGNANCY)

Eclampsia is a specific disease of pregnant women, of unknown origin. The term eclampsia is reserved for the severer phase marked by convulsions, pre-eclampsia indicating the non-convulsive phase characterized by hypertension, albuminuria, and edema. Patients who have once had eclampsia or pre-eclampsia are more likely to have subsequent toxemia and a higher incidence of stillbirths and abortions than patients who have experienced uncomplicated pregnancies. Generally the toxemia is promptly relieved by uterine evacuation.[256,278] The renal lesion is primarily glomerular, the capillary tuft being bloodless and swollen; there is clumping and fusion of the loops and eventual hyalinization of some tufts Occlusion of the capillaries is brought about by thickening of the basement membrane and swelling of the mesangial cells between the capillaries The changes are of a degenerative rather than inflammatory character; unlike acute glomerulonephritis, the endothelial nuclei are not increased.[115]

CHAPTER XXI

Disturbances of Renal Function in Non-renal Disease

PREGNANCY

Chesley and Chesley [372] reported an average diodrast clearance in 8 normal pregnant women near term of 610 cc., a figure to be compared with their control observations on 9 normal non-pregnant women of 518 cc. The corresponding whole blood figures were 915 and 900 cc.* They concluded that pregnancy has no effect upon the renal blood flow (These whole blood figures are lower than those reported by others, possibly because of technical differences in the clearance procedure.) In view of the fact that anemia *per se* is not accompanied by an increased whole blood flow to the kidney, the plasma flow remaining constant, the difference in these plasma clearances (518 *vs.* 610 cc.) may indicate moderate renal hyperemia in late pregnancy. The endogenous creatinine chromogen/diodrast clearance ratio averaged 0.129 in pregnancy and 0.122 in non-pregnant women.†

Welsh, Wellen, and Taylor [2168] examined 22 women in the twelfth to forty-first week of pregnancy, and re-examined 11 of these postpartum. The average antepartum and postpartum data were: inulin clearance 124 and 116 cc., phenol red clearance 371

* These data are corrected for the effect of oxalate on the hematocrit, made in accordance with a personal communication to the writer.

† The method of determining the chromogen may be responsible for these low ratios.

women who did not have hypertension before pregnancy but in whom hypertension persisted after toxemia, the urea clearance averaged 53.1 and the diodrast clearance 428 cc., the estimated filtration fraction 0.208. The last figures may be compared with those reported by Chesley for 11 women with essential hypertension who had had no pregnancies: the estimated filtration rate averaged 106 and the diodrast clearance 351 cc., the filtration fraction 0.302. Chesley believes that post-toxemic hypertension differs from essential hypertension in showing a lower filtration fraction because of the glomerular lesion. His data also support the suggestion that it is among those women who have a substantially reduced filtration fraction during toxemia that the potential victims of persistent hypertension (7 of 14 patients) are to be sought, those having normal filtration fractions showing a lower incidence (1 of 16 patients) of post-toxemic effects.

In 10 women with pre-eclampsia, Dill *et al.*[622] report an average inulin clearance of 84 ± 35.3, diodrast clearance 680 ± 283, and renal blood flow 905 ± 425 cc., the filtration fraction being 0.167. After delivery these figures were: inulin, 105 ± 38.5; diodrast, 482 ± 179; renal blood flow, 746 ± 193 cc.; filtration fraction, 0.228. Again, as in their group of normal pregnant women, the increase in the filtration fraction is referable to an increase in filtration rate. In 10 pregnant women with essential hypertension (some of whom had had toxemia at one time) examined in the twenty-eighth to forty-first week of pregnancy, the inulin clearance averaged 87 ± 34, the diodrast clearance 515 ± 234 cc., and the filtration fraction 0.228; after delivery these figures were inulin 95 3 ± 31.9, diodrast 464 ± 115, and filtration fraction 0.234. Again, the filtration fraction is reduced in toxemia and elevated in essential hypertension The authors ascribe the reduction of filtration fraction in toxemia to changes in glomerular pressure rather than decreased glomerular permeability. There seems to be no way to distinguish the two factors at the present time, because all renal hemodynamic calculations must assume an unchanged glomerular permeability coefficient, an assumption that is here invalid because of the glomerular lesion. The authors suggest that the same fundamental vascular abnormality is responsible for the

In 21 women with pre-eclampsia and eclampsia, Chesley, Cornell, Chesley, Katz, and Glissen [274] report an average diodrast clearance of 554 cc., endogenous creatinine chromogen clearance of 75.7 cc., and urea clearance of 66.8 cc., the estimated filtration fraction being 0.148; all these figures are close to their control values in normal pregnant women The authors conclude that the renal blood flow in the mean is not affected, though the variation is greater. Their patients with eclampsia were, however, examined shortly after delivery.

Corcoran and Page [414] report on 28 women during toxemia. Some of these were studied by the phenol red clearance (before the introduction of diodrast for renal blood flow measurement) and the authors have made an appropriate correction to approximate the corresponding diodrast clearance. They divide their subjects into three groups: A (13 cases), those with a low filtration fraction, B (8 cases), those in whom the filtration fraction was increased and, group C (7 cases), those in whom the filtration fraction was in the normal range. In group A, the average approximate renal blood flow was 989 cc., the average filtration fraction 0.135. Seven of the 13 cases were considered severe, with marked proteinuria in every instance, constriction of retinal arterioles in 12, and retinal edema or papilledema in 6. Postpartum, these patients showed an increase in filtration fraction and a decrease in renal blood flow. The authors attribute the reduction in filtration fraction to swelling of the basement membrane of the glomerular capillaries and note that in this group the clinical course of the disease was most severe. Three of these patients developed persistent hypertension In group B, the average approximate renal blood flow was 688 cc. and the filtration fraction 0.247. Three of these patients had pre-existing essential hypertension and the authors infer that the group as a whole had pre-existing or latent hypertension. In group C, the approximate renal blood flow averaged 853 cc. and the filtration fraction 0.165. These were considered to be instances of mild toxemia.

Chesley [268] reports that, in 7 women with normal blood pressure after toxemia, the urea clearance averaged 58.0 and the diodrast clearance 507 cc., the estimated filtration fraction 0.189. In 15

increased interstitial pressure, or thickening of the basement membrane of the glomerulus.

Those patients in whom hypertension persists could not be distinguished antepartum from those in whom the blood pressure returned to normal after delivery, except perhaps that they showed a greater decrease in C_D/Tm_D on delivery; the antepartum value of this ratio was above the mean normal in 4 out of 5. The authors suggest that, in the permanently hypertensive group, elevation of the filtration fraction, characteristic of essential hypertension, is prevented by some unknown factor that increases renal blood flow so long as pregnancy continues This suggestion is supported in the later study of Wellen, Welsh, Taylor, and Rosenthal,[116] who find that the renal blood flow, as judged by the C_D/Tm_D ratio, is increased during pregnancy relative to observations made before conception and after delivery, the filtration rate and Tm_D remaining unchanged Supplementary evidence on this point is derived by them from phenol red and inulin clearances. Comparison of results obtained during pregnancy and for an observation period of 1 to 4 years after delivery indicate that pregnancy itself, when uncomplicated by specific toxemia, does not cause any deterioration of renal function in women with essential hypertension or chronic glomerulonephritis.

Dill, Isenhour, Cadden, and Robinson [121] examined 6 pregnant and 9 non-pregnant women who had had a toxemia of pregnancy 1 to 12 years previously but who were considered normal by both clinical and laboratory methods during the interim. In the 6 pregnant women examined antepartum the filtration rate averaged 84.1 cc.; the renal plasma flow, 500 cc.; the renal blood flow, 750 cc.; the filtration fraction, 0 185. Postpartum these figures were 97 9 cc , 394 cc., 690 cc., and 0.225, again showing a slight increase in renal blood flow and decrease in filtration rate during pregnancy.

In the 9 non-pregnant women, the filtration rate averaged 94 cc., the renal plasma flow, 469 cc ; the renal blood flow, 781 cc.; and the filtration fraction, 0.207. The authors conclude that toxemia, even in the absence of other signs, is usually followed by a reduction in renal function, the degree of which increases with time.

hypertensive diseases and for the toxemias of pregnancy and their sequelae, but this broad generalization must be accepted cautiously.

Wellen, Welsh, and Taylor [2161] report on 11 women examined antepartum and postpartum. They compiled data on normal nonpregnant women by combining the observations of Goldring *et al.*[797] on 9 women with further observations of Welsh, Wellen, and Taylor [2168] and refer to these normal values graphically. Relative to their normal statistics, Tm_D was equally distributed above and below the mean in the pre-eclamptic patients; in only 1 did it deviate more than -2σ, and in this patient it returned to normal after delivery. The changes in Tm_D before and after delivery were, with the one exception mentioned, slight and of random sign. The filtration rate was low, relative to postpartum values, and the ratio C_{IN}/Tm_D was below the mean normal value in all but 2 patients (in 1 this ratio was below -2σ). The C_D/Tm_D ratio, on the other hand, was above the mean normal in 8 of the 11 patients, in 2 instances in excess of $+2\sigma$. In 9 patients (including the 8 above) the ratio fell after delivery, in 3 subjects reaching values below -2σ. The filtration fraction was low (0.11 to 0.20) in all antepartum observations. The data indicate a normal or moderately increased renal blood flow antepartum, with a somewhat reduced filtration rate, giving a low normal filtration fraction.

In the group with clinical cure on delivery, the decrease in diodrast clearance and increase in inulin clearance brought these values and the filtration fraction to a normal range. But in 5 patients who were left with persistent hypertension, the decrease in diodrast clearance and the increase in inulin clearance resulted in high filtration fractions (0.288, 0.210, 0.240, 0.266, and 0.267) typical of patients with essential hypertension, though the C_D/Tm_D ratio was below normal in only 1 subject. The authors reject the view that renal ischemia is an essential factor in the production of hypertension in toxemia of pregnancy because in the presence of hypertension the renal plasma flow is normal and supernormal. Without preference, they suggest that the low filtration rate observed in some patients antepartum could be attributed to increased afferent arteriolar tone, renal edema, and

the fetal heart is lost, these changes take place just as if the uterus had been emptied, and delivery of the dead fetus does not alter the clearances, which remain at the normal level. The data do not permit a firm conclusion, but most investigators believe that the reduced urate clearance is sufficient to account for the hyperuricemia. Whether the decrease in urate clearance is entirely attributable to the decrease in filtration rate or involves increased tubular reabsorption is undetermined. A frequent drop in the uric acid/urea clearance ratio points to participation of the latter. (Chesley, pers com.)

The serum sulphate may rise, in many instances of pre-eclampsia, before or out of proportion to the urea [1055] This may be related to the fact that (in the dog, at least) the plasma sulphate level is almost precisely balanced against sulphate Tm through the filtration rate, and any reduction of the latter will be reflected in an increase in plasma concentration, irrespective of urine flow. The urea clearance, on the other hand, is probably more variably affected by urine volume.

There is some evidence that estrogens are causally related to the retention of sodium in pre-eclampsia, since sodium is retained during periods of high estrogen concentration and lost during periods of diminishing hormones [2050]

Large amounts of both VEM and VDM are regularly present in peripheral blood during the period of pre-eclamptic hypertension, sometimes VEM, sometimes VDM predominating. These factors disappear on return of the pressure to normal levels.[1884]

BILATERAL CORTICAL NECROSIS

'Bilateral cortical necrosis' is a pathologic term applied to certain relatively rare cases of anuria of unknown etiology. The condition is characterized by focal cortical necrosis of varying severity and distribution, both kidneys being generally about equally involved. The inner third of the cortex is usually unaffected but, in severer cases, necrosis may extend into the medulla along the columns of Bertin. In the necrotic zone the interlobular arteries, afferent arterioles, and glomerular vessels are dilated and generally obstructed by thrombi variously composed of fibrin, platelets, conglutinated red cells, and amorphous fatty substance. Thrombus

The data are inadequate to establish that the changes in renal function are significant, but they indicate that, whereas uncomplicated pregnancy has no effect on renal function, in pre-eclampsia the filtration rate is reduced (possibly by the glomerular lesion) with at least a corresponding reduction in filtration fraction. The renal plasma flow and the C_D/Tm_D ratio appear to be elevated. In patients who do not develop persistent hypertension, these deviations in function disappear after delivery; in those who do develop persistent hypertension, the functional pattern shifts to that characteristic of essential hypertension, *viz.* a reduction in renal plasma flow and in the C_D/Tm_D ratio, and an elevation to supernormal levels of the filtration fraction. But these changes, which are always relative, may merely express the development of the essential hypertensive pattern. In no way do they imply that altered renal function is related to the genesis of persistent hypertension.

A rise in blood uric acid without nitrogen retention has been stated to be one of the most consistent signs of pre-eclampsia and eclampsia. Schaffer, Dill, and Cadden [1775] reported reduced uric acid clearances in pre-eclampsia (their clearances may have been elevated by the simultaneous administration of diodrast); the inulin and urea clearances were likewise reduced, and the reduction in uric acid clearance was attributed by them to reduction in filtration rate. Pregnancy itself has no effect on this clearance. Bonsnes, Dill, and Dana [209] report the uric acid clearance in normal women, 1 to 8 days postpartum, as 15.4 ± 3.2 cc. in one series of 9 subjects and 14.0 ± 2.9 in another series of 11 subjects. Chesley and Williams [370, 377] report this value in 10 normal women as 15.7 cc. antepartum and 14.9 postpartum, the uric acid/inulin clearance ratios averaging 0.122 and 0.117, respectively. In pre-eclampsia the clearances were 7.8 antepartum and 15.4 postpartum and the clearance ratios 0.081 and 0.137 respectively.

Bonsnes and Stander [210] find that the 24 hr. uric acid clearance is generally lower (6.4 cc.) during active pre-eclampsia than during the postpartum or early puerperium period (10.4 cc.), paralleling a reduction in the urea clearance (42 and 55 cc. respectively). The normal 24 hr uric acid clearance in pregnant and non-pregnant women averages about 12 cc., the urea clearance 63 cc. If

the body. The blood thus made available in the males amounts to some 500 cc/min.

On the average, the inulin clearance was reduced (to 89 cc. in males and 107 cc. in females; normal, 127 and 118, respectively) but in some subjects this function was normal. The filtration fraction was low or low normal. Renal blood flow and filtration rate returned to normal as the hematocrit increased under therapy.

Diodrast Tm was depressed by 22.5 per cent in females and 39 per cent in males. Glucose Tm fell within the normal range in 6 out of 7 patients studied; in the exception, who had diabetes mellitus, it was low In 2 patients Tm_D improved under therapy, the others showing no significant change.

Bradley and Bradley suggest that the edema of chronic anemia, which is unrelated to decreased oncotic pressure or increased venous pressure, may be attributable to the reduced filtration rate, which may fall below 80 cc, and this may also account for reduction in the urea clearance and the development of azotemia in some patients They also comment on the fact that this marked degree of renal ischemia is not accompanied by hypertension, and pre-existing hypertension remains unchanged in chronic anemia Reduction in whole blood flow rather than plasma flow is also indicated in 2 of 3 subjects reported by Aas and Blegen.[2] Restoration of red cell volume effected a large increase in blood flow with no increase in plasma flow. The hyposthenuria observed in some patients with pernicious anemia is apparently not attributable to anoxia of the renal tubules, since concentrating power in dogs is not impaired when the hemoglobin is kept at low levels for one or two months by repeated bleeding.[941]

HEMATEMESIS

Stevens, Schiff, Lublin, and Garber [2001] report that the urea, inulin, and phenol red clearances may be either normal or reduced in the presence of the increased blood urea concentration that follows hematemesis. The reduction in the urea clearance is insufficient to account for the elevation of blood urea and persists in spite of the return of the blood urea to normal The intragastric administration of 2 liters of blood had no effect on renal function.

formation appears to be secondary to renal ischemia, which may be of neural or humoral origin. The condition occurs most frequently in the last trimester of pregnancy and in association with some catastrophic complication. Some investigators believe that, with rare exceptions, true bilateral cortical necrosis is confined to this circumstance and represents one of the toxemias of pregnancy. However, the disease is not to be identified with eclampsia and an entirely similar lesion may occur in males.[115] Others, however, do not distinguish so firmly between the lesion in pregnancy and the bilateral focal ischemic atrophy observed in lupus erythematosus disseminatus, scleroderma, rheumatic fever, periarteritis nodosa, septic abortion, staphylococcus bacteremia, and other conditions giving rise to embolic phenomena in the kidneys and other organs. It is said that treatment is of no avail, and some writers have considered the condition as invariably fatal. However, it is obviously impossible to assert that the same causes and processes underlying those fatal instances of protracted anuria, which at autopsy are identified as 'bilateral cortical necrosis,' may not be present in non-fatal cases where partial recovery of renal function occurs.[61, 64, 134, 323, 549, 1686]

CHRONIC ANEMIA

Bradley and Bradley[236] have reported on 15 patients with severe chronic anemia (pernicious anemia in relapse, paroxysmal nocturnal hemoglobinuria, duodenal hemorrhage, hemorrhoids, iron deficiency, and lymphatic leukemia). Regardless of etiology, the most striking functional alteration is that the renal plasma flow is only slightly reduced, but the renal blood flow, because of the low hematocrit, is markedly reduced. Thus the diodrast clearance was decreased in males to 522 cc., or by 20 per cent from the normal mean of 655 cc., and in females to 534 cc., or by 11 per cent from the normal mean of 600 cc. These figures are in sharp contrast to 654 cc. whole blood flow in males (normal 1166 cc.), or a 44 per cent reduction, and 673 cc. in females (normal 940 cc.), or a 28 per cent reduction. Since the extraction ratio of PAH is not reduced in anemia[2144] and since the mean arterial pressure is not reduced, the data indicate that in anemia, as in shock, etc., renal vasoconstriction occurs in order to divert blood to other parts of

tients with diabetes mellitus and found Tmo values in the low normal range. It is probably safe to say that the kidneys are in no way involved in its pathogenesis. Overload of glucose in the proximal tubules leads, however, to osmotic diuresis and polyuria, and some disturbance of salt and water balance is to be expected from this osmotic diuresis. The disturbance of acid-base balance represents primarily a metabolic rather than a renal acidosis.

Despite a marked rise in plasma glucose sufficient to produce frank glucuresis in normal subjects, the urine in some diabetic patients may be almost glucose free, this may reflect a reduction in filtration rate associated with dehydration, which in uncontrolled diabetes can be extreme. An equally important consideration, however, is that, in some elderly patients with a long history of disease, a deposit of hyalin material is formed between the glomerular capillary loops, all or most of the glomeruli being involved to some degree and a few to the extent of almost complete obliteration This condition, called intercapillary glomerulosclerosis by Kimmelstiel and Wilson, who first described it in 1936, increases in frequency with age, and it is occasionally seen in senile non-diabetics. It is frequently accompanied by massive proteinuria, edema, azotemia, arteriosclerotic hypertension, and other signs of vascular sclerosis.[1380 1727] A similar lesion has been produced in dogs with experimental pituitary diabetes,[1293] and in rats with alloxan diabetes [1381]

Hogeman [1025] reports that, in 12 patients with uncomplicated diabetes, renal function did not deviate significantly from his normal controls; the mean inulin clearance was 117 ± 15.4 cc., diodrast clearance 395 ± 68.3 cc.,* and filtration fraction 0.300 ± 0 02. In 12 patients with proteinuria, hypertension, and retinitis, these figures were significantly different from his normals, the mean inulin clearance being 59.2 ± 37.1 cc., diodrast clearance 271 ± 135 cc , and filtration fraction 0.206 ± 0 021. The majority, in respect to both filtration rate and renal plasma flow, fell below -3σ The reduction in filtration fraction is also statistically significant. Hogeman concludes that diabetes mellitus *per se* does not necessarily cause any demonstrable disturbance in renal func-

* Hogeman's diodrast clearances are consistently low in comparison with those of other investigators

In a patient in moderate oligemic shock caused by severe alimentary hemorrhage, Black, Powell, and Smith [184] report an inulin clearance of 23 cc. and a diodrast clearance of 50 cc. Seventeen hours after transfusion of 850 cc. of blood these figures were 55 and 116 cc., and 3 months later 89 and 453 cc. Similar though less spectacular changes were observed in a second patient before and after recovery. A third patient on admission, when the blood volume was little if at all reduced, showed an inulin clearance of 177 cc and a diodrast clearance of 505 cc. (filtration fraction, 0.35); 20 hr. after transfusion (1200 cc.) these figures were 158 and 325 cc. (filtration fraction, 0.49), and 5 months later the inulin clearance was 112 cc The reason for this high filtration rate is unknown. The patient was severely anemic (23 per cent cells) but, as Bradley *et al* [236] have shown, this circumstance is not generally accompanied by an increase in filtration rate or filtration fraction. Recognizing that E_D may have been reduced by renal injury, the authors conclude that intestinal hemorrhage with moderate oligemic shock is accompanied by renal ischemia.

Studies showing reduction in the urea and creatinine clearances in hematemesis and in other circumstances involving vomiting or hemorrhage, are reviewed by others.[181, 859]

DIARRHEA

Water loss in diarrhea results in shock and extrarenal azotemia, as does salt and water loss through any other portal. In this instance, however, acidosis is the rule, because alkaline intestinal secretions are discharged in large volume,[738] but it is unlikely that acidosis itself causes renal dysfunction.[2236] Rarely, alkalosis may develop.[469, 740] Dehydration is undoubtedly of prime importance, a fact implicit in the recognition by Latta, more than a hundred years ago, that salt and water replacement is the treatment of choice.

DIABETES MELLITUS AND INTERCAPILLARY GLOMERULOSCLEROSIS

In relation to renal function, diabetes mellitus primarily represents a disturbance of metabolism in which the plasma glucose is elevated to such an extent that the load of filtered glucose delivered to the proximal tubules exceeds Tm_G. Nielson [1527] studied 5 pa-

other factors frequently lead to a reduction in blood pressure; if severe, this hypotension may embarrass renal function [1297] McCance and Widdowson [1304] examined 5 subjects in diabetic coma and found that the filtration rate was considerably below normal. The urea clearance was excessively low, partly because of the low filtration rate and partly because of severe oliguria. However, the exogenous creatinine clearance in 5 out of 5 patients was less than the inulin clearance, the creatinine/inulin clearance ratio ranging from 0.42 to 0 85, in contrast to the normal ratio of 1.2 to 1.4, indicating back diffusion of creatinine (and possibly inulin) as a result of tubular injury.

The excretion of sodium and chloride is low in diabetic coma, probably because of the disturbance in glomerular-tubular balance The excretion of ammonia may be unimpaired, however, which is to be expected, since ammonia synthesis by the distal tubules is not primarily dependent on glomerular filtration.

The available data do not exclude tubular impairment as a result of metabolic default in the absence of insulin, or some deleterious influence of ketosis.[829 917, 1998]

CONGENITAL CYANOTIC HEART DISEASE

Scott and Elliott [1814] have reported studies on 19 patients with congenital circulatory anomalies associated with arterial oxygen unsaturation. They distinguish two groups· in group 1 the patients were younger, somewhat smaller, and had higher hematocrits than the patients in group 2 In group 2, renal function was measured simultaneously with cardiac or renal vein catheterization, conditions conducive to anxiety The two groups differed only in respect to a lower renal blood flow in group 2.

In group 1 (10 subjects), T_{mPAH} averaged 71.7 mg , a figure only slightly below normal (79 mg.). Of group 2, 7 subjects gave an average E_{PAH} of 0 87, showing essentially normal extraction. The filtration rate in the entire series ranged from 53 to 176 and averaged 110 cc. The PAH clearance ranged from 150 to 666 cc and averaged 379 cc , a definitely low figure. The hematocrit was high, as is characteristic in chronic anoxia, averaging 73 4 per cent cells; consequently, the whole blood flow was relatively greater than indicated by the plasma flow, averaging 1625 cc (1164 cc. is

tion, but in the presence of the Kimmelstiel-Wilson syndrome, renal function is markedly impaired. The reduction in filtration rate probably contributes to the high glucose threshold observed in many elderly diabetics.

Farber, Conan, and Earle [618] report that in 10 diabetic subjects without clear evidence of intercapillary glomerulosclerosis the filtration rate was within normal limits, as were most of the Tm_G values. The C_F/Tm_G ratio, however, was lower than normal, perhaps foreshadowing glomerular involvement. Insulin reduced Tm_G in some normal subjects tested and in all the diabetics, raising the C_F/Tm_G ratio toward normal. In several patients the excretion of glucose actually increased after insulin, despite a decrease in plasma glucose concentration. Studies on electrolyte excretion before and after the administration of glucose, or glucose plus insulin, are also reported.

Corcoran, Taylor, and Page [432] report that in 5 patients with intercapillary glomerulosclerosis the filtration rate ranged from 13 to 82 cc. and the diodrast clearance from 139 to 657 cc. Tm_D was subnormal in all but 1 (58 mg. of iodine), ranging from 11 to 26 mg. of iodine. The filtration fraction was low (0.08 to 0.18), as was the C_{IN}/Tm_D ratio (1.05 to 3.12), but the C_D/Tm_D ratio was high, 18.6 to 36, a circumstance the authors attribute to vicarious clearance. They see the lesion as one of the glomerular capillaries, which obstructs filtration more than perfusion, supplemented by loss of function in whole nephrons.

Hilden [1005] reports that in 7 diabetic patients the thiosulphate clearance ranged from 14 to 75 per cent, and Tm_D from 12 to 88 per cent of normal. The thiosulphate clearance/Tm_D ratio ranged from 1.60 to 3.02. The authors conclude that filtration rate and Tm_D are affected about equally.

Data on the reabsorption of glucose by 3 depancreatized dogs are reported by Govaerts and Muller,[829] but control data are unfortunately lacking.

DIABETIC COMA

Extreme dehydration, ketosis, and acidosis culminate in diabetic coma. If for no other reason, it is to be expected that the filtration rate would be reduced in consequence of reduction in the extracellular fluid volume. In addition, reduction in blood volume and

than 10 per cent in 7, the largest increase being from 1310 to 2100 cc. In only 1 did the blood flow decrease by more than 10 per cent. The filtration rate increased by more than 10 per cent in 5, the largest increase being from 111 to 171 cc., and it fell by more than 10 per cent in only 2. The filtration fraction fell in 6 and increased in 4. These patients, plus 5 additional ones not studied postoperatively, confirm the conclusion that aortic coarctation is generally accompanied by moderate to severe renal ischemia with a rise in filtration fraction, indicative of renal arteriolar spasm.

SICKLE CELL ANEMIA

In 5 children with sickle cell anemia, the thiosulphate clearance was subnormal (50.7 to 94.0 cc.), but in the normal range (121 and 150 cc.) in 2 with sickle cell trait and in 1 (145 cc.) with anemia secondary to uncinariasis.[320]

HEPATIC CIRRHOSIS

Cirrhosis of the liver is a chronic degenerative disease of unknown origin, characterized by profound metabolic disturbances leading to hypoproteinemia and cachexia and by the formation of edema. Unlike the edema of cardiac failure, cirrhotic edema is most marked in the abdominal cavity (ascites), a circumstance generally related to increased capillary pressure in the portal circulation.

Factors that might contribute to edema formation are (1) increased portal capillary pressure, (2) hypoalbuminemia, (3) decreased glomerular filtration rate, (4) increased sodium retention, (5) increased water reabsorption by the renal tubules. Nothing is known about variations in portal capillary pressure in man. Hypoalbuminemia, although contributory, appears to be relatively unimportant, since the continued administration of salt-poor human albumin with restoration of the plasma albumin concentration may fail to induce diuresis, and spontaneous diuresis may occur despite continued hypoalbuminemia.[613, 614] Sodium excretion, with or without increased salt administration, is invariably subnormal, the deficiency is not relieved by restoration of the plasma albumin concentration, but ascites formation can be reduced by restriction of salt intake or by the use of mercurial diuretics to

taken as normal by the authors). This renal blood flow represented a greater than normal fraction of the cardiac output; in 11 subjects the average renal fraction was 0.348, whereas the normal probably does not basally exceed 0.20. (This figure varied from 0.18 to 0.603, and 4 observations above 0.40 may reflect multiple errors in cardiac output and renal clearance determination.) The renal arterial-venous oxygen difference (0.7 to 3.4, average 1.7 cc/100 cc.) was within the normal range, as was the renal oxygen consumption (3.0 to 35.0, average 16.2 cc/min.). The uncorrected filtration fraction ranged from 0.20 to 0.55 and averaged 0.31; the filtration fraction corrected for E_{PAH} in 7 subjects averaged 0.24, a slightly elevated figure.

The authors conclude that, in general, cyanotic patients maintain satisfactory excretory function despite polycythemia and a marked reduction in renal plasma flow. The renal blood flow, in this group with congenital cyanotic heart disease, tended to be elevated above normal (possibly as a compensation for diminished renal plasma flow) by vascular adjustments in the kidney rather than by an increase in cardiac output.

COARCTATION OF THE AORTA

Friedman, Selzer, Rosenblum, McLean, and Picard [714] report that, in 4 male and 2 female patients with aortic coarctation, the renal plasma flow was substantially reduced (average 465 cc., range 445 to 531). The filtration rate, however, was much less affected (average 122 cc., range 119 to 130), giving rise to a markedly elevated filtration fraction (average 0.265, range 0.228 to 0.29).

Aortic coarctation is characteristically accompanied by arterial hypertension which is not attributable to anatomic obstruction of the aorta, the diastolic hypertension is equally evident in the femoral arteries,[1992] and it has been suggested that systemic vasoconstriction is related to the release of a pressor substance from the kidneys. Friedman *et al.* consider that the renal ischemia observed by them may also be attributable to this humoral mechanism.

Genest, Newman, Kattus, Sinclair-Smith, and Genecin [761] report pre- and postoperative data on 12 patients with aortic coarctation. The renal blood flow increased postoperatively by more

companied by a marked increase in filtration rate, renal plasma flow, and T_{mPAH}. A period of fluid accumulation does not apparently militate against normal renal function after the ascites is controlled and may possibly enhance renal function by some compensatory mechanism.

The hepatic blood flow is also generally reduced in cirrhosis, falling well below the normal values.[232]

HEPATORENAL SYNDROME

A voluminous literature has been written on the so-called 'hepatorenal syndrome.' In the main, two points of view have evolved. One maintains that, following biliary or hepatic surgery, thyroidectomy or extensive gastrointestinal operations, a profound derangement of liver function may result in 'liver death,' a rapidly fatal condition characterized by high fever, coma, and usually shock. If the course is less rapid, renal damage results and death occurs in uremia associated with jaundice and other signs of hepatic failure, the 'hepatorenal syndrome.' The opposing view holds that the liver is not primarily involved, and that the syndrome is attributable in most cases to overwhelming sepsis or to obscure infection. Both agree that the kidneys are damaged by toxins that may be released from the damaged liver or that may accumulate in the blood in the absence of the hepatic route of removal. Unfortunately, there is inadequate information on pathology and cardiovascular, renal, and hepatic function to afford a clear understanding of what is probably a mixed group of physiological disturbances.

Bradley [226] points out that renal and hepatic impairment may appear simultaneously in many conditions (intoxication by a variety of substances such as heavy metals, chloroform, cinchophen, dioxane, diethylene glycol, and carbon tetrachloride), in septicemia, Weil's disease, yellow fever, liver trauma, Waterhouse-Friderichsen syndrome, fever therapy, and profound disorders of both the liver (subacute yellow atrophy) and kidney (pyelonephritis). Moreover, cases of acute diffuse glomerulonephritis or acute interstitial nephritis complicating the course of infection or liver disease associated with jaundice may have been

force the excretion of sodium. Mercurial diuretics may, however, fail to increase the excretion of sodium in some cirrhotic patients, as it fails in some patients with edema of chronic congestive heart failure.

Farnsworth and Krakusin [622] report low filtration rate and renal plasma flow in 2 patients in the edematous stage of cirrhosis.

Patek, Mankin, Colcher, Lowell, and Earle [1581] report that, in 3 patients in the edematous stage, the filtration rate was low (75 cc.) in 1, normal (122 cc.) in a second, and elevated (190 cc.) in a third. The corresponding PAH clearances were 356, 512, and 752 cc. One hour after the injection of 50 gm. of human plasma albumin in 0.3 M sodium chloride solution, the renal plasma flow increased to 503, 842, and 821 cc., respectively. (The increase was apparently not maximal at this time, and, in view of Cargill's [327] demonstration that, during renal hyperemia induced by albumin in normal subjects, T_{PAH} is decreased below the normal value of 0.92, the increase in total renal plasma flow may have been considerably greater than is indicated by the foregoing data.) Repeated albumin appeared to lead to sustained improvement in renal function, and indeed to marked renal hyperemia. Patek *et al* conclude that ascites formation is not determined solely by the level of the plasma colloid osmotic pressure and suggest that changes in the permeability of the portal vascular bed and in salt and water metabolism are involved.

Leslie, Johnston, and Ralli (pers. com.) find that, among 29 patients in whom ascites had never been present, or not present to a degree requiring paracentesis, renal function was normal or supernormal, the filtration rate ranging from 113 to 376 cc., renal plasma flow from 540 to 1451 cc., and Tm_{PAH} from 65 to 130 mg. In patients who had at some time required paracenteses but at the time of study had no significant ascites, all measurements fell within the normal range: filtration rate, 109 to 172 cc.; renal plasma flow, 592 to 779 cc.; and Tm_{PAH}, 64 to 82 mg. In patients who were rapidly accumulating ascites, all measurements were depressed: filtration rate, 39 to 106 cc.; renal plasma flow, 253 to 440 cc.; and Tm_{PAH}, 32 to 60 mg. Diuresis under therapy with purified liver extract (intraheptol) and multiple vitamins was ac-

solute quantities of protein excreted in these tests were slight, their significance was validated by Chesley and his coworkers by comparison with the simultaneous excretion of endogenous creatinine, which eliminates faulty urine collections. As judged by this clearance, the filtration rate decreased in 9 of 11 subjects studied who showed proteinuria, the maximal decrease (to 76 per cent of the control) occurring in the interval 4 to 8 min.

Chesley and his coworkers concluded that, as Starr had suggested, proteinuria is associated with renal vasoconstriction and glomerular ischemia, proteinuria beginning when the vascular spasm begins to relax at the end of the cold stimulus. However, it may be noted that the proteinuria is almost instantaneous and, in their data, precedes by 2 to 4 min. the maximal indicated change in filtration rate, and it is difficult to believe that so short a period of ischemia would have this effect. Moreover, the studies of Talso, Crosley, and Clarke [2044] on normal subjects do not indicate an invariably rapid response in the kidney to the cold pressor test. The problem invites further investigation by the ureteral catheterization method

POSTURAL PROTEINURIA

Intermittent proteinuria occurs in about three-fourths of youths,* one-third of young men, and one-tenth of old men,[291] during appropriate circumstances chiefly related to posture. The critical factor is the erect, extreme lordotic position. During the proteinuria there is a marked reduction in urine flow and the appearance of large numbers of renal epithelial cells and casts in the urinary sediment, a small increase in red blood cell count occurs inconstantly and congo red escapes into the urine.[1760] In a few subjects protein has been reported as coming from one kidney only.[1881,2282]

Medes and Berglund [1427] determined the creatinine clearance in normal subjects and in subjects with mild and extreme lordotic proteinuria, during 30 min. of recumbency. The rates were 171 ± 4 cc., 158 ± 5 cc., and 155 ± 7 cc. in these three groups. During

* In 22,000 presumably healthy young men the incidence of proteinuria in single urine samples collected on a day free from undue physical activity was only 1.7 per cent [2164]

reported as cases of hepatorenal syndrome. The terms appear to embrace a large group of diverse entities and may be used only in a descriptive clinical sense.

PROTEINURIA ASSOCIATED WITH TRANSIENT RENAL ISCHEMIA

Many circumstances that are accompanied by severe vasomotor reactions frequently cause the transient excretion of small quantities of protein in subjects who show no evidence of renal disease. Among such circumstances are exposure of the whole body, or even of an arm or leg, to cold water, the administration of adrenalin and ephedrine, the inhalation of carbon dioxide, hemorrhage, and excitement. It has been generally argued, on the basis of Starr's [1982] demonstration of the relation of proteinuria to vasomotor responses, that the excretion of protein is attributable to ischemia and increased permeability of some of the glomeruli, though this explanation is not fully established.

Chesley, Markowitz, and Wetchler [875] tested a number of women ranging from the third month of pregnancy to the third month after delivery, some with and some without toxemia. One-third of the group had no proteinuria prior to the test, while the rest had some degree of proteinuria ranging from faint traces to 5 gm/liter. While urine was being collected by ureteral catheterization, one hand was immersed in ice water for 1 min. As a result of this procedure, systemic vascular constriction, as indicated by the arterial pressor response, appears and disappears within 2 min Among those subjects who were not excreting protein normally, proteinuria occurred consistently in all who showed blood pressure rises of more than 16/16 mm. Hg, i.e. whose vasomotor response was fairly severe, whereas, of 24 subjects in whom proteinuria did not occur, in only 2 did the blood pressure rise exceed these figures. Protein excretion appears at a maximal rate in the interval 2 to 4 min after the application of the stimulus and thereafter the rate of excretion diminishes, returning to or near control levels within 14 min. Allowing for a 2 to 3 min. first appearance time, the excretion of protein must be initiated almost instantly. The right and left kidney usually reacted similarly, though in a few cases proteinuria occurred on only one side. Proteinuria did not correlate with changes in pulse pressure. Although the ab-

MARCH HEMOGLOBINURIA

March hemoglobinuria designates a syndrome associated with exercise and ranging in severity from mild albuminuria without hemoglobinuria or subjective symptoms, to heavy hemoglobinuria and proteinuria preceded by temporarily disabling backache and weakness. The syndrome is so named because it was first observed in an active soldier. The disease is benign, appearing predominantly in young men engaging in certain types of physical exercise, and disappears later in life. The element of lordotic posture is believed to be an important etiological factor, as in postural proteinuria, but there is a suggestion that attacks in some individuals can be abolished by the administration of vitamin C.[654]

PERIARTERITIS NODOSA

This is a relatively rare, necrotizing, vascular disease affecting medium-sized and small arteries and arterioles, usually in several organs. The kidneys are involved in about 80 per cent of the cases, the renal lesion leading to hematuria and albuminuria, renal infarcts, and fibrosis. Death in uremia is common.[878,479,1672] The etiology is unknown but it is possibly a manifestation of an anaphylactic type of hypersensitivity.[479] Clinical and experimental data indicate that it may be induced by drugs (sulfa drugs, antisera, iodine, phenobarbital, thiouracil). Hypertension is commonly present.[2269] No renal function studies are available.

MULTIPLE MYELOMA

Multiple myeloma is a generalized disease of unknown etiology which has its most marked manifestations in the bone marrow, the lesion being characterized by infiltration with so-called 'plasma cells' and local demineralization of the bone.[1239] In a considerable proportion of patients, the disease is accompanied by the excretion of an ill-defined group of proteins known collectively but somewhat inaccurately as Bence-Jones protein. Such protein has a low molecular weight (*c.*37,000) and is identified by the fact that in slightly acid solution it precipitates in the temperature range of 40 to 60° C. and redissolves on boiling. On cooling, the solution

20 min. of standing in the lordotic position, the rates were, respectively, 167 ± 5 cc., 153 ± 7 cc., and 102 ± 9 cc.; i.e. the creatinine clearance fell only in those with the more severe proteinuria.

Rytand [1760] examined 2 subjects in whom unilateral changes related to posture were revealed roentgenographically and found that the Addis urea excretion ratio and the creatinine clearance fell in the second hour, with the subject erect, to approximately one-half the levels observed with the subject recumbent. In a third, renal function decreased by 20 per cent in the upright position, while in 2 who showed gross anomalies, posture did not affect renal function. Gómóri and Greiner [809] record consistent reduction, averaging 44 per cent, in the creatinine clearance in 6 subjects with orthostatic proteinuria, when assuming the erect position, as compared with a 17 per cent reduction in 7 normal subjects. The former also showed a more marked and more consistent reduction in urine flow.

Bull,[291] who reviews the literature and himself experimentally excluded a number of variables, found that renal function remained essentially unchanged in the recumbent and erect positions, but in the erect lordotic posture the renal plasma flow fell to 33 to 80 per cent of the figure observed in recumbent lordosis, and the filtration rate to 50 to 95 per cent, while the filtration fraction increased. The urine flow was markedly reduced and formed urinary elements of all types were increased in number. In the 2 subjects examined, he obtained protein from both kidneys. From anatomical dissections and various experimental approaches he concludes that in the erect lordotic position, and to a lesser extent in the recumbent lordotic position, the inferior vena cava is compressed against the spine by the posterior surface of the liver, and this induces increased renal venous pressure and passive renal congestion. The compression only occurs when the subject is in a lordotic posture and when the anterior surface of the liver rotates inferiorly. This rotation of the liver normally occurs when the subject is lordotic and is maximal in the erect lordotic position. But it seems probable that some cases of postural proteinuria may be related to distinct anatomical anomalies.[1759]

sometimes by anuria. The renal lesion consists chiefly of focal interstitial inflammation. The glomeruli are not often conspicuously involved. The proximal epithelium is swollen, degenerated, and even necrotic, and commonly obstructed by granular and bile-containing casts. *Leptospirae* can be demonstrated in the cells, lumen, interstitial spaces, and urine.[2011, 2224, 2277]

ERGOSTEROL INTOXICATION

Corcoran, Taylor, and Page [432] report that 2 patients with an illness characterized by malaise, nausea, and vomiting showed evidences of renal impairment, metastatic vascular calcification, and hypercalcemia, which appeared during treatment with a product of the irradiation of ergosterol. Tubular injury was present, as evidenced by low values of Tm_D (10 and 12.6 mg of iodine), but the filtration rate was also low (37 and 48 cc.), as was the renal plasma flow (192 and 285 cc.) and renal blood flow (286 and 407 cc.) The authors speak of the renal disturbance as 'toxic nephrosis.'

HYPERTHYROIDISM AND MYXEDEMA

In 2 patients suffering from hyperthroidism (BMR +83 and +58 per cent), reported by Corcoran and Page,[427] the inulin clearance was 112 and 74, the diodrast clearance rather high (810 and 812 cc.), but Tm_D was in the normal range (35.4 and 40 mg. of iodine). Thyroidectomy had no effect on the clearances and reduced Tm_D by only 10 per cent in 1 patient, while, in the second, thyroidectomy was followed by a moderate decrease in renal plasma flow (812 to 615) and filtration rate (74 to 67 cc.) and a decrease of Tm_D of 10 per cent. In 2 patients reported by Aas and Blegen [2] (BMR +50 and +54 per cent), the inulin clearance was 163 and 121 cc. and the PAH clearance 903 and 927 cc. After therapy with methyl thiouracil, the PAH clearance was reduced in the first patient to 697 cc. but remained unaffected by surgery in the second. In neither did the filtration rate drop.

In 2 patients with myxedema, the renal plasma flow was in the low normal range (509 and 448), the filtration rate definitely low (55 and 33.6 cc.), and Tm_D equally reduced (11.1 and 13.6). Treatment with desiccated thyroid increased the renal plasma flow to 600 and 617, the filtration rate to 101 and 80 cc., and Tm_D

again shows turbidity which disappears on further cooling. The excretion of Bence-Jones protein may amount to more than 10 gm/day over a period of several years.

Multiple myeloma is frequently associated with chronic renal disease which appears to result in part from tubular obstruction by cast formation.[115 1427 1470] Armstrong[61] reports that, in 8 patients, the filtration rate, renal plasma flow, and Tm_{PAH} were depressed to some degree. In 3, Tm_{PAH} was better preserved than the filtration rate. Severity of renal impairment did not correlate with the hematologic or serum protein abnormality, or with the amount or duration of Bence-Jones proteinuria. Armstrong concludes, from these and other data, that tubular obstruction by casts will not adequately explain the impairment of renal function, and he suggests that cast formation may be part of the terminal picture and not the cause of renal failure.

FOCAL GLOMERULONEPHRITIS

Focal glomerular lesions may accompany infection, and particularly staphylococcus, gonococcus, and pneumococcus bacteremia. Focal hyalin and fibrous lesions are frequent in subacute bacterial endocarditis of streptococcus viridans origin. The severity of renal involvement ranges from a few glomeruli or portions of glomerular tufts through the formation of hyalin and fibrous lesions in many glomeruli to a form of focal glomerulonephritis in which glomerulitis involves almost every nephron, leading to renal insufficiency. Some writers believe that this type of glomerulitis is glomerulonephritis. If this proves to be the case, the terms 'focal glomerulonephritis' may be discarded.

Hematuria occurs in the majority of children with subacute bacterial endocarditis and is usually a result of a focal glomerular lesion not associated with renal insufficiency. Among children with subacute bacterial endocarditis who have hematuria, a few prove to have glomerulonephritis and these usually develop renal insufficiency and die in uremia.[221, 2113]

WEIL'S DISEASE

Weil's disease, a systemic infection with *Leptospira icterohemorrhagica*, is frequently accompanied by severe renal damage and

CHAPTER XXII

Chronic Congestive Heart Failure

'BACKWARD' AND 'FORWARD' THEORIES

Many diseases of the circulation (arteriosclerosis, essential hypertension, and valvular disease) may terminate in the clinical syndrome designated as chronic congestive heart failure, characterized by dyspnea, orthopnea, cyanosis, increased venous pressure, incapacitating edema, and associated disturbances of function in the liver, kidneys, and other organs. The one invariable sign is enlargement of the heart.

The sequence of events in congestive failure has been the subject of inquiry and debate for over a hundred years. Until the last decade, the most widely held view was roughly as follows: under the principle enunciated by Starling, and long designated as Starling's 'law of the heart,' the energy liberated during contraction increases within limits as the diastolic volume increases (fig. 121). Hence, if for any reason input momentarily exceeds output in either ventricle (and it must be remembered that, considered as a mechanical pump, the heart consists of two independent chambers), the imbalance tends to be physiologically corrected by the resulting distention of the chamber involved; elongation of the muscle fibers makes increased energy available and maintains or increases the stroke volume, thus bringing input and output relative to that chamber back into balance. Under prolonged increased loading, for example such as is imposed on the left ven-

probably both are involved. The author's conclusion appears to be sound, however: tubular function (if we include reduction in renal blood flow) is more severely impaired by prostatic obstruction than is filtration.

PYRIDINE HEPATIC INJURY

Rats fed diets containing pyridine regularly develop acute hepatic necrosis, and animals surviving long enough develop cirrhosis. In some animals, the kidneys show degenerative or necrotic changes Renal injury was most severe in animals which remained in shock for considerable periods or which survived recurrent episodes of shock. Armstrong [61] infers that the renal injury is, at least in part, owing to renal anoxia associated with shock-induced renal ischemia.

All other circumstances remaining constant, whenever the output of the left ventricle decreases blood tends to drain from the arterial to the venous side of the circulation in consequence of the differential between arterial and venous pressure. This is, of course, the sequence of events during every diastolic interval. Momentarily the quantity of blood on the arterial side decreases and that on the venous side increases The venous pressure rises as blood fills the venous system, and increased venous pressure increases right ventricular filling and output, so that an increased volume of blood is pumped into the pulmonary circuit, leading to increased pulmonary pressure. Increased pulmonary venous pressure in turn increases left ventricular filling and output, and operates to increase the quantity of blood in the arterial system and to diminish the quantity in the venous system.

Precisely the same sequence of events transpires whenever, over a longer period, the output of the left ventricle falls below that of the right. Hemodynamic transmission moves blood from the arterial to the venous system and operates to increase venous pressure. So long as the right ventricle maintains its output equal to the venous return, venous pressure is maintained at normal levels, but blood accumulates in the lungs in excessive quantity, leading to pulmonary congestion with edema, dyspnea, and orthopnea. A steady state is reached when the increase in pulmonary venous pressure suffices by dilatation of the left ventricle to restore left ventricular output to a level equal to the output from the right ventricle.

heart failure as a condition in which the cardiac output is inadequate in relation to the filling load '

It may be noted, however, that the venous return is not accurately reflected by the peripheral venous pressure alone because the flow through the venous system is influenced by venous diameter, even as in the arterial system, and venomotor tone is significantly variable Nor can the venous return be judged by right atrial pressure, any more than the cardiac output can be judged by arteriolar pressure.

It is improper to speak of the 'backward' transmission of pressure in the circulatory system because the heart is the only pump and the pressure imparted to the blood by the heart is (excluding valvular incompetence) only transmitted forward, i e from the arterial to the venous side Every dynamic increment in venous pressure has its origin in the left ventricle, every increment in pulmonary pressure in the right ventricle

tricle in essential hypertension, long-continued increased work induces hypertrophy of the muscle and enlargement of the organ. Similarly, under prolonged increased work the right ventricle may undergo hypertrophy, while in other circumstances both ventricles may hypertrophy in a parallel manner. But in any heart

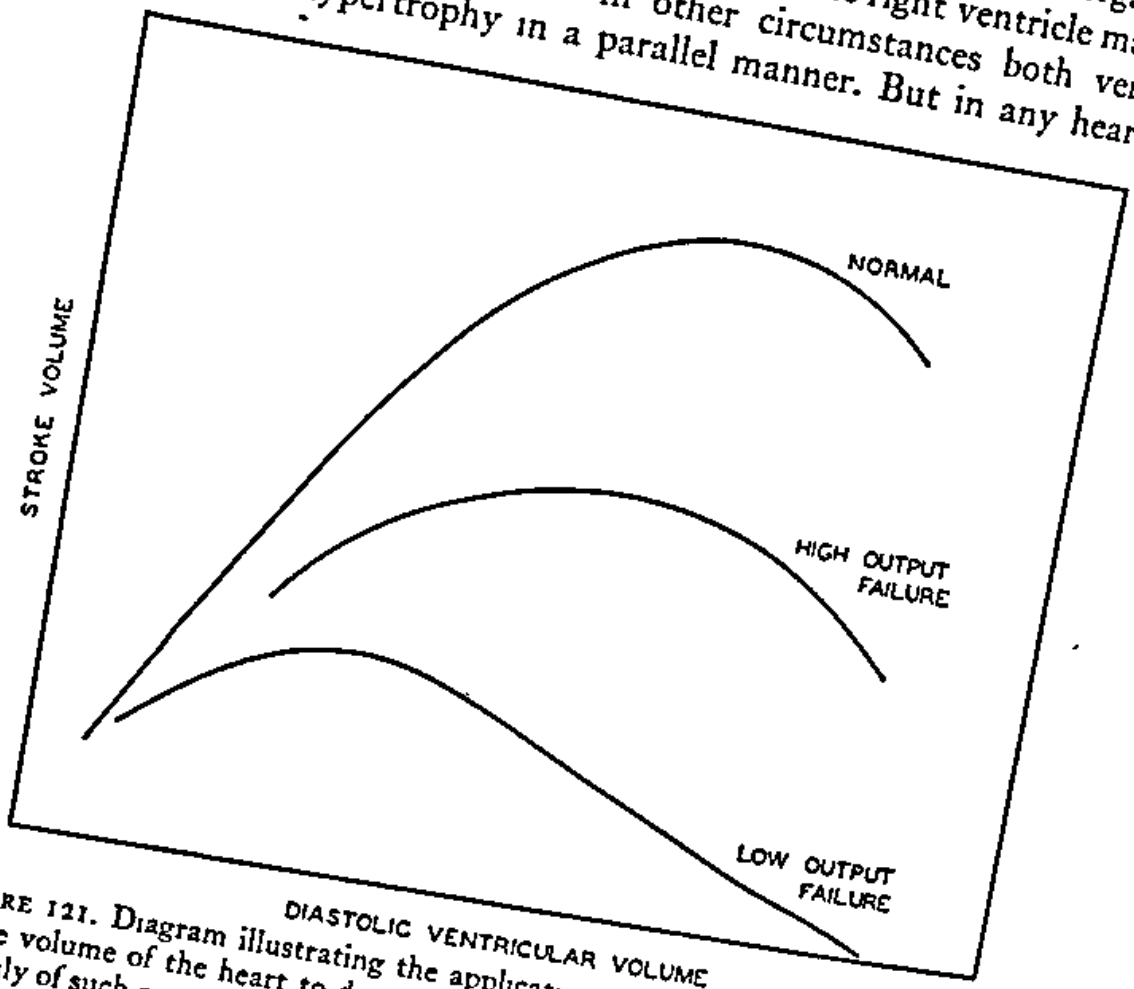

FIGURE 121. Diagram illustrating the application of Starling's law relating the stroke volume of the heart to diastolic ventricular volume One must visualize a family of such curves, since no 1 curve is applicable to all hearts. (Richards 1729)

(normal or enlarged) there is a limit beyond which the myocardium fails, on further dilatation, to respond with increased energy and hence increased stroke volume, as shown in figure 121, and further loading and dilatation lead to reduced stroke volume and to imbalance between input and output.* This point marks the onset of congestive cardiac failure.

*As Huckabee, Casten, and Harrison 1043 remark, 'the *sine qua non* of myocardial failure is therefore to be found not in the cardiac output [with reference to the body's needs] but in the completeness of the cardiac emptying . Pending additional and more complete knowledge it appears justifiable to define

or at least the accuracy of its measurement, has been challenged.[1595]

Starling's views on chronic congestive cardiac failure are frequently misquoted or confused with the interpretations of later investigators. These views are clearly set forth in his article, 'Physiological factors in the causation of dropsy'[1980]

The sequence, as he saw it, consists of:

'Stage 1 —Heart-pump failure; fall of arterial pressure; rise of pressure in the venous trunks near the heart; fall of capillary pressures in the peripheral parts of the body, in the kidneys, and in the intestine; and absorption of fluid by bloodvessels from intestines and peripheral tissues. Stage 2 —Continued absorption from the alimentary canal with diminished excretion from the kidneys, and production of hydraemic plethora with rise of mean systemic pressure. This leads to Stage 3.—Rise of capillary pressure in all dependent parts of the body, capillaries injured by malnutrition, and excessive transudation, leading to dropsy. Stage 4 —The continued hydraemic plethora leads to ever-increasing over-filling of the heart cavities and to ultimate failure of the already incompetent heart.'

It will be noted that Starling invoked diminished excretion by the kidneys to explain the hydremic plethora, and hydremic plethora to explain increased capillary pressure and ultimate failure of the heart.

With the development of improved methods for the measurement of cardiac output it was discovered that, although in the average the cardiac output is reduced in congestive failure, there were notable exceptions in that some persons have a high cardiac output Consequently, certain authors came to believe that a reduced cardiac output is not essential to the production of congestive failure, and that the syndrome involves balancing the cardiac output against the metabolic requirement of the individual; where the cardiac output is antecedently high (cor pulmonale, arteriovenous fistula, thyrotoxicosis, Paget's disease, beri-beri, chronic anemia) cardiac insufficiency will become apparent at a higher level of cardiac output than in a person with antecedently normal output[44 924, 1722, 1723, 1988 1989] The difficulty in this view is that there is no method of ascertaining the 'metabolic requirement of the individual.'

After right ventricular failure, a steady state is reached only after peripheral venous pressure has increased to such levels as restore the right ventricular output to a rate equal to venous inflow. At this time peripheral congestion, hypoxia, and edema make their appearance.

Many writers recognize that increased venomotor tone may supplement these hemodynamic factors in contributing to the increased venous pressure.

It is to be accepted that increased capillary pressure (supplemented by capillary hypoxia) leads to increased capillary filtration and to the formation of edema, in the pulmonary circuit only in left ventricular failure, in both the pulmonary and peripheral circuits where both ventricles are incompetent.

The foregoing sequence, here deleted of some subordinate considerations and contradictory opinions, has generally been known as the 'backward' theory of failure, the term 'backward' stemming *from the (here conceived to be inaccurate) concept that the in*crease in pulmonary (or alternatively venous) pressure is due to the 'backward' transmission of pressure from the ventricles into *the antecedent reservoirs. (Pressure is never transmitted back*wards in the circulation so long as the atrial-ventricular valves are competent. Every increment in pressure in the venous system has *its genesis in arterial pressure,* i e. *in the left ventricle;* in the pulmonary system, in the right ventricle). The term 'backward' has in part served to distinguish the pure hemodynamic sequence to be expected from myocardial failure from those forms of circulatory insufficiency which have a peripheral origin (hemorrhage, shock, syncope, etc.) and which were usually characterized as 'forward' failure. We prefer to designate the sequence as described above as the 'hemodynamic sequence' in congestive failure.

It is fairly well established that in congestive failure there may be an increase in blood volume,[478 774, 1436, 1534] sometimes with hypoproteinemia and reduced hematocrit, but generally with normal protein and red cell content (despite the fact that decreased blood volume and hemoconcentration would be expected to issue from this sequence hemodynamically). The mechanism of this increase in blood volume has been a matter of dispute, and even its reality,

(generally below 1.0 gm/day) arrested edema accumulation or caused diuresis, and Futcher and Schroeder[728] demonstrated that mercurial diuretics, long used clinically in the reduction of edema, markedly increased sodium and chloride excretion. They suggested that sodium retention and hence edema formation issued from increased tubular reabsorption of sodium by the renal tubules.

Warren and Stead,[2147] on the basis of the foregoing observations, examined the effects of administering sodium chloride to 2 edema-forming patients, and observed that accumulation of extracellular fluid, as judged by increase in body weight and plasma volume, occurred before there was any increase in venous pressure. They concluded with Starr that the rise in venous pressure issued directly from the increase in plasma volume, which they attributed to the edema itself, i.e. to the expansion of the extracellular fluid. Seeking the cause of the latter, they emphasized the diminished renal excretion of sodium and concluded that the edema of congestive failure results not from capillary pressure but from the failure of the kidney to excrete salt (and secondarily water), for reasons then unknown.

In this view, the renal retention of salt and water leads to expansion of the extracellular fluid and this leads to expansion of the plasma volume, which in turn leads to increased venous pressure. As hemodilution occurs in consequence of the retention of salt and water, reduction of the concentration of plasma proteins serves as a stimulus to protein production, and the plasma protein concentration is restored to or near normal so that the plasma volume and systemic venous pressure tend to be stabilized at supernormal values even though interstitial fluid pressure is not greatly increased.

This view, which emphasizes excessive conservation of sodium by the kidneys as a result of circulatory insufficiency, is sometimes designated the 'forward' theory of failure without due regard to the older usage of this term. It must be noted that, although it shifts emphasis away from the hemodynamic sequence, the sodium retention theory does not abandon basic hemodynamic principles in their entirety. Indeed, even the proponents of the 'forward' theory still envisage the pulmonary edema which accom-

There remains the question whether increased venous pressure should be explained on a pure hemodynamic basis, or as a complex reaction on the part of the body to compensate for cardiac weakness by increasing the heart's filling pressure, a view which had at one time been held by Starling and which has been defended recently by Harrison,[924] Starr,[1983] McMichael,[1882] and Landis, Brown, Fauteux, and Wise.[1206]

Reinterpretation of this problem began in 1940 with Starr and Rawson,[1967] who reported that in a mechanical circulation model 'simulated heart failure' did not cause an increase in 'venous' pressure unless the capacity of the 'circulatory system' was reduced or the 'blood' volume increased simultaneously with weakening of the pump. Starr [1953] further noted that immediately after death the static pressure in the heart and blood vessels was some three times as high in patients dying with cardiac failure as in others without heart disease, and he concluded that the elevation of venous pressure observed in congestive failure is to be attributed largely to a combination of increased blood volume and venoconstriction rather than to 'backward' congestion issuing from cardiac weakness. In other studies, Starr, Jeffers, and Meade [1956] showed that acute and chronic damage to the right ventricle of the dog produces at best only a minimal increase in peripheral venous pressure.

On the basis of these and other studies, Starr emphasized essentially non-cardiac factors (pressure on the vessels by tense, edematous tissue, active constriction of the venous reservoir, increased blood volume accumulating in the most distensible vessels, i.e. in the veins) as of primary importance in the production of venous congestion and thus shifted emphasis away from the hemodynamic sequence.[1984]

SODIUM RETENTION

Meanwhile Schroeder [1803] found that the capacity to excrete sodium chloride is greatly reduced in patients with congestive heart failure and persistent edema, an observation which has been confirmed by Burch and his colleagues, as reported in the *Festschrift for Thomas Addis* [293] and others. Schroeder showed that the restriction of salt intake to a level below the output in the urine

...tients with

... than 110 cc. requi...

... cc/min. They found ...

...enomenon which has been demonstrated in normal ... her investigators (ch. XIV), this reaction being exaggerated in some cardiacs so that during exercise the filtration rate, otherwise above the critical level, might fall well below this level, i.e. the renal blood flow was somehow decreased disproportionately whenever the cardiac output proved to be insufficient to meet the demands of the body. In normal subjects the cardiac output increases during exercise, but there is little or no increase in persons with congestive failure, and consequently there develops a large systemic oxygen arterial-... which, Hickam and Cargill [987] suggest, reflects an ... in the tissues. ... leads by some mechanism unknown to ... im retention.*

The renal oxygen arterial-venous difference in congestive failure has been found to be consistently elevated in 9 subjects studied by Breed and Maxwell (unpubl. data), with an average of 2.8 cc/100 cc as compared to their control average of 1.4.

But it seems that the renal ischemia in congestive failure is not generally of such a degree as to impair tubular excretion, and that the PAH clearance used to measure renal blood flow may be accepted at its face value † It has been noted elsewhere (ch. VI) that E_{PAH} in normal subjects averages 0.92 (0.88 to 1.00). In 9 observations on subjects with no renal pathology but in congestive failure Merrill [1438] reported 2 below 0.85 (0.64, 0.63); Warren, Merrill, and Brannon [2145] list 2 determinations as 0.82 and 0.90; Edelman and his coworkers [587] report an average of 0.90 ± 0.037 (0.88 to

* ... determine whether the oxygen supply or par... hypoxia do not cause ... in (ch. XIV), nor does ... failure (*vide infra*). ... tration to patients ... ared glucose deriv-ative (ch. V)

panies left ventricular failure as a simple hemodynamic (albeit erroneously 'backward' failure) sequence.[1984, 1988]

RENAL ISCHEMIA

Why the kidneys retain salt and water in congestive failure was then explored by Merrill,[1438, 1439] who showed in patients with persistent edema (i.e. who were in such a state of failure that they required repeated mercurial diuresis to avoid edema on bed rest) that the filtration rate is reduced to one-third or one-half of the normal, the renal plasma flow to an even greater extent, indicating a marked diversion of blood away from the kidneys. Reduction in inulin, phenol red, and urea clearances had previously been recorded by Seymour, Pritchard, Longley, and Hayman;[1812] after compensation effected by digitalis and mercurial diuresis, the phenol red clearance increased in proportion to the cardiac output but the inulin clearance showed no consistent change.

Merrill believed that the decrease in filtration rate reduced the quantity of sodium delivered to the tubules and, assuming normal reabsorptive activity, this circumstance permitted 'unsaturation' of the tubules and almost complete reabsorption of sodium. Since water is invariably retained in the body in proportion to sodium, this reduction in filtration rate led to the retention of both sodium and water. The mechanism by which the renal plasma flow was decreased was unknown; Merrill was unable to correlate this decrease with either increased peripheral venous pressure or increased pressure in the right atrium; on the other hand, the degree of renal ischemia did correlate well with the decrease in cardiac output, and he concluded that the decrease in renal circulation was related to circulatory insufficiency. Here is the only warrant for the use of the term 'forward' failure in this connection; on the widely accepted but unsubstantiated premise that cardiac output is reduced relative to the oxygen requirements of the body (in the majority of patients studied by Merrill, the systemic oxygen arterial-venous difference exceeded the normal value of 4.0 to 6.0 cc/100 cc.), one may liken chronic congestive failure to shock or syncope.

Merrill and Cargill[1440] subsequently reported that, among 25 patients with a filtration rate less than 80 cc/min., all required

which is scarcely beyond $\pm 1\sigma$ from the mean normal value of the inulin clearance/Tm_D ratio of 2.63 ± 0.344.

CONTRARY VIEWS

With the exceptions noted, the observations above are in agreement with Merrill's thesis that in patients with persistent edema the renal blood flow and filtration rates are so low as to demonstrate a reduction in the renal circulation. As a concomitant of this renal ischemia, the filtration rate is reduced and sodium excretion becomes difficult or impossible. The salt retention theory has not escaped criticism, however.

Landis, Brown, Fauteux, and Wise [1205] have emphasized, relative to Starr's experiments on dogs, that he measured the venous pressure at rest; they point out that in the face of even severe cardiac incompetence the venous pressure may increase only during exercise or other conditions where the venous return is increased and the weakened heart overloaded. These investigators demonstrated, moreover, that the intravenous administration of blood or saline to normal dogs in amounts equal to or substantially greater than the normal blood volume does not produce a sustained rise in venous pressure, and they note that conspicuous edema occurs in nephrosis without increase in blood volume or elevation of venous pressure. They suggest that the hypervolemia of failure is a compensatory reaction to many episodes of reduced 'effective' blood volume, and that renal retention of sodium and water as well as overproduction of erythrocytes and plasma proteins fall into this compensatory pattern.

Warren, Merrill, and Stead [2146] reported that 1 hr. after an amount of saline equal to the body weight had been given intravenously to 3 dogs (over a period 6 to 8 hr.) the plasma volume was increased by only 9 per cent in one dog and 4 per cent in a second, while it decreased by 2 per cent in a third; the venous pressure was unchanged in 2 dogs and increased by only 80 mm. saline in the third. Calculations from the recorded weights indicate that at the time these measurements were made the extracellular fluid in these 3 animals had been increased by some 90, 130, and 135 per cent. In view of this demonstration that saline in

0.91) in 10 subjects, and Breed and Maxwell (pers. com.) report an average of 0.93 (0.88 to 0.96) in 4 subjects.

Numerous investigators have confirmed the presence of renal ischemia in most patients with congestive failure. Mokotoff, Ross, and Leiter [1489] report that, in 16 patients with persistent edema at rest, the mannitol clearance averaged 66.8 ± 13.2 and the PAH clearance 191.5 ± 54.4 cc., figures to be compared with 103 ± 12.8 and 627 ± 86.6 cc. in their immediate series of 14 normal or non-failure controls. Briggs, Fowell, Hamilton, Remington, Wheeler, and Winslow [252] report that in 14 uncompensated patients the thiosulphate clearance averaged 70 cc. Aas and Blegen [2] report inulin clearances ranging from 21 to 97 cc. and PAH clearances ranging from 47 to 335 cc. in 4 patients with slight to marked edema; the filtration fraction ranged from 17.2 to 38.4. In 5 patients, with a variety of cardiac impairments but without edema, the inulin clearance ranged from 86 to 109 cc., the PAH clearance from 319 to 538 cc. They confirm the effects of exercise in reducing the renal blood flow. Baldwin, Villarreal, Sirota, Schreiner, and Wesson (pers. com.) report that in 11 uncompensated patients the inulin clearance ranged from 47 to 129 cc., but 4 of them had persistent edema although the filtration rate (92, 97, 98, and 101 cc.) was above Merrill's critical range. In 10 patients in congestive failure due to rheumatic valvular disease, studied by Edelman and his coworkers,[567] the renal plasma flow was reduced about 70 per cent, the filtration rate about 50 per cent. The corrected filtration fraction averaged 0.319 ± 0.074 as compared with their control figure of 0.175 ± 0.033.

In keeping with this interpretation, Weston and Escher [2175] attribute the resistance to mercurial diuresis, which is sometimes shown by patients in congestive failure, to an excessively low filtration rate. They state that, if the filtration rate is increased by aminophylline or hypertonic saline, a marked rise in sodium and water excretion occurs.

Hilden [1008] reports that the thiosulphate clearance in 6 patients in congestive failure ranged from 48 to 83 per cent, while Tm_D ranged from 45 to 98 per cent of normal. The thiosulphate clearance/Tm_D ratio was remarkably constant in the range 2.1 to 2.73,

used digitalis or mercurial therapy to promote compensation, and it would seem that this only demonstrated that compensation can be effected by therapy (mercurials certainly, and digitalis possibly) which specifically promotes sodium excretion regardless of the filtration rate.

The thiosulphate clearances observed by Briggs *et al.* ranged from 20 to 120 cc. (extremely low to low normal) in uncompensated patients, and in only 4 did the clearance increase with compensation under therapy. The mean thiosulphate clearance in 14 uncompensated patients was 70.0 cc. and in 9 compensated patients 81.2 cc They note that the thiocyanate space decreases consistently with compensation, which is to be expected with reduction of edema. However, the thiocyanate space is notoriously variable and unreliable as a measure of extracellular fluid.

Data on cardiac output, oxygen arterial-venous difference, and approximate oxygen saturation of mixed venous blood lead them to emphasize the lowered venous oxygen saturation, 55 per cent in 14 uncompensated patients as compared with 67 per cent in 11 studied after compensation (calculated as venous/arterial contents × 100), as an important causal factor in the genesis of events in congestive failure and possibly related to reduced sodium clearance. They affirm that edema does not have a hemodynamic origin, since right atrial pressure, though higher than normal, was not consistently higher in the uncompensated than compensated state.

Farnsworth [617] found no correlation between filtration rate and chloride clearance in a patient in congestive failure, the chloride clearance varying from 0.09 to 1.74 cc. at filtration rates of 30 to 64 7 cc., and Farnsworth and Krakusin [621] report a normal filtration rate and renal plasma flow in 1 out of 2 patients.

Kattus, Sinclair-Smith, Genest, and Newman [1093] observed in a young subject with valvular rheumatic heart disease that exercise

mg/min. of sodium at their mean sodium plasma concentration of 3 22 mg/cc. At a plasma level of 25 mg/100 cc. of sodium thiosulphate, a filtration rate of 100 cc would entail the obligatory excretion of 7 mg of sodium, so that the recorded 'sodium clearances' are in great part or in whole thiosulphate clearances, and the changes observed before and after compensation may be related incidentally to variations in the plasma level of this test substance or the rate of its oxidation to sulphate

sufficient quantity to double the extracellular fluid fails to increase either blood volume or venous pressure, one may wonder if some 20 pounds of edema, or an amount sufficient to double the extracellular fluid volume in man, would be associated with an increase in both blood volume and venous pressure to the extent observed in cardiac failure.

Reichsman and Grant [1690] report that, after the withdrawal of digitalis in 3 patients with mitral stenosis and auricular fibrillation, the venous pressure clearly rose ahead of the gain in weight and the formation of edema, but this is to be expected hemodynamically and throws no light on the origin of edema because, as Merrill [1439] notes, it is probable that in these patients the rise in venous pressure is coincident with the fall in cardiac output, and the latter may be the effective factor in inducing sodium retention.

Roos and Smith [1742] have shown that acute left ventricular failure, induced in dogs by coronary embolism following the injection of starch into the left ventricular chamber while the aorta is obstructed, leads immediately to pulmonary congestion and increased systemic venous pressure, these effects being augmented if the blood volume is moderately increased. They visualize the sequence in hemodynamic terms, without reference to the present issues.

Borst,[218] reviewing the earlier evidence, rejects the interpretation that reduction in filtration rate represents a disturbance in renal function. He favors the view that sodium retention and expansion of blood volume constitute an adaptive reaction, the end effect of which is to increase cardiac output by increasing venous pressure. He marshalls to the support of this interpretation numerous data on other clinical disturbances.

Briggs and his coworkers,[252] studying 10 patients before and after compensation effected by bed rest, low salt diet, diuretics, and digitalis, argue that the sodium clearance improves with compensation independently of the initial magnitude or direction of change in the filtration rate.* However, these investigators

* To measure the filtration rate these investigators used sodium thiosulphate, which involves the obligatory excretion of 2 or more equivalents of sodium for every mol of thiosulphate administered. The sodium clearances recorded range from 1 to 3 cc., equivalent in sodium chloride to 9 to 27 gm/day, or 3 to 9

aortic stenosis do not react to hypoxia is not clear. Blegen also records the interesting observation that the renal plasma flow is reduced in subjects with valvular lesions but with no signs of right heart failure.

Threefoot, Gibbons, and Burch [2077] affirm that weight and venous pressure vary directly with sodium and water retention, but were unable to show that either one preceded the other.

Davis and Shock [477] find that, of 6 patients in congestive failure, 4 showed a low sodium clearance despite a normal filtration rate, whereas in the 2 patients who had low filtration rates the sodium clearance was higher than the mean of their 25 normal subjects. These 2 subjects were found, after compensation was effected, to have (arteriosclerotic?) renal disease as judged by loss of concentrating power. (All were receiving saline at 3 cc/min.) This lack of correlation leads them to conclude that reduction of filtration rate is not the primary mechanism for sodium retention. All 4 subjects without renal disease showed a marked or extreme reduction in renal plasma flow, the filtration fraction being correspondingly elevated (0.379 to 0.60). Theophylline ethylene diamine had a more variable effect on renal function in these subjects than in normal subjects. The filtration rate and effective renal plasma flow failed to increase at all in some patients and increased over 100 per cent in others, but there was no consistent change in filtration fraction. Similarly, the sodium clearance increased markedly in some and only slightly in others. The failure of the sodium clearance to increase consistently during a period of increased filtration rate supports this conclusion.

RENAL VENOUS PRESSURE

Winton [2218] showed that increasing venous pressure in the isolated perfused kidney of the dog leads to increased reabsorption of salt and water. Bradley and Bradley [236] observed that, in normal subjects, experimentally increased intra-abdominal pressure, which raises vena caval pressure to 20 mm Hg, increases reabsorption of water, as indicated by increased U/P ratio of inulin or mannitol, effect which passes off immediately when the pressure is removed; and Bradley, Mudge, Blake, and Alphonse [242] have shown decrement in water output is associated with an even greater

consistently decreased renal blood flow, filtration rate, and sodium excretion; however, during recovery the filtration rate returned to the control level before the excretion of sodium did. Normal subjects show the same decrease in sodium excretion during exercise, and sometimes to just as marked an extent as did the cardiac patient, but with no change in filtration rate. Hence they conclude that sodium retention is due to increased tubular reabsorption, and is a normal response to exercise and may be expected in the cardiac as well as in the normal subject, although the response is exaggerated in cardiac failure. Extending these observations, Sinclair-Smith *et al.*[1902] have challenged the low filtration rate theory on the grounds that mild exercise, which causes sodium retention in normal subjects without significant reduction in filtration rate, invariably causes sodium retention in patients with congestive failure whether the filtration rate decreases or not, and, where the filtration rate is decreased, the sodium retention effect outlasts it. Sodium retention occurred where the endogenous creatinine chromogen clearance had a value of 100 cc. or slightly better, as opposed to Merrill and Cargill's [1440] critical value of 70 cc. Moreover, 1 patient observed over a period of 24 days had a filtration rate (109 cc. by endogenous creatinine chromogen) within normal limits when first studied in the edematous state. Under digitalis, bed rest, and salt restriction, diuresis and decrease of peripheral venous pressure occurred, without change in filtration rate. The renal plasma flow increased, however, from subnormal values (188 cc.) toward normal (417 cc.), decreasing the filtration fraction from 54 to 23 per cent. The authors believe that physical stress, operating by the same mechanism as operates in normal subjects during exercise, increases sodium reabsorption; in more advanced stages or with greater stress, the filtration rate is reduced, causing added retention of sodium by lowering the filtered load.

In a preliminary report Blegen [192] reports that in 8 normal subjects he and Aas obtained a significant increase in renal plasma flow with no change in filtration rate while breathing 9.5 per cent oxygen. Excluding patients with aortic stenosis, patients in congestive failure reacted like the normal subjects, and they infer that renal ischemia is not due to hypoxia *per se*. Why patients with

age figure was 22.4 (12.7 to 30.0) mm. Hg; although there is some overlap, the average figure in failure is well within the range which leads in the experiments of Blake *et al.* to sodium and water retention in the dog.

Maxwell *et al.* consider whether the observed increase in renal venous pressure can account for the reduction in renal blood flow and filtration rate in congestive failure, as has been suggested by Seymour *et al.*[1342] Using the equations of Gomez (ch. XVIII) and typical data on renal function they find that in congestive failure the total renal resistance is in the mean increased by 146 per cent, afferent arteriolar resistance by 200 per cent, efferent arteriolar resistance by 110 per cent, and the terminal renal venular resistance by 172 per cent (See also fig. 118.) In relation to overall resistance, the venous component represents only an 18 per cent increase Substituting an elevated (22 mm. Hg) for control (11 mm. Hg) renal venous pressure in calculations on an idealized normal subject, the renal blood flow would be reduced from 1200 to 1032 cc., representing a reduction of only 14 per cent, far less than occurs in congestive failure. They conclude that in failure active constriction of the afferent and efferent arterioles largely accounts for the renal ischemia, the increased renal venous pressure being an additional factor in some cases only, and never the important one. This conclusion is supported by the observation of Merrill that the decrease in renal blood flow does not correlate with the increase in peripheral venous pressure.

Bradley[234] has called attention to the fact that a reduction in filtration rate does not necessarily imply that there is glomerular-tubular imbalance; if some nephrons are inactive, glomerular-tubular balance may be maintained in the residual functional tissue. He notes that although the filtration rate is generally reduced in congestive failure, the increase during compensation is relatively slight,* and patients may live for years with a marked reduction in filtration rate (essential hypertension, some nephritics) with no obvious disturbance in sodium and water balance and no edema. More cogently, perhaps, he emphasizes that left ventricular failure with circulatory insufficiency may develop

* The process of spontaneous compensation, without artificial natriuresis, is one on which there is little information (*vide infra*)

diminution of sodium excretion. These effects are clearly demonstrable in patients with diabetes insipidus and are apparently not referable to changes in ADH secretion. Here, however, the effects of increased renal pelvic (urine) pressure cannot be separated from those of increased renal venous pressure. But Blake, Wegria, Keating, and Ward [188] have found that, if the renal venous pressure is increased into the range of 21 to 27 mm. Hg in laparotomized, anesthetized (pentobarbital) dogs, sodium and water reabsorption by the renal tubules is substantially increased, with no significant change in filtration rate or renal blood flow. The effect is immediate and it is limited to the kidney involved, and hence it is not related to the release of pituitary, adrenal, or other hormones. There was no associated change in Tm_G. Without discounting the role of reduced filtration rate in edema formation, Blake *et al.* argue (incorrectly, the writer believes) that in heart failure the increase in right ventricular pressure at the end of diastole is probably an early if not the first event in failure, and this may lead to an increase in renal venous pressure somewhat ahead of the decrease in cardiac output itself.

Whereas Blake and his coworkers observed no change in renal blood flow or filtration rate in dogs when the renal venous pressure was raised to 27 mm. Hg, Selkurt, Hall, and Spencer [1824] under similar conditions found that these functions decreased proportionally as the perfusion pressure across the renal circuit decreased. An elevation of renal venous pressure of such a magnitude as to decrease the arterial-venous pressure difference across the kidney by about 11 per cent reduced the renal blood flow and filtration rate by 15 per cent, but the authors believe that this is *not enough to favor sodium retention*, and that mechanisms other than increased renal venous pressure must be operative in congestive failure. Their results are qualitatively in agreement with those of Bradley and Bradley [236] on abdominal compression in *man, but the difference in respect to the effects of increased renal* venous pressure on filtration rate and renal blood as reported by Selkurt *et al.* and Blake *et al.* remains unexplained.

Maxwell, Breed, and Schwartz [1419] report an average renal venous pressure in 17 normal subjects of 11.7 (10 to 14.6) mm. Hg. In 9 subjects in congestive failure with persistent edema the aver-

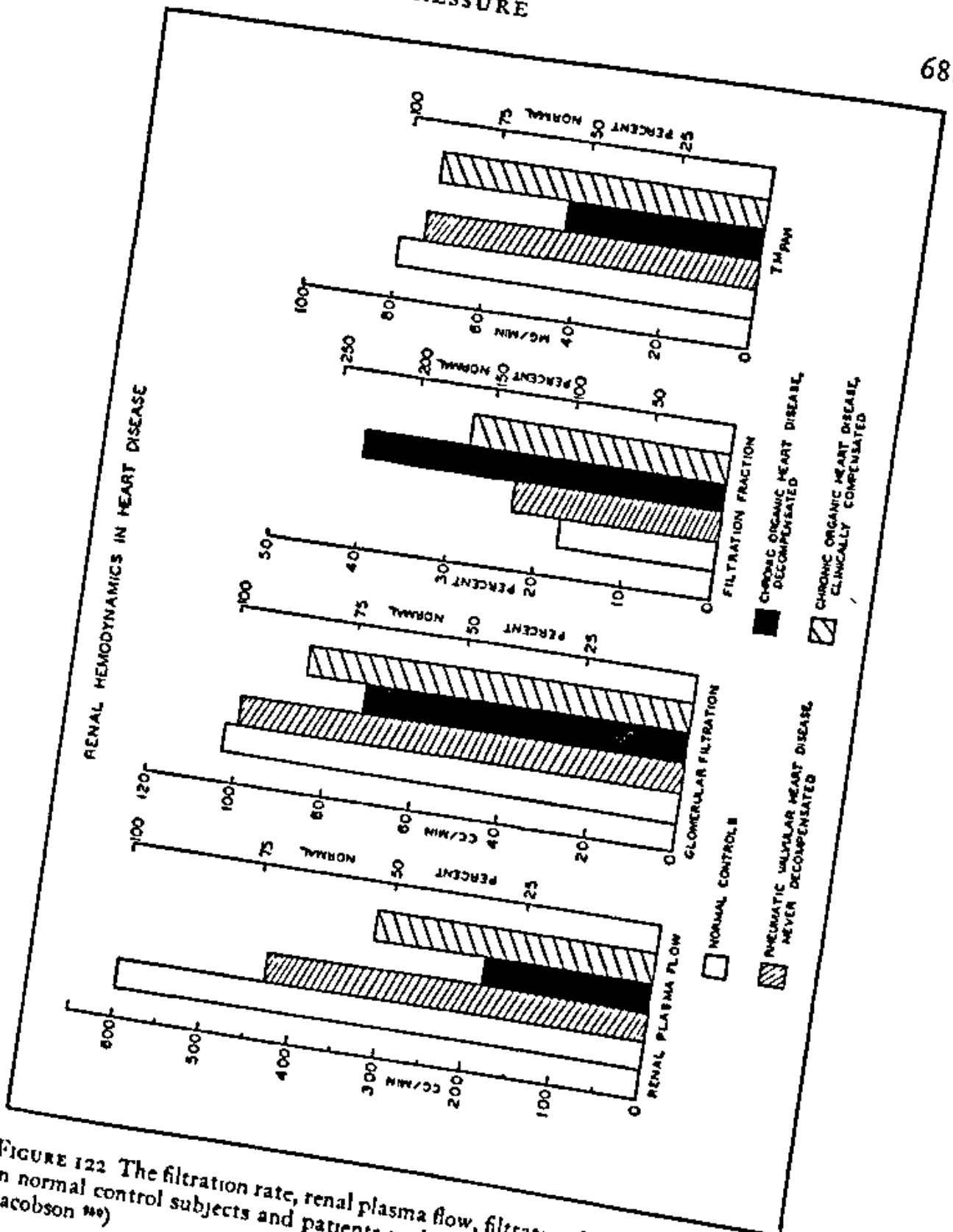

FIGURE 122 The filtration rate, renal plasma flow, filtration fraction, and T_{mPAH} in normal control subjects and patients with organic heart disease (Heller and Jacobson [860])

and persist for years with no formation of edema, so long as venous pressure does not rise. He concludes that increased venous pressure and reduction of filtration rate both operate (with perhaps other factors) to produce sodium and water retention; the production of edema will operate to embarrass the already inadequate circulation by further increasing blood volume, venous pressure, and tissue hypoxia, and thus contribute to a vicious cycle. Conversely, it may be noted that hypoxia associated with chronic pulmonary disease or congenital cardiac defects does not lead to edema, so that hypoxia alone does not seem adequate as a stimulus to sodium retention, either by reduction of filtration rate or increased tubular reabsorption. Neither does acute hypoxia reduce the filtration rate in normal subjects or in patients in congestive failure.[2,125]

Heller and Jacobson [950] have studied 3 groups of patients without history of hypertensive disease (figs. 122 and 123):

Group A, 5 patients with rheumatic valvular heart disease but without previous or present evidence of congestive failure.

Group B, 12 patients who had been in congestive failure but who were edema-free and clinically compensated at the time of study. Compensation had been achieved by digitalis, bed rest, and a salt-free diet.

Group C, 13 patients who were in a state of cardiac decompensation at the time of study. Nine had edema varying from a trace to 4+; the other 4 had pulmonary congestion and hepatomegaly.

In those patients in the edematous state at the time of study (group C) the filtration rate ranged from 54 to 105, and averaged 75 ± 20.9 cc.; the renal plasma flow ranged from 90 to 313, and averaged 190 ± 58.2 cc.; the filtration fraction ranged from 0.323 to 0.554, and averaged 0.405 ± 0.083. These figures are to be compared with the authors' data on 8 normal subjects of 103 ± 7.4, 603 ± 84.4, and 0.174 ± 0.023, data which are in reasonable agreement with those summarized in table XII. These patients showed the reduction in both filtration rate and renal plasma flow which characterizes the edematous state in congestive failure.

In those patients who had been in edema but were edema free at the time of study (group B) the filtration rate ranged from 64 to 117 and averaged 86 ± 18.6 cc.; the renal plasma flow ranged

tration rate was close to normal (range 85 to 146, average 101 ± 25.7 cc.) yielding a high filtration fraction (range 0.172 to 0.281 average 0.234 ± 0.04). The demonstration of reduced renal plasma flow in the presence of rheumatic valvular disease but without congestive failure is a highly interesting observation; it should be noted, however, that the renal response differs qualitatively from that in congestive failure, in that the filtration rate is not reduced, and the renal ischemia may have a different mechanism.

In 6 patients studied during the edematous state and after 'compensation' effected by digitalis, bed rest, and salt restriction, the filtration rate increased in only 2 out of 4, and this increase was only 16 and 18 cc , the renal plasma flow, however, increased in all, from an average of 225 to 355 cc., the average filtration fraction falling from 0.481 to 0.319

Hilden's [1008] observations on the reduction of Tm_D in patients with congestive failure have been cited above. Heller and Jacobson find that in edematous patients (group C) Tm_{PAH} is substantially reduced (range 20 9 to 79 7, average 44.2 ± 17.8 mg.) as measured at load/T ratios of 1 5 or more In the 'compensated' group (group B), Tm_{PAH} averaged 71 6 ± 16.5 (range 44 5 to 97.1 mg), and in 2 patients studied before and after compensation this function increased from 36.0 to 65.4, and 53 0 to 78.4 mg., respectively. Tm_{PAH} was essentially normal in the 5 patients with valvular disease (average 73.1 ± 19.2, range 47.9 to 91.0 mg.). These figures may be compared with the authors' average value for Tm_{PAH} in 7 normal subjects of 80.3 ± 20.3 mg (range 60.8 to 105), a figure which agrees excellently with that given in table XII In interpreting the reduction in Tm_{PAH} in the edematous state of congestive failure, the authors dismiss the possibilities of an anatomic reduction of the number of active nephrons, intermittent glomerular occlusion, blockage of 'low pressure' nephrons by elevated venous pressure, and specific tubular injury, in favor of the interpretation that extreme (efferent) arteriolar spasm leads to tubular ischemia. The fact of this reduction is important, but in view of the circumstances that Tm_{PAH} is sensitive to hormonal control from the anterior pituitary, to anoxia and perhaps other factors, the interpretation may perhaps be left open.

from 214 to 444 and averaged 320 ± 86.5 cc.; the filtration fraction ranged from 0.178 to 0.380 and averaged 0.283 ± 0.075. Thus, despite 'compensation' effected by digitalis and sodium restriction, renal ischemia and reduced filtration rate persisted, al-

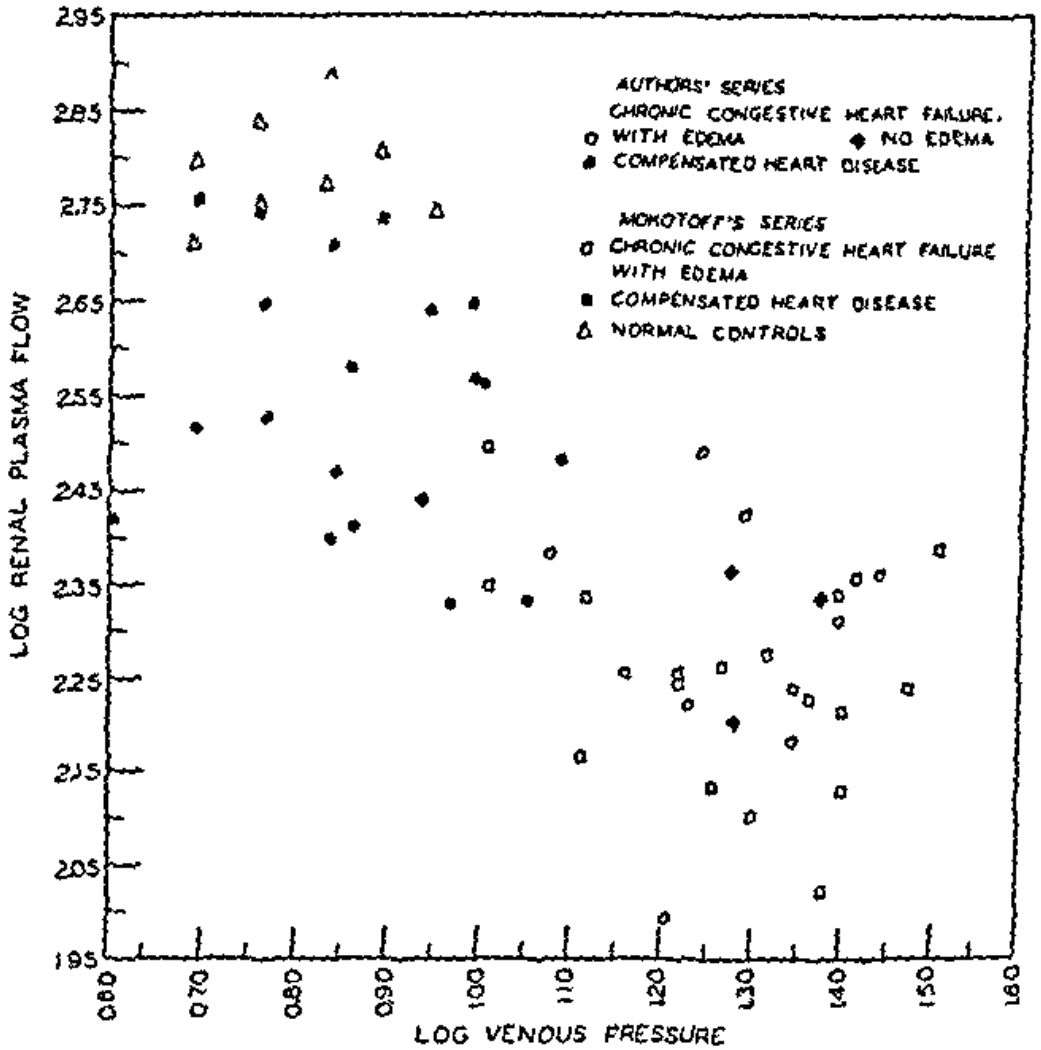

FIGURE 123. Correlation between log renal plasma flow and log venous pressure. Correlation coefficient $r = -0.6969$. P is less than 0.01, indicating a significant degree of correlation (Heller and Jacobson [369])

though renal ischemia was not so severe as in the edematous patients.

As previously recorded by Blegen,[192] Heller and Jacobson found that in 5 patients with rheumatic valvular disease who had never been in congestive failure (group A) the renal plasma flow was reduced (range 338 to 556, average 433 ± 97.2 cc.). (This represents a statistically significant decrease, P less than 0.01.) But the fil-

creased during sleeping hours in all, the average increase being 17 per cent (range +6 to 35). The urine flow increased rather more than the filtration rate (average 25 per cent, range −7 to +50) so that in the mean the inulin U/P ratio fell (average −8 per cent, range −22 to +9); hence there is apparently some diminished water reabsorption superimposed upon increased filtration. The interpretation of this diuresis is rendered difficult, however, by irregularity in water intake and by the possibility of diurnal changes in sodium diuresis. The maximal rates of urine flow were, however, all low (0.38 to 0.69 cc/min.). This inversion of the diurnal cycle is less frequently observed in patients with congestive failure who are not in the edematous state. The data are insufficient to establish whether the change in filtration rate is correlated with increased sodium excretion, which in 3 patients studied increased by an average of 34 per cent. It has been noted (ch. xi) that in normal subjects sodium excretion is generally decreased during sleep, despite a constant filtration rate. It seems likely that here sodium excretion and filtration rate are not directly related.

SPONTANEOUS DIURESIS

Brod and Fejfar [261] report that spontaneous changes in diuresis in uncompensated patients are always secondary to changes in renal plasma flow, increased diuresis is always accompanied by an increase in filtration rate and *vice versa* Such spontaneous changes in diuresis and renal plasma flow are neither preceded nor accompanied by consistent changes in right auricular pressure. They believe that changes in renal plasma flow are independent of changes in cardiac output, and issue from altered distribution of blood in the body. They accept that the retention of salt and water is primarily a result of decreased renal blood flow and filtration rate. Hemodilution is known to occur in normal subjects at night, when the urine flow decreases (ch. xi) and fluid moves from tissues to plasma. Patients in congestive failure and with permanent oliguria, Brod and Fejfar report, show this same nocturnal hemodilution, whereas in patients who show nocturia a transient hemoconcentration occurs shortly after the onset of the nocturnal increase in urine flow.

In group C the average peripheral venous pressure during decompensation was 18.4 ± 5.5 cm. of saline. With clinical recovery this value returned to the normal level of 8.4 ± 2.7 cm. In the 6 patients studied before and after compensation, these figures were 20.2 and 7.6 cm. In both groups the renal plasma flow increased after compensation, but in view of the observations of Maxwell, Breed, and Schwartz it seems unlikely that the decrease in venous pressure could account for the change in renal plasma flow. The correlation coefficient between renal plasma flow and venous pressure among patients with congestive failure was not significantly different from zero, as Merrill [1432] has noted. But if one combines all groups (congestive failure with edema, congestive failure without edema, and compensated heart disease) the correlation is high (fig. 123). To the writer, this does not imply that the increase in venous pressure causes the reduction in renal plasma flow, but only that both terms are grossly related to the severity of cardiac insufficiency, however this operates to affect either term.

DIURNAL VARIATIONS

Perera and Berliner [1333] have shown that, both in normal subjects and in patients with chronic congestive failure, the plasma protein concentration, hematocrit, and red cell count vary in a diurnal cycle, being lowest in the early morning after a night's bed rest. Their interpretation is that in the horizontal position extracellular fluid moves into the vascular tree in the manner of an autoinfusion and increases the blood volume. They believe that this phenomenon plays a significant role in the genesis of orthopnea, paroxysmal dyspnea usually occurring during the early morning hours or after prolonged rest.

Brod [268] concluded from endogenous creatinine chromogen clearances that the filtration rate in many subjects with congestive heart failure increases during sleep, in contradistinction to normal subjects where, if any change occurs, it decreases. Baldwin, Villarreal, Schreiner, Sirota, and Wesson (pers. com.), in studies paralleling those which Sirota, Baldwin, and Villarreal [1304] have reported on normal subjects (ch. XI), find in a small number (6) of patients with persistent edema that the inulin clearance in-

nous pressure leads to increased sodium reabsorption and edema, this sequence occurring without a decrease in resting cardiac output, renal plasma flow, filtration rate, or arterial blood pressure. Expansion of the extracellular fluid prevents hemoconcentration and reduction in blood volume despite progressive edema formation. Eventually, anasarca and increased blood volume develop

The ability of the heart with tamponade to increase its output to meet the needs of activity is limited and, with exercise, inadequacy of cardiac output may bring into play 'forward failure' mechanisms (e.g. inordinately decreased renal plasma flow and filtration rate), which contribute to the salt and water retention.

Progressive tamponade leads to further rises in venous pressure, but pre-terminally a critical level is reached; increased venous pressure no longer suffices to maintain adequate resting cardiac output and arterial blood pressure falls. Both renal plasma flow and filtration rate decrease precipitously and this circumstance, with increased renal venous pressure, now operates to accelerate fluid retention and aggravate circulatory embarrassment.

MECHANISM OF RENAL ISCHEMIA

That the renal circulation is susceptible to physiological control is well demonstrated (chs. XI and XIV), but no information is available on how the reduction in renal blood flow in congestive failure is effected. That renal ischemia is not neurogenic in origin seems fairly certain from the observations of Mokotoff and Ross,[1459] who obtained no increase in either renal blood flow or filtration rate in patients subjected to high spinal anesthesia, the blood pressure being maintained by ephedrine, a drug which does not act on the renal arterioles (ch. XIV). It is improbable that the reduction in blood flow is attributable to the continuous secretion of adrenalin, since chronic congestive failure does not present the cardinal symptoms of sympathetic excitation. Since this renal ischemia is apparently not neurogenic and probably not adrenergic in origin, one turns with interest to other possible humoral agents. Merrill, Morrison, and Brannon [1461] very tentatively suggested that it might be mediated by renin, since renal venous blood in 8 out of 11 cardiac patients examined by them showed a significant amount of this agent.

PERIPHERAL VENOUS CONGESTION

Wilkins, Culbertson, Burrows, Tinsley, Judson, and Burnett[2217] have shown that venous congestion of the legs for periods of 10 to 20 min. leads to a transient decrease in filtration rate, renal plasma flow, decreased excretion of sodium, potassium, and chloride, and antidiuresis, and they suggest that peripheral venous congestion resulting from the increased venous pressure in congestive failure may contribute to decreased renal function and sodium excretion. Their studies seem to be equally pertinent to the problem of tourniquet shock (ch. XXIV).

LYMPHATIC DRAINAGE

The role of impaired lymphatic drainage in promoting the edema of chronic congestive failure has not been well defined. In 1876, Gaskell showed that the small lymphatics are connected to the formed elements of the connective tissues by fibrils. As edema forms, distention of the tissues pulls the lymphatic walls apart rather than compressing them. McMaster[1310] has confirmed this observation and finds that, despite wide open lymphatic channels, regions of edema failed to show evidence of lymph flow when locally injected with dye.[1319] The absence of flow is difficult to reconcile with the dilated lymphatics, and he suggests that lymphatic stasis issues from the fact that during dilatation of the vessels the valves are incompetent. Certainly, the efficiency of lymphatic drainage must be taken into account in an already complicated problem.

CARDIAC TAMPONADE

Fishman, Stamler, Katz, Miller, Silber, and Rubenstein[660] have shown that pericarditis with tamponade in dogs causes an increase in peripheral and central venous pressure *pari passu* with increased intrapericardial pressure. The initial rise in peripheral venous pressure occurs without increase in blood volume. The authors accept that this increased venous pressure supports right atrial effective filling pressure and helps to preserve cardiac output. Increased capillary pressure causes extravasation of fluid from the vascular tree, while simultaneously increased renal ve-

secretion of renin or VEM by the kidneys, or of VDM by the liver, has to renal ischemia or other disturbances in congestive failure.

ENDOCRINE FACTORS

The importance of the adrenal cortex in salt and water balance is discussed in chapter XII, where it is noted that certain cortical hormones and related compounds, notably DCA, promote the tubular reabsorption of sodium.

Futcher and Schroeder [728] and Warren and Stead [1147] recognized that changes in endocrine activity might play a role in the retention of sodium in congestive failure, and numerous investigators cited above have had this possibility in mind, but information on the point is lacking because of the absence of reliable tests for adrenal cortical activity. Parrish [1378] reports that the urine of patients in congestive failure shows increased glycogenic activity, and in 4 out of 10 instances there was an increased excretion of corticoids which prolonged the life of adrenalectomized rats Deming and Luetscher [498] report increased excretion of a DOCA-like compound in congestive failure and nephrosis. Parrish recognizes that increased corticoid excretion may represent a result rather than a cause of the electrolyte disturbances. It will presumably be no easier to disentangle cause and effect in this area than in the sequence of increased venous pressure and edema formation.

INDUCTION OF DIURESIS

Despite the retention of sodium, water is retained to a proportional or greater degree, so that the plasma concentration of sodium is generally low (129 6 to 139.1 as compared with 140.9 to 147 1 mEq/liter in normals),[457 484] this hyponatremia of course being aggravated by salt restriction and mercurial diuresis.[1198]

It is now recognized that mercurial diuretics promote diuresis by reducing the tubular reabsorption of sodium, probably in the distal tubule. Whether mercury also specifically reduces water reabsorption is not determined (ch. XXVII). It seems probable that, once sodium is excreted, readjustment of water balance is effected through the normal operation of the supraopticohypophysial system.

Alternatively, Mokotoff, Shorr, and their collaborators (pers. com.) [1458] report that VEM was present in large amounts in the renal venous blood of 10 out of 12 patients in congestive failure, and especially those showing a high filtration fraction, in contrast to the presence of only trace amounts in 3 out of 13 control subjects. In such patients the oxygen saturation of renal venous blood was reduced; the mean renal capillary oxygen tension was calculated to be 44 mm. Hg as compared with 62 mm. in the control group, i.e. the renal parenchyma is suffering from significant hypoxia as judged by the oxygen tension which is critical for the aerobic enzyme system which destroys VEM. Although the renal oxygen arterial-venous difference is increased (3.35 ± 1.09 cc/100 cc.) above their normal figure (1.29 ± 0.31 cc/100 cc.), the renal oxygen consumption is somewhat reduced because of a reduced blood flow (12.0 cc/min. as compared with 15.8 cc. in the controls). The critical state of renal hypoxia necessary for the liberation of VEM appears to be reached when the renal blood flow falls below 600 cc/min., or about half the normal. VDM was present in hepatic venous blood samples in 10 of 11 patients in congestive failure, while only 3 of 14 controls showed mild VDM activity. In femoral arterial blood there was a slight preponderance of VEM in 5 failure patients, but 4 showed preponderance of VDM, while a neutral response occurred in 2 failure patients as compared with 13 controls, all of whom showed a neutral reaction. By decreasing the oxygen tension in the inspired air in 2 normal subjects, it was shown that VEM is produced by the kidney after 15 min. of low oxygen, without a change in renal oxygen consumption or oxygen arterial-venous difference. The increase in VDM is significant in view of Myers and Hickam's [1497] demonstration that in congestive failure the hepatic blood flow is reduced to some 60 per cent of normal.

VDM is an antidiuretic substance which apparently acts by increasing the secretion of ADH, and Shorr and his colleagues have suggested that it may play a role in the retention of water in the formation of edema. However, there is no evidence as yet that the retention of water *per se* will lead to the retention of sodium (ch. xi). It remains to be determined what relation, if any, increased

physiologically well grounded, and in the hands of others has not proved superior to sodium restriction alone.[1811]

In the absence of any method of improving the renal circulation and increasing glomerular activity, the therapy of congestive failure must for the time being follow the conventional lines of improving cardiac action by digitalization, coupled with salt restriction and such diuretic measures as promote the excretion of sodium.

Dock has recently raised the question whether our salt intake has become excessive by habituation. He notes [625] that among the great apes, living on seeds, nuts, and fruit, sodium intake rarely exceeds 250 mg. on a 3000 calorie intake; among primitive people in the tropical rain forests it is rarely more than 500 mg/day, and often is much less The average intake for many Americans may exceed 5 gm/day. What significance, if any, this high salt intake has in accelerating the crisis of congestive failure remains concealed, along with many other questions, for future examination.

A concise summary of the evidence bearing on the role of the kidney in chronic congestive heart failure would be as difficult as a final interpretation It will perhaps suffice to emphasize a few outstanding points.

When Starr, Warren, and Stead and Merrill approached a reinterpretation of this problem, no quantitative data were available on the problem of glomerular-tubular balance and sodium excretion, but those data which have become available in the interim (ch. XI) support their emphasis upon the importance of glomerular-tubular balance; the operations of the distal tubule upon some small fraction (perhaps one-eighth) of the filtered sodium determine the retention or excretion of this ion, and hence the overall retention or excretion of salt and water. The writer and his colleagues are prepared to accept that, all other factors remaining constant, a reduction in filtration rate of the order of magnitude suggested by Merrill (to 70 to 80 cc.) will result in persistent sodium retention.

It must be recognized, however, that sodium reabsorption, either distally or proximally, is profoundly influenced by adrenal cortical hormones, ADH, and possibly other factors, a circum-

Xanthine derivatives tend to increase the filtration rate, but their effect in this respect is moderate, transient, and uncertain. Several investigators have presented evidence that, in addition to this hemodynamic effect, the xanthine derivatives, and particularly theophylline, specifically depress sodium reabsorption by the renal tubules (ch. XXVII).

The therapeutic value of digitalis has long been attributed to its cardiac action, but McMichael and Sharpey-Schafer have argued [1263] that it dilates the venous reservoir and in some instances may improve the stroke volume of the heart by reducing ventricular volume into the physiological range of Starling's law. Handley and Telford [903] reaffirm that in dogs this drug decreases the plasma volume, increases the hematocrit and increases the thiocyanate space, the last involving movement of water out of the tissues. They state, however, that there is no evidence that these extracardiac effects are concerned in its therapeutic use. Ferrer and Sokoloff [637] report that morphine and demerol may reduce mercurial diuresis, even though in the absence of a mercurial diuretic, morphine tends to increase natriuresis, presumably by release of ADH.

Earle, Farber, Alexander, and Eichna [564] have some evidence, not conclusive as yet but strongly suggestive, that digoxin also has a specific renal effect in blocking sodium reabsorption, independently of its effects on cardiac output or venous pressure (ch. XXVII). The question may be raised whether compensation under digitalis, as well as under salt restriction and mercurial therapy, throws any light upon the importance of the filtration rate in edema formation.

Water diuresis tends to be blunted in congestive failure, presumably because of the reduced filtration rate, and the effects of prolonged water diuresis on sodium excretion are rather ambiguous even in the normal subject (ch. XI). There is no convincing evidence that water diuresis increases the excretion of sodium either in the normal subject or in the subject in congestive failure. Schemm [1180] has recommended a regime of salt restriction coupled with the administration of very large quantities of water for the reduction of edema. This regime, however, cannot be said to be

part and to ascertain, where possible, the sequence of events, which may differ markedly not only in relation to easily described pathology, but in relation to less easily described physiological circumstances.

The chairman of a recent scientific session facetiously remarked that the current trend was to demonstrate that the heart had nothing to do with congestive heart failure. It may be that the heart is remotely involved in chronic congestive failure but, when the problem is fully resolved, a great deal of non-cardiac physiology will certainly have been added to this chapter.

stance which in part explains the maintenance of salt and water balance in the face of wide changes in filtration rate in health and disease; that, as Blake and his coworkers have shown, a sufficient increase in renal venous pressure can reduce sodium and water excretion; that pure hemodynamic factors contribute to the increase in systemic venous pressure and to the formation of edema; and, most importantly, that the renal ischemia and reduction in filtration rate cannot be attributed to the increase in renal venous pressure alone.

Sometimes it is disadvantageous to look upon physiological reactions in health and disease as teleologically adaptive; they operate as they do because of an infallible sequence of cause and effect. The fact of renal ischemia in the majority of patients in chronic congestive failure is incontrovertible. The reason for this ischemia, and the means by which it is effected, remain mysterious. It is probably not caused by hypoxia *per se*, and apparently not mediated neurogenically. There is no reason at this time to believe that it is an adaptive phenomenon. It may be accepted that the blood volume is increased, but it is not proved that this increase is solely a result of expansion of extracellular fluid volume. Apart from McMaster's demonstration of lymphatic stasis, nothing is known about lymphatic activity in the edematous state.

There are good reasons for believing that the renal circulation and the endocrine control of sodium excretion are normally coordinated in such a manner as to maintain a normal volume of extracellular fluid (which is itself part of the circulatory system, in a broad sense). In chronic congestive heart failure this coordination has broken down. Renal ischemia, perhaps increased sodium reabsorption, certainly sodium and water retention, follow, with the formation of edema, which serves not to increase the blood volume and the venous pressure in order to increase the filling of the heart in an attempt to increase cardiac output, but only to embarrass an already deficient heart and circulatory tree.

Accurate information on the sequence of events will not be obtained by overemphasizing one part of this complex and delicately co-ordinated system to the prejudice of another, but rather by an effort to acquire more precise quantitative information on each

cardiac output in the basal condition does not cover all the exigencies of life but, at least as far as the basal state is concerned, the elevation of pressure may be attributed to increased peripheral resistance. The fact that it is the diastolic pressure which is typically and persistently elevated, implying increased resistance to outflow, supports this conclusion.

The data of Bolomey *et al.* (which include control observations on 6 patients reported by Goldring and Chasis [792]) show an average peripheral resistance of 1160 absolute units in 18 subjects without hypertensive disease; in 19 subjects with hypertensive disease the average figure was 1950 absolute units: i.e. the peripheral resistance was 68 per cent greater than normal.

Since no obstruction exists in the major arteries and the evidence is against any increase in capillary resistance, the critical physiological change in the vascular tree may be referred to increased tone in the arterioles which stand intermediately between the larger arterial conduits and the capillaries; these arterioles contribute the larger fraction of the total hemodynamic resistance of the circulatory tree, and in transit through them the arterial blood suffers the greatest decrement in pressure and the greatest expenditure of that energy which is imparted to it by the contraction of the heart (see fig. 53, p. 299). It is by variation in this arteriolar tonus, through neural or humoral mechanisms, that blood is diverted from one organ to another and that the vasomotor reflexes operate to maintain the median pressure in the arterial reservoir. The systolic pressure is hemodynamically related to the stroke volume of the heart and the volume elasticity coefficient of the arterial reservoir; it is elevated in hypertensive disease, with a concomitant increase in pulse pressure, not because of any increase in stroke volume but in part because there is some decrease in the volume elasticity of the arterial tree and in part because of the increased diastolic pressure. The diastolic pressure is hemodynamically related to the 'run-off' or residual pressure in the arterial reservoir at the end of diastole, and it is increased by any circumstance that impedes outflow from the arterial reservoir. Hence the diastolic pressure is the more significant in interpreting the hypertensive status of the patient. Although the arterioles in the advanced stages of essential hypertension show medial hy-

CHAPTER XXIII

Essential Hypertension

Various disorders of the cardiovascular system lead to an increase in diastolic or systolic pressure, or both, but the most frequent and the most mysterious is the condition known as essential hypertension, the etiology of which is unknown. This disease is characterized by elevation of both diastolic and systolic pressure, elevation of the diastolic being a *sine qua non* and serving to distinguish essential hypertension from arterial sclerosis, aortic insufficiency, arteriovenous fistulas, hyperthyroidism, and other conditions wherein only the systolic pressure typically rises above normal limits. The upper limits of 'normal' blood pressure are difficult to define, but as an arbitrary basis these limits are widely taken as 90 mm. Hg diastolic and 140 mm. Hg systolic pressure.

It is now well established that the basal cardiac output is not increased in essential hypertension.[249,795] In a recent study by Bolomey, Michie, Michie, Breed, Schreiner, and Lauson,[307] the cardiac index as determined by the direct Fick method in 19 hypertensive subjects averaged 3.97 liter/min. per sq. m., in 18 nonhypertensive subjects, 4.07 liter/min. per sq. m. (Both figures are probably elevated slightly by the multiple procedures of cardiac output and clearance determinations, as pointed out on page 552.) The mean arterial pressure averaged 145 mm. Hg in the hypertensive subjects, and 92 mm. in the controls. Admittedly, the

factory, heart disease in all forms is the cause of death in nearly one-half of the adult population; in the category of heart disease, the sequelae of essential hypertension appear to account for about half of these deaths, or some 25 per cent of the total adult figure.

In about two-thirds of victims of hypertensive disease,[785] heart failure in one form or another is the immediate cause of death. In some, death is caused by coronary thrombosis; in others, the heart, continuously faced with the expulsion of blood against an elevated pressure, undergoes hypertrophy and ultimately dilates beyond compensatory limits, precipitating congestive heart failure. It is to be noted that despite left ventricular failure (and elevated pulmonary arterial pressure) right ventricular pressure and systemic venous pressure are not increased, and edema is absent in hypertensive heart disease unless and until congestive failure supervenes in consequence of right ventricular failure.

In some 10 to 20 per cent of cases, death is due to catastrophic cerebral hemorrhage or thrombosis, precipitated by pathologic changes in the cerebral arteries. Disturbances of the cerebral circulation are often evident early in the disease; headache is one of the earliest and most frequent symptoms, and transient episodes of sensory and motor disturbances, aphasia, or amaurosis are frequent. In the eye the arteriolar changes lead to a reduction in the caliber of the retinal vessels, venous obstruction, hemorrhages, and retinal edema, often with serious impairment of vision.

Death ensues from specific renal damage in about 10 per cent of subjects, although the kidneys appear to be neither more nor less fortunate in escaping the ravages of the disease in all subjects. In some 12 per cent death occurs from causes unrelated to hypertensive disease.

The increase in mean arterial pressure offsets the increased arteriolar resistance, with the result that there is a normal blood flow everywhere throughout the body; every major circuit has been examined in patients with essential hypertension without eliciting any evidence of selectivity for any particular vascular circuit in its early stages. Whether the heart, the brain, or the kidneys will prove to be the weak point in physiological endurance cannot be predicted before the organic derangement becomes an overt fact. But, because of enhanced arterioral tonus and possibly because of

pertrophy and intimal hyperplasia which tend to narrow the lumen,[114] these pathological changes are not responsible for the increase in peripheral resistance, which has a functional origin. Hypertension of long duration may be associated with little if any visible vascular damage,[2042] while the vascular disease may persist and progress even after sympathectomy has reduced blood pressure.[795, 868, 1951, 1952]

The raw statistics indicate that the incidence of essential hypertension, quite low before the age of 20, rises rapidly thereafter until at the age of 40 approximately 25 per cent of the population are affected, this figure increasing to 60 per cent or more in elderly persons. One extreme estimate implies that one-half of the male population of the United States and 60 per cent of the female population 40 years of age or over are hypertensive.[1932] The writer believes that these statistics should be accepted with great caution; they do not exclude arteriolar sclerotic disease, they too frequently depend upon single blood pressure measurements, and the question may be raised whether in any instance they represent a true cross-section of the population. The basic fact, perhaps, is that blood pressure is so labile that it is an unreliable guide to the presence or severity of true hypertensive disease. Perera [1586] believes that the incidence of essential hypertension does not exceed 5 per cent, an estimate so different from previous statistics as to emphasize the need for larger and more reliable studies.

In some instances, the hypertensive process is for unknown reasons accelerated, leading to the rapidly fatal form known as the malignant phase of hypertensive disease. It is possible that new causal factors become operative in this accelerated state, since the malignant phase has been reported (if rarely) in patients with no history of pre-existing hypertension. In most instances essential hypertension is a relatively benign disease, and it is not established to what extent it shortens life.[112 795] Perera [1586] records one woman, still in reasonably good health, who had definitely established hypertension for more than 41 years, whereas survival for more than 20 years is not uncommon.[195] In its more severe forms, however, it may be incapacitating, and its sequelae appear to be the cause of death in a large proportion of the general population. Again to revert to vital statistics, which are anything but satis-

as elsewhere throughout the body (ch. XIV). By *in vitro* tests with smooth muscle or by perfusion preparations (none of them highly specific) small concentrations of renin and hypertensin can be detected in blood, and it has been shown that for a week or so after the induction of Goldblatt hypertension in the dog the renin concentration is increased in the systemic blood.[508] Ultimately, however, this pressor activity disappears despite the persistence of hypertension, which leads some investigators to believe that, after the hypertensive process is initiated by renin secretion, it becomes independently sustained by a neurogenic or other humoral mechanism.[1543] Renin is present in the renal venous blood in approximately the same amount and with the same frequency in hypertensive and normotensive subjects, but occurs in increased amounts in the renal venous blood of some patients with eclampsia, acute glomerulonephritis, and in circulatory failure.[508, 943, 1498]

Other investigators believe that the normal kidney is the source of a substance that has the ability to prevent hypertension, and that it is the absence, destruction, or neutralization of this substance which results in elevated blood pressure.[874, 875] There is also the possibility that pressor agents, formed by failure of deamination, may be involved.[170, 174] Selection between these divergent views (if any of them contains the answer) is impossible at the present time. It may be emphasized that in benign experimental hypertension the arterioles, particularly of the kidneys, undergo hyperplasia and hypertrophy, presumably because of increased 'work' in the face of elevated pressure, but the endarteritis and arteriolar necrosis which characterize the advanced form of the disease in man do not occur.[791]

VDM AND VEM IN EXPERIMENTAL HYPERTENSION

(For definitions of VDM and VEM see p 788)

Shorr, Zweifach, and their collaborators [1521] have shown that, within 30 min. after partial constriction of the renal artery in the dog, VEM appears in the renal venous blood and a few hours later can be detected in the peripheral blood, where significant concentrations remain during the time when the blood pressure is increasing. However, after the pressure has become stabilized at hy-

inadequate venopressor mechanisms, the hypertensive subject is particularly susceptible to hypotension under circumstances that block sympathetic vasomotor tone or impair the venous return to the heart (spinal anesthesia, the pyrogenic reaction, orthostatic syncope, etc.).[230]

HYPERTENSION OF RENAL ORIGIN

Renin

Until something over a decade ago, the invasion of the renal vascular bed, with its sequelae of glomerular and tubular degeneration, was accepted as merely indicative that the kidneys were not immune to the widespread arteriolar sclerosis which also affects the brain and retinae, the skeletal muscles, the coronary vessels, and the vasculature of other viscera. However, impressed by the frequent association between hypertension and acute or chronic glomerulonephritis, which has been recognized since Bright first described nephritis, investigators had attempted to initiate the hypertensive process by partial nephrectomy, reduction of the renal blood supply, or other measures designed to impair renal function. It remained for Goldblatt, Lynch, Hanzal, and Summerville [792] to establish that the blood pressure of the dog and other animals could be permanently elevated to pathologic levels by partial constriction of the renal artery on one side, the other kidney being removed. This demonstration evoked new interest in the possible role of the kidneys in the genesis of essential hypertension, and has stimulated a larger body of experimental work than any other observation in the last two decades.[249,789,790,791,799,1543,1565]

The most generally accepted interpretation of the Goldblatt experiment is that alterations in the renal circulation, not necessarily ischemic in nature, lead to the secretion of renin, a substance first extracted from kidney tissue by Tiegerstedt and Bergman in 1898. Renin is a proteolytic enzyme which is known to react with plasma alpha-2-globulin (hypertensinogen); in this reaction there is liberated an actively pressor polypeptide, angiotonin, or hypertensin, of small molecular weight. When given in pharmacological doses, renin and angiotonin cause vasoconstriction in the kidney as well

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pertensive levels, the blood becomes 'neutral,' due to the presence of large quantities of VDM.

Examination of kidney tissue from chronically hypertensive animals reveals that the kidney has undergone transformation into an organ that has lost the capacity to inactivate VEM and which, therefore, produces this agent continuously, even under aerobic conditions. Although the initial derangement of the VEM inactivating system might have its explanation in the reduced blood flow which immediately follows the application of the clamp to the renal artery, there is no explanation for the persistence of this derangement during chronic hypertension when the renal blood flow has returned to normal.*

The 'neutral' reaction of the blood of the chronically hypertensive dog is attributed to the presence of large quantities of VDM (which is normally absent), and this agent can be uncovered when the blood is incubated with normal kidney tissue in the presence of oxygen to destroy VEM. Thus, a new equilibrium, with both factors present in large amounts, appears to be established after the blood pressure has stabilized at hypertensive levels. The presence of large amounts of VEM can be explained by the derangement of the renal inactivation system, but why the liver should liberate large quantities of VDM is unexplained.

Adrenalectomy in rats leads to a loss of the capacity of renal tissue to elaborate VEM, even in animals maintained on a high salt intake, this deficiency being prevented by DCA. In adrenal insufficiency the blood vessels of the test animals lose their responsiveness to adrenalin as well as to VEM. An intact adrenal cortical mechanism is apparently necessary for the operation of the VEM mechanism, both in the kidney and on the peripheral vessels.

Shorr and his collaborators emphasize that a causal relationship between the VEM mechanism and the development of renal hypertension cannot be established on the present information. VEM in tested doses has no pressor effect, presumably because it acts

* Complete renal ischemia of 150 to 240 min in the rat leads to deterioration of the VEM elaborating mechanism, as might be expected from renal survival studies. Forty to 90 min. of ischemia destroys the inactivating mechanism but leaves the VEM elaborating mechanism intact. However, studies of complet ischemia throw little light on the hypertensive mechanism.

on that part of the vascular bed distal to the arterioles which contribute the major variable component to the peripheral resistance and on which angiotonin and other pressor agents have their action. The meta-arterioles and precapillaries contribute relatively little to the peripheral resistance; they are under the dual influence of systemic and local tissue factors; their primary function concerns the distribution of blood within the capillaries and the capillary pressure. At the present time, a relationship between VEM and essential or renal hypertension is purely speculative. If a relationship does exist, it is probably indirect. In response to reduced capillary circulation and tissue anoxia, persistent hyperreactivity of the meta-arterioles and precapillaries may be induced, which may in turn induce arteriolar constriction by humoral or reflex action. But this postulated sequence has not been proved.

HYPERTENSION AND UROLOGIC DISEASE

With the demonstration of the production of a hypertensive state in experimental animals by the Goldblatt technique, the pendulum of interpretation at first swung far to the left, and numerous writers took the position that all essential hypertension in man has its origin, if not in renal ischemia, at least in renal disease. A review of the evidence on the coexistence of hypertension and urologic disease does not bear out this assumption.[1933] The already high incidence of hypertension is not increased by such disease (nephrolithiasis, hydronephrosis, prostatic hypertrophy, intrarenal pelvis, nephroptosis, perinephritis, congenital aplasia, pyelonephritis), and, conversely, the incidence of urologic disease is no greater among hypertensive than among normotensive subjects. At present, the only way a causal relationship between urologic disease and hypertension can be demonstrated in any particular patient is by 'curing' the hypertension by removing the offending organ. Because of the lability of pathologically elevated blood pressure, rigid criteria must be observed: i.e. pre-existing hypertension of some duration must be clearly demonstrated, the blood pressure must be reduced by the operation to normal levels (140/90 or below), and it must remain at normal levels for one year or longer. Review of the literature on unilateral nephrectomy

directed toward the treatment of hypertension reveals that these criteria have apparently been fulfilled in only 47 out of 242 reported operations. In these 47 instances unilateral renal pathology may have been the cause of hypertension, but the very rarity of success (19 per cent), coupled with the evidence that the bulk of urologic disease does not cause hypertension, still leaves a reasonable doubt that they should be so interpreted.*

RENAL BLOOD FLOW IN EXPERIMENTAL HYPERTENSION

Dock and Rytand,[526] from *in vivo* perfusion studies, concluded that the renal blood flow is not diminished in rats in which hypertension has been induced by subtotal nephrectomy. Levy, Light, and Blalock,[1232] however, using the venous sound method, found that partial constriction of both renal arteries sufficient to produce Goldblatt hypertension in 10 dogs reduced the renal blood flow from an average of 291 cc. to 172 cc. (−41 per cent). The renal oxygen consumption decreased in a parallel manner (−43 per cent), the oxygen arterial-venous difference remaining essentially unchanged (2.9 and 2.8 cc/100 cc.). A similar conclusion with regard to oxygen consumption was reached by Mason, Evers, and Blalock,[1417] using the explanted kidney technique. In all cases reported by Levy *et al.*, the blood pressure in the renal artery distal to the clamp was decreased below the level existing in the femoral artery, averaging 50 mm. and 38 mm. Hg lower in the right and left renal artery, respectively. The reduction in renal blood flow reported by them is in contradiction to all subsequent studies, the reason for the discrepancy being undetermined.

Friedman, Sugarman, and Selzer [716] found that in acute experiments (30 min. duration) constriction of the aorta in anesthetized (pentobarbital) dogs, to such an extent as to reduce the mean pressure below the constriction by 30 to 40 mm. Hg and to greatly reduce the pulse pressure, had no consistent effect on the diodrast clearance but the filtration rate was reduced by an average of 20

* The advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure If bilateral disease is present, and it usually is associated with advanced hypertension, nephrectomy may shorten life by removing an important fraction of total available renal function All such unfavorable cases are perhaps not re ported in the literature.

per cent. They conclude that the maintenance of renal blood flow in the face of this reduced pressure implies vascular dilatation in the kidneys. If the pressure was reduced for more than 30 min., the renal blood flow uniformly decreased. After restoration of pressure, the filtration rate returned to the control level but the renal blood flow decreased further (−20 per cent), this ischemia persisting for about an hour. Greater reduction in pressure (by 40 to 60 mm. Hg) decreased both the filtration rate (−16.5 per cent) and renal blood flow (−14.5 per cent). Again, on release of the pressure the filtration rate returned to normal but the renal blood flow again decreased further (−24 per cent). From additional experiments in which the constriction was placed above the left but below the right renal artery, these investigators were led to attribute this ischemia to a humoral agent formed in the kidney during the period of reduced mean pressure and pulse pressure.

In similar but chronic experiments on uninephrectomized dogs, they found that the renal blood flow was again maintained despite a marked reduction in mean pressure and pulse pressure, even after a period of 14 days when the dogs had developed hypertension. They conclude that reduction in renal artery pressure (both mean and pulse) is followed by renal vasodilatation and, if the decrease in pressure is not too great, there will be no renal ischemia. During the period of reduced renal artery pressure, however, a humoral agent capable of neutralization by a kidney with

is, however, not necessary for its production, and they infer that renal ischemia is neither the initiating nor the maintaining factor in experimental hypertension.

Corcoran and Page [416] similarly examined renal function in uninephrectomized dogs in which hypertension was induced by constriction of the renal artery or cellophane perinephritis of the remaining kidney some months after nephrec

and diodrast, they found that the induction of hypertension may occur without constant or persistent changes in the clearance of

any of these substances and without significant changes in Tm_D or Tm_O and, therefore, probably in the absence of renal ischemia. Measurements of the total renal blood from the clearances and ex-

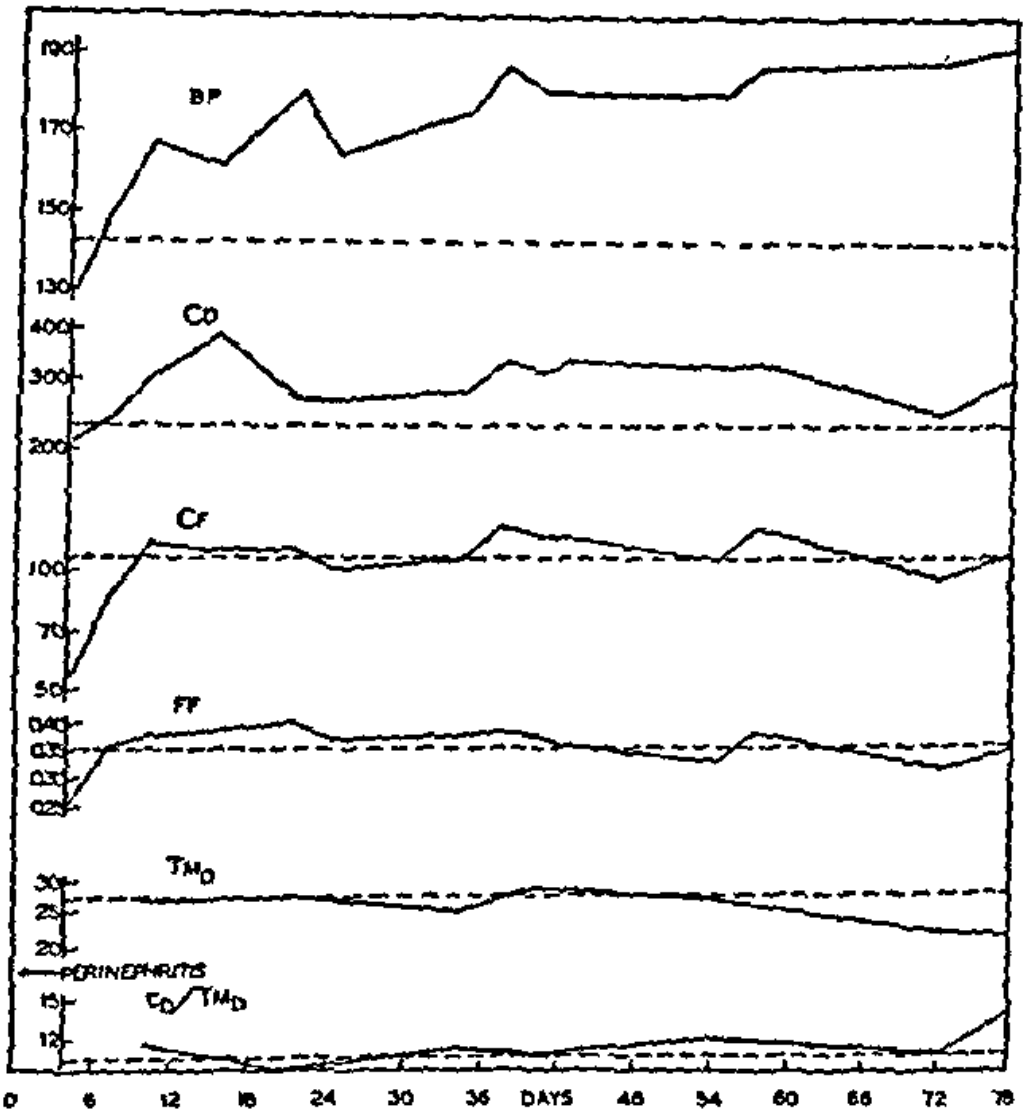

Figure 124. Renal function in a dog with experimental hypertension induced by the application of silk to both kidneys The dotted lines represent the averages of several control observations on each function made prior to the induction of perinephritis. (Corcoran and Page [416])

*traction ratios of phenol red and inulin showed no correlation be*tween mean arterial pressure and renal blood flow, and demon*strated that hypertension may persist in the absence of renal* ischemia. In one uninephrectomized dog in which hypertension *had persisted for nearly 3 years, the last observed values were dio-*

drast clearance 275, inulin clearance 92 cc., Tm_D 15.4 mg. iodine, and Tm_O 293 mg/sq. m. These values are within the normal range to be expected of a uninephrectomized dog, and were made at a time when retinal hemorrhages and partial retinal detachment boded the onset of the malignant phase. Histological study of the kidney, which weighed 80 gm., showed one small scar of the ischemic type and rare hyalin glomeruli. Data on one dog are given in figure 124, and show that hypertension developed without a decrease in diodrast clearance or the C_D/Tm_D ratio, and without an initial reduction of Tm_D. The late decrease in Tm_D may represent infiltration with scar tissue.

Corcoran and Page note that the rate of renal blood flow in experimental hypertension depends upon a balance between increased arterial pressure and increased renal resistance, the latter arising either from primary arterial compression or compression of the renal parenchyma or, secondarily, to renal vasoconstriction induced by the unopposed activity of the humoral mediators of renal hypertension. The fact that in the hypertensive animal the renal blood flow tends to be maintained at a normal level implies that the increased renal resistance is just about offset by the increase in the mean blood pressure. In the absence of renal ischemia, they conceive the exciting factor leading to the secretion of renin (or other humoral agents) may be a reduction in pulse pressure, or some subtle variation in pulse wave, which follows clamping of the renal artery or development of perinephritic scar tissue. It may be noted that arteriovenous fistula between the renal vessels, leading to renal necrosis, is not accompanied by hypertension.[1213]

Rodbard and Katz [1734] have shown that abscess formation induced by local injections of turpentine or carbon tetrachloride or the subcutaneous implantation of kidney tissue causes a sustained fall in blood pressure in both nephrogenic and spontaneous hypertensive dogs. Stamler, Rodbard, and Katz [1978] find that this reduction in pressure is associated with an increase in renal blood flow. Since the provocative agents are equally effective in eliciting the reduction in blood pressure, it is concluded that the depressor response to the abscess is a non-specific reaction. Abscess production elicits a persistent increase in renal blood flow, but the renal

hyperemia may follow the decrease in blood pressure. The latter is therefore not directly dependent upon relief of renal ischemia. Injury produced by inhalation of chloroform or by oral administration of carbon tetrachloride consistently failed to reduce the blood pressure of hypertensive dogs. Instead, the blood pressure was sometimes elevated. The mechanism involved in the fall in blood pressure, therefore, appears to be part of the pattern of systemic reaction to the abscess. Nephrogenic hypertensive dogs, with and without a reduced renal blood flow, respond to tissue injury with a renal hyperemia as well as do spontaneous hypertensive animals with normal kidneys, indicating that reversible vasoconstriction is involved in the renal ischemia observed in some nephrogenic hypertensive dogs.

Stamler, Katz, and Rodbard [1977] report that, in 6 dogs in which both renal arteries were partially occluded, some showed normal renal function while in others the filtration rate and renal plasma flow were reduced below the normal range, with or without an increase in filtration fraction. Serial observations revealed no tendency for renal function to suffer progressive deterioration, whether the immediate postoperative clearances were normal or reduced and regardless of the duration of hypertension, nor did renal function improve in those animals in which it was immediately depressed postoperatively. In 3 animals that came to autopsy, impaired renal function correlated with gross anatomic alterations in the kidney; whereas the kidney usually showed no pathologic changes when renal function was not depressed,* normal function did not mean normal anatomy. The data afford no evidence of the development of collateral circulation in the kidneys of Goldblatt dogs.

Stamler *et al.* have also studied 3 male dogs with spontaneous benign hypertension,† i.e. with persistent pressures in excess of 185/100 mm. Hg of over 2 years' duration. All 3 animals had renal

* In one animal, clearance data within the normal range served only to mask advanced unilateral atrophy accompanied by contralateral compensatory hypertrophy.

† For normal blood pressure in dogs, Katz and his coworkers [1094] analyzed the protocols of 127 trained, unanesthetized dogs and found the mean systolic pressure to be 155 ± 11 mm Hg (range 130 to 185), the mean diastolic pressure 80 ± 6 mm. Hg (range 65 to 100).

clearances within the normal range (PAH clearances of 241, 272, and 294, and filtration rates of 82, 84, and 100 cc. per sq. m.) and on repeated examination renal function remained unchanged for 39, 34, and 64 weeks, respectively. (The last figure is probably equivalent to 7 years, the authors say 10 years, of the human life span.) Pathological studies on 2 of these dogs revealed slight to moderate chronic focal renal lesions and bilateral adrenal cortical adenomatous hyperplasia. The authors suggest that both lesions may be without pathogenic significance. Though these blood pressures may represent the upper range of normal values, they are as truly hypertensive as Goldblatt animals with similar blood pressure elevations Spontaneous canine hypertension may be extrarenal in origin, but whether or not it is related to abnormal adrenal function cannot be determined from the available data.

Stamler *et al* reaffirm that neither dogs with spontaneous benign hypertension nor dogs with chronic nephrogenic hypertension develop the sclerotic changes in the renal, coronary, or cerebral arterioles characteristically complicating long-standing essential hypertension in man, a fact which they believe reflects a species difference in susceptibility to arteriosclerosis rather than a fundamental difference in the underlying hemodynamic processes. The believe that mechanisms other than elevated blood pressure *per* operate to produce these sclerotic changes.

Stamler, Fishman, Katz, and Rodbard 1935 find that in u anesthetized, spontaneous, and Goldblatt hypertensive dogs, d ing the depressor response to abscess, the cardiac output and bl volume remain normal. The sustained fall in blood pressure is tributable to decreased peripheral resistance. Renal hyper and increased renal fraction are components of the systemi sponse to abscess and indicate a decrease in renal resistance gr than the overall decrease in peripheral resistance.

By contrast, anesthetized (nembutal) hypertensive dogs e increased cardiac output, renal ischemia, and markedly re renal fraction during the depressor response to inflamm These results are interpreted as representing the response combined acute depressor effects of the abscess and of ne anesthesia, the drug inducing a further decrease in total pe resistance. The observed hemodynamic pattern is appa

compensatory response serving to maintain blood pressure. The authors conclude that the cardiodynamic pattern of spontaneous hypertension in dogs is similar to that of Goldblatt and human essential hypertension.

A high protein diet increases the renal plasma flow and filtration rate in dogs with experimental hypertension in a manner which is indistinguishable from the normal animal, another fact which argues against renal ischemia as the primary factor in the genesis of this type of hypertension.[42]

RENAL FUNCTION IN ESSENTIAL HYPERTENSION

Numerous clearance studies are now available on renal function in subjects in all stages of hypertensive disease. The interpretation of all such clearance studies is contingent upon the validity of the clearance method in the diseased kidney. Bradley, Curry, and Bradley,[239] from observations on 14 subjects with well-established hypertensive disease, conclude that a PAH extraction ratio of 0.88 or more may be expected except in very advanced stages of renal injury (C_{PAH} less than 440 cc.), when it may decrease to 0 60. Reubi and Schroeder [1699] report E_{PAH} in 8 patients; all except 3 (0.698, 0.797, and 0.807) were above 0.88. Cargill [328] reports E_{PAH} in 3 patients of 0.87, 0.90, and 0.90. Cargill's data indicate that E_{PAH} is not substantially reduced until the PAH clearance falls below 300 cc., when it may decrease to 0.58. Throughout the following discussion it will be assumed that the diodrast or PAH clearance, so long as it is above 300 cc., may be taken as a reliable indication of renal plasma flow.

Investigators are generally agreed that, in many subjects with well-established hypertension, the renal blood flow is within the normal statistical range.* In the larger proportion, however, the renal blood flow suffers reduction, the degree of this reduction being interpretable only in relation to the quantity of residual functional tissue. Perhaps the most distinctive change effected in the kidneys by essential hypertension is the progressive destruction of tubular tissue, a destruction which can be discovered only by measurements made during tubular saturation. Goldring,

* This may be true only in younger people, but the writer does not believe that the data permit the establishment of any firm correlation with age.

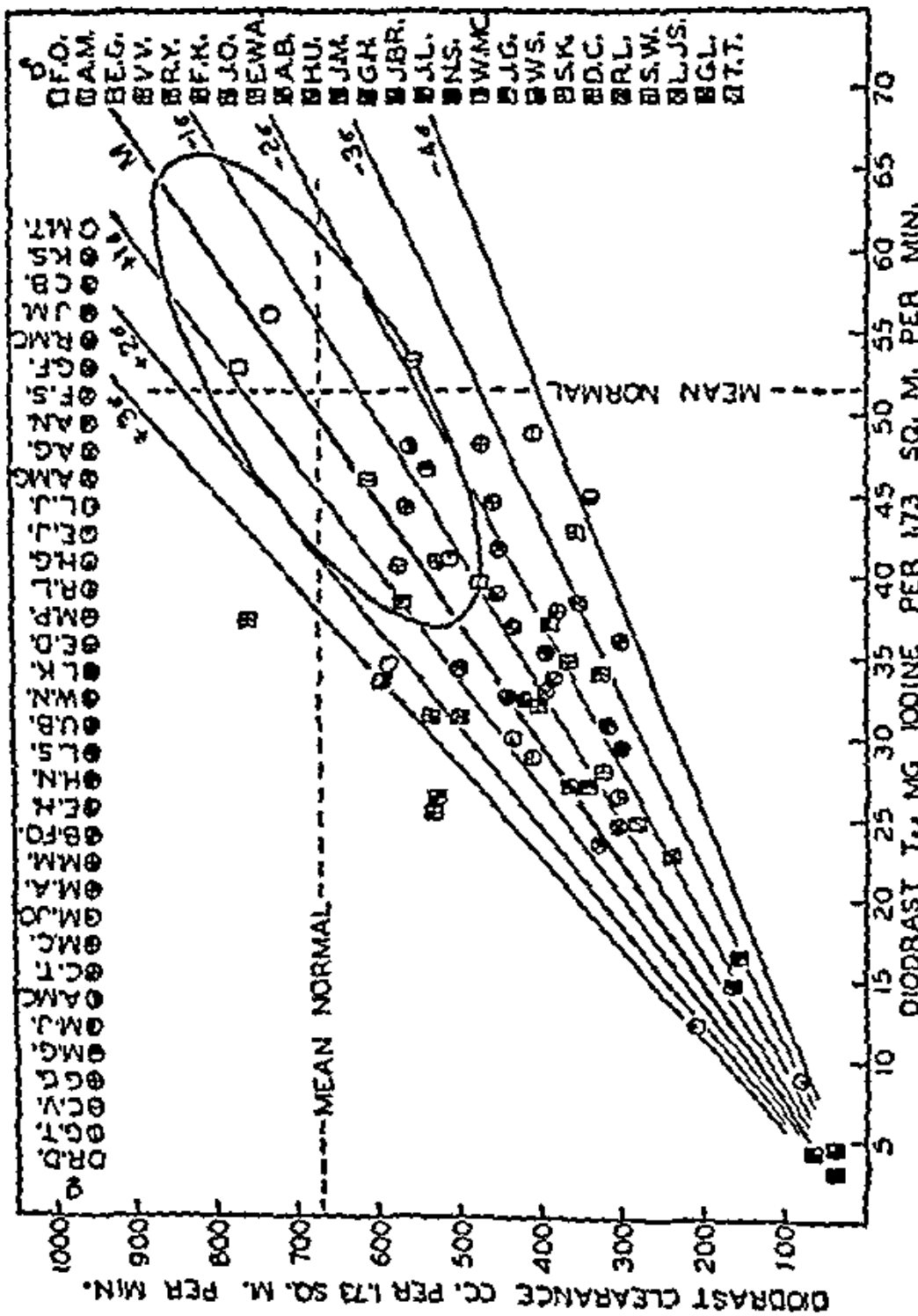

FIGURE 125. Diodrast clearance in hypertensive subjects related to T_{MD}. The statistical background is based on data from normal subjects,[79] the ellipse being calculated to contain 70 per cent of the normal data, and actually containing 72 per cent. (Goldring, Chasis, Ranges, and Smith [88])

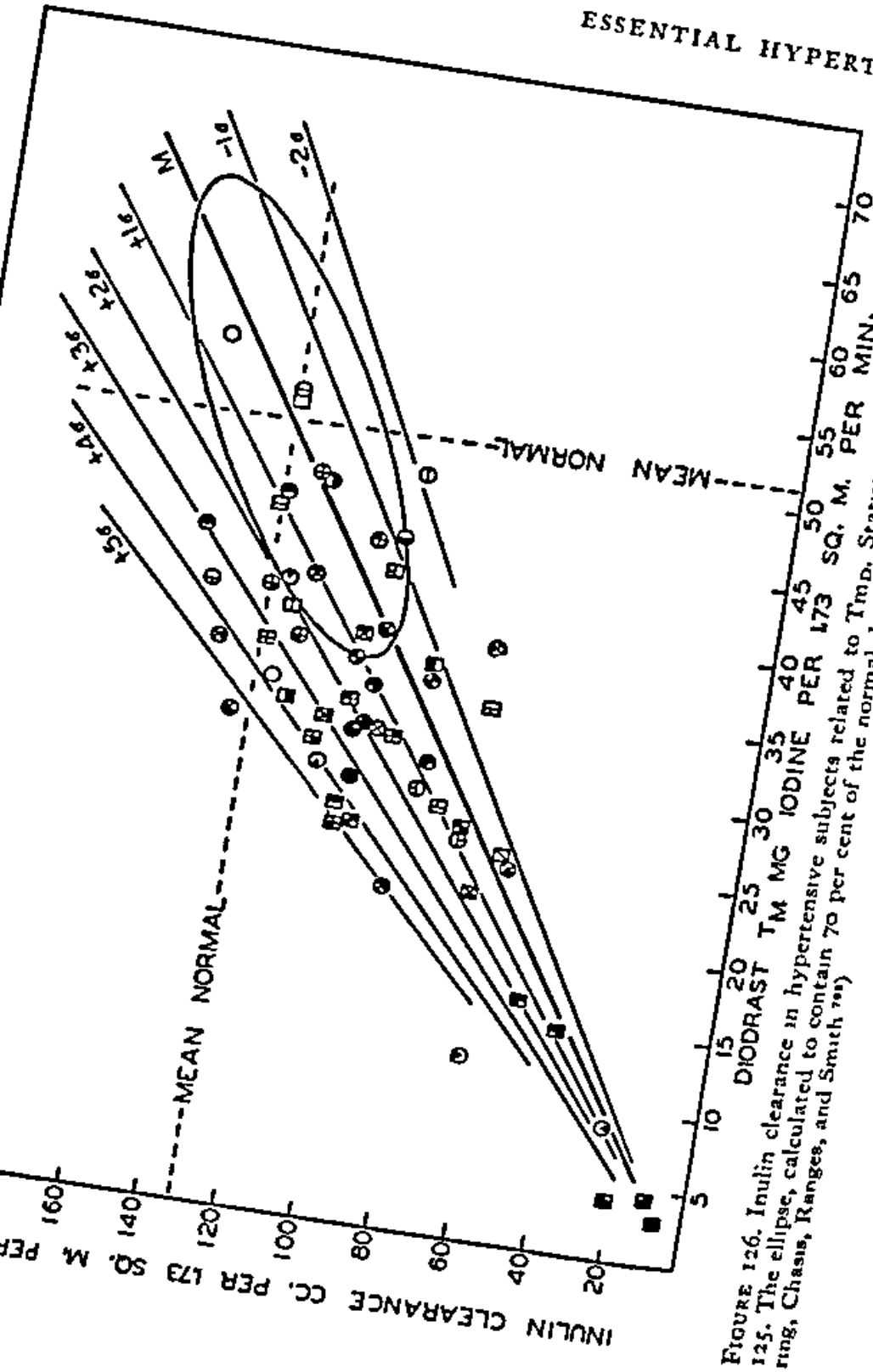

FIGURE 126. Inulin clearance in hypertensive subjects related to T_{MD}. Statistical background as in figure 125. The ellipse, calculated to contain 70 per cent of the normal data, actually contains 75 per cent. (Goldring, Chasis, Ranges, and Smith [88])

Chasis, Ranges, and Smith [198] therefore analyzed their data on 60 hypertensive subjects in terms of T_{mD}.

Figure 125 shows the diodrast clearance (C_D) in relation to T_{mD}, plotted against the normal parameters * previously established by these investigators.[197] In their normal subjects the ratio C_D/T_{mD} had a mean value of 13.4 ± 1.4 and is here represented by the heavy line, M, the light lines above and below M denoting multiples of the standard deviation (The ellipse was calculated to contain 70 per cent of the normal observations and actually contained 72 per cent.)

If we were to start with a normal (statistical mean) kidney in which $C_D/T_{mD} = 13.4$ and were to reduce the quantity of tubular excretory tissue and the renal blood flow by proportional amounts, we should pass down the line M until we reached the intersection of the zero ordinates This is not to imply that the statistical regression line relating C_D to T_{mD} in normal subjects extrapolates to zero, for it does not, the concept of proportional regression is merely an artifice convenient to functional interpretation. A variation of the ratio within the limits of $\pm 2\sigma$ would be expected to contain 95 per cent of the normal observations, and it is in keeping with the artifice of proportional regression to conceive that any distribution of the data disproportionate with this statistical expectation is indicative of significant functional changes in C_D, T_{mD}, or both.

It will be observed that, with the exception of 3 subjects (F. O., R. D., and G T.), T_{mD} is below the mean normal value (51.6 mg. of iodine) and ranges from slightly subnormal to very low values. The lowest values of T_{mD} are found in subjects with advanced retinopathy and significant proteinuria. It is evident that in many hypertensive subjects the renal tubules, as judged by T_{mD}, have been severely injured, and it may be assumed that this injury proceeds, however irregularly, throughout the course of the disease. It is possible that some tubular injury had occurred in the 3 sub-

* The normal parameters used in these figures are calculated from the limited series of observations reported by Goldring *et al* in 1940, but these data are in good agreement with the larger series published subsequently [191, 199] and with the data summarized in table XII

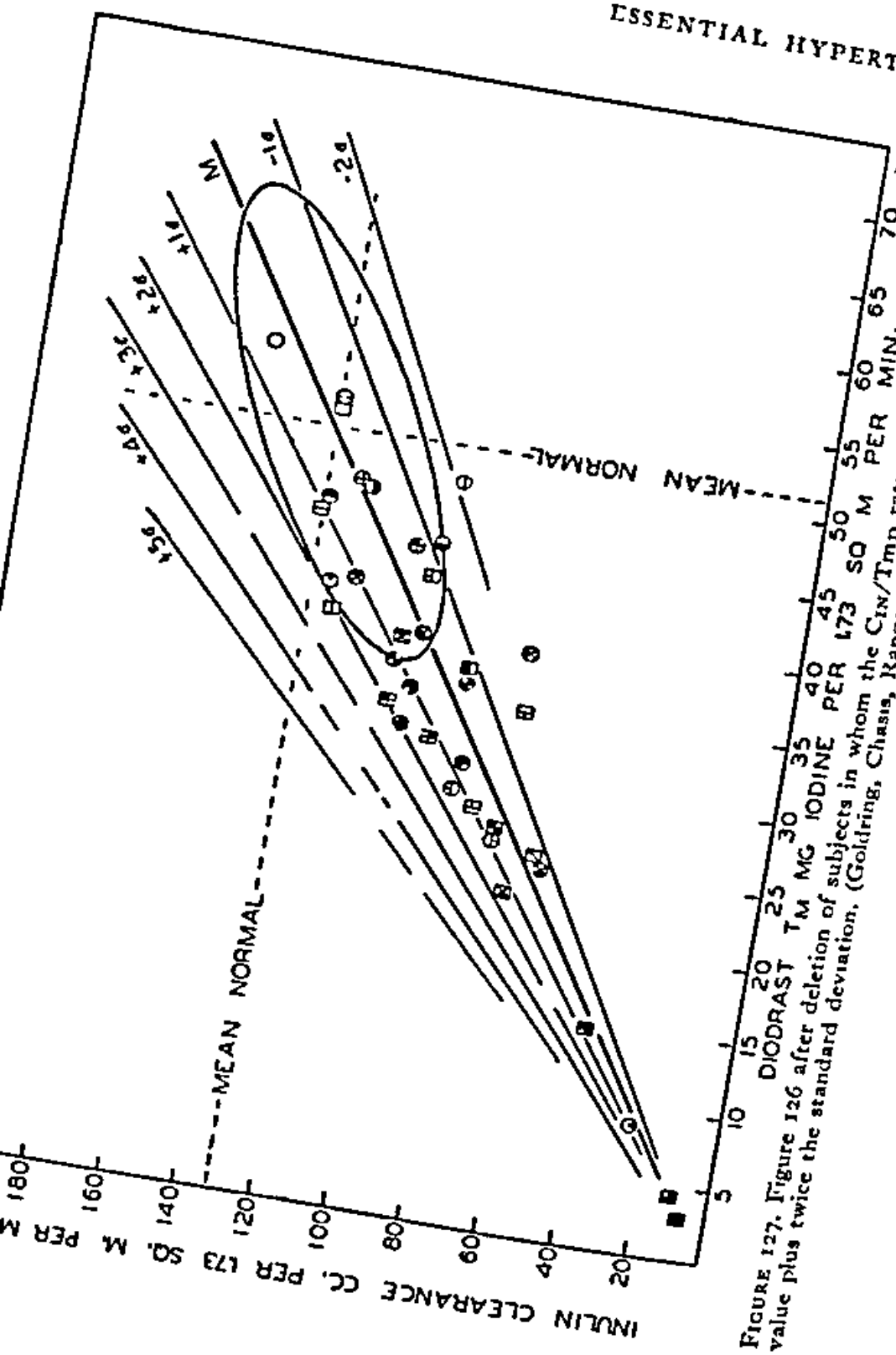

FIGURE 127. Figure 126 after deletion of subjects in whom the C_{IN}/T_{mn} ratio exceeds the mean normal value plus twice the standard deviation. (Goldring, Chasis, Ranges, and Smith ***)

jects in whom T_{mD} exceeded the mean normal figure, as well as in those in whom T_{mD} was above 40 mg. of iodine.

With the exception of 3 subjects (F. O., R. D., and V. V.), C_D is also below the mean normal value (669 cc.) and ranges from slightly subnormal to very low values.

The ratio C_D/T_{mD} is distributed about the mean value in an uneven manner, 45 out of 60 subjects falling on or below M. This preponderant distribution below M suggests that some factor is operating in hypertensive subjects to produce a relative ischemia the residual functional tissue.

Figure 126 presents the inulin clearance (C_{IN}) in relation to T_{mD}. (Again the ellipse was calculated to contain 70 per cent of the normal observations and actually contained 75 per cent.) In all but 5 subjects (R. D., M. C., R. L., F. S., and K. S.) C_{IN} is on or below the mean normal value (131 cc.). There is, however, a ndency for C_{IN} to remain within the lower range of normal alues (92 to 131 cc.) until T_{mD} has been markedly reduced, as shown by the horizontal, leftward displacement of the data.

In spite of the absolute reduction in C_{IN}, its relative value per unit of functional tubular tissue (C_{IN}/T_{mD}) exceeds the mean normal value, M, in 43 out of 60 subjects, and in 21 of these it falls above $M + 2\sigma$. Three factors might operate to maintain a relatively high filtration rate: (a) increased mean arterial pressure; (b) dilatation of the afferent glomerular arterioles; and (c) the formation of impotent nephrons. We cannot immediately distinguish among these alternative possibilities, but failure to do so is not critically important, since the net result upon the blood flow to the residual functional tissue will be the same, namely, the production of apparent hyperemia in this tissue. In the expectation, therefore, that an abnormally high value of C_{IN}/T_{mD} may be expected to be accompanied by an abnormally high value of C_D/T_{mD}, a further analysis of the blood flow picture presented in figure 126 may be made as follows: all those subjects, 21 in number, in whom C_{IN}/T_{mD} exceed $M + 2\sigma$ were deleted, the picture after this deletion is effected being given in figure 127. The remaining subjects are now approximately equally distributed above and below M, because those in whom the C_{IN}/T_{mD} ratio was hi have been deleted.

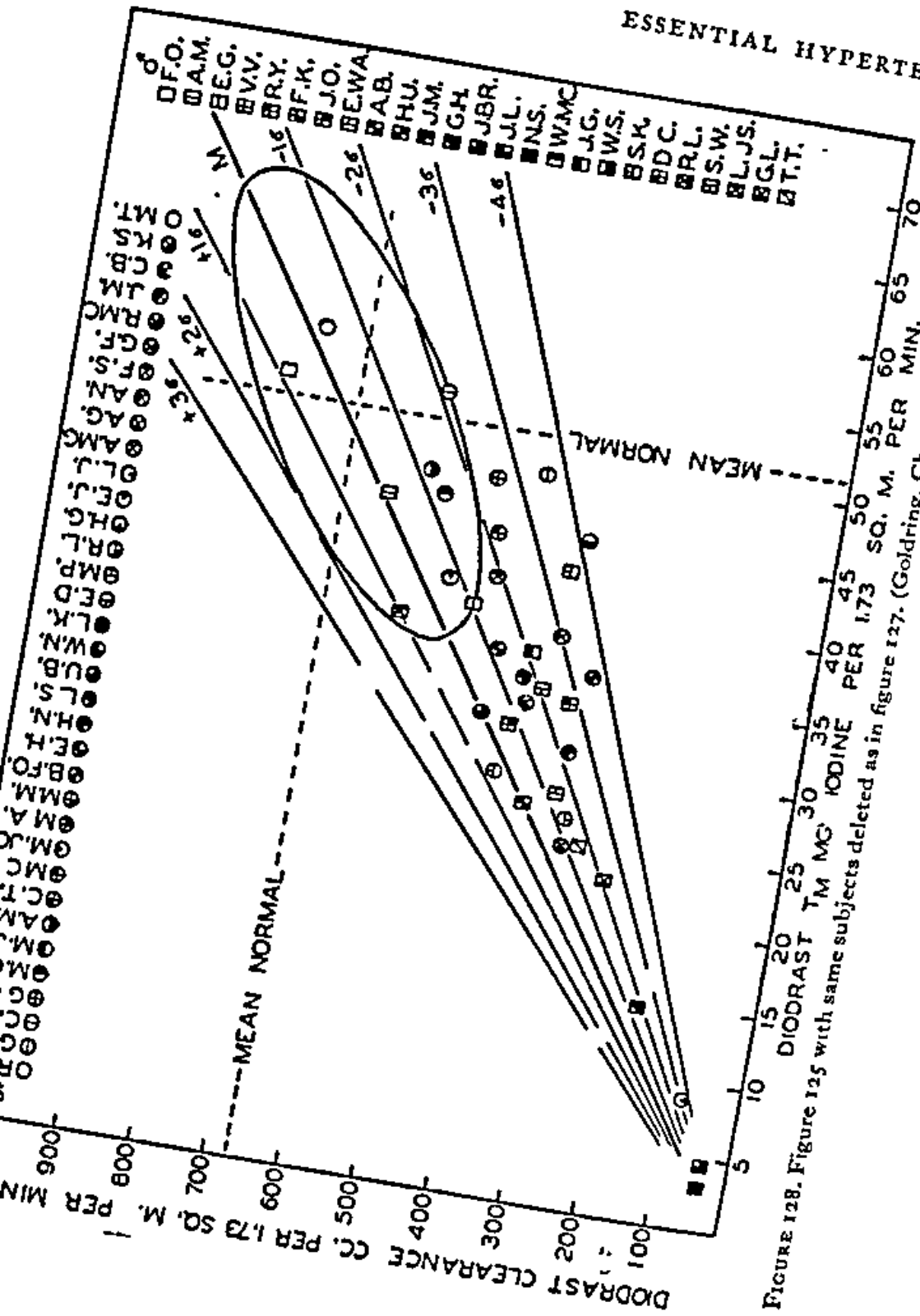

FIGURE 128. Figure 125 with same subjects deleted as in figure 127. (Goldring, Chasis, Ranges, and Smith

Figure 128 is figure 125 with the same subjects deleted, and it will be seen that in the remaining subjects the ratio C_D/Tm_D is in general below, and in some instances far below, the mean normal

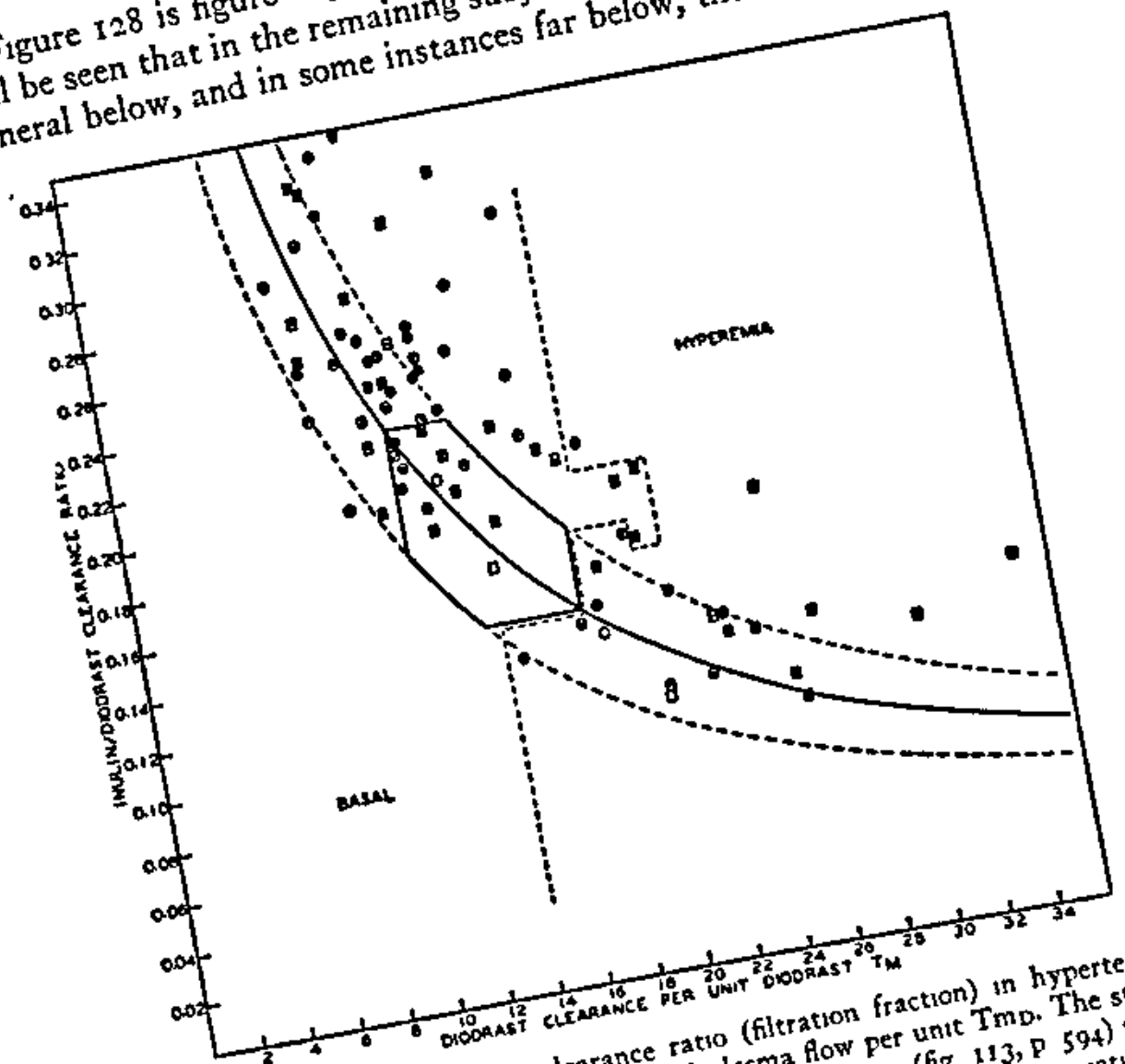

Figure 129 Inulin/diodrast clearance ratio (filtration fraction) in hypertensive subjects, related to the effective renal plasma flow per unit Tm_D. The statistical background is taken from data on normal subjects (fig 113, p 594) the hexagon containing 95 per cent of the normal basal data Basal observations on hypertensive subjects are shown to the left of the vertical dotted line, observations during pyrexial hyperemia to the right (Goldring, Chasis, Ranges, and Smith [798])

value. Thus, when those subjects who show a high filtration rate per unit of functional tubular tissue (C_{IN}/Tm_D), presumably because of elevated glomerular pressure and/or the formation of impotent tubules, and in whom we may expect active or vicarious hyperemia to occur in consequence of these circumstances, are

deleted from the picture, it is revealed that in the remaining subjects the renal blood flow per unit of functional tubular tissue is, with 3 exceptions, below the mean normal value, and in many it falls to very low values. This analysis led the authors to conclude

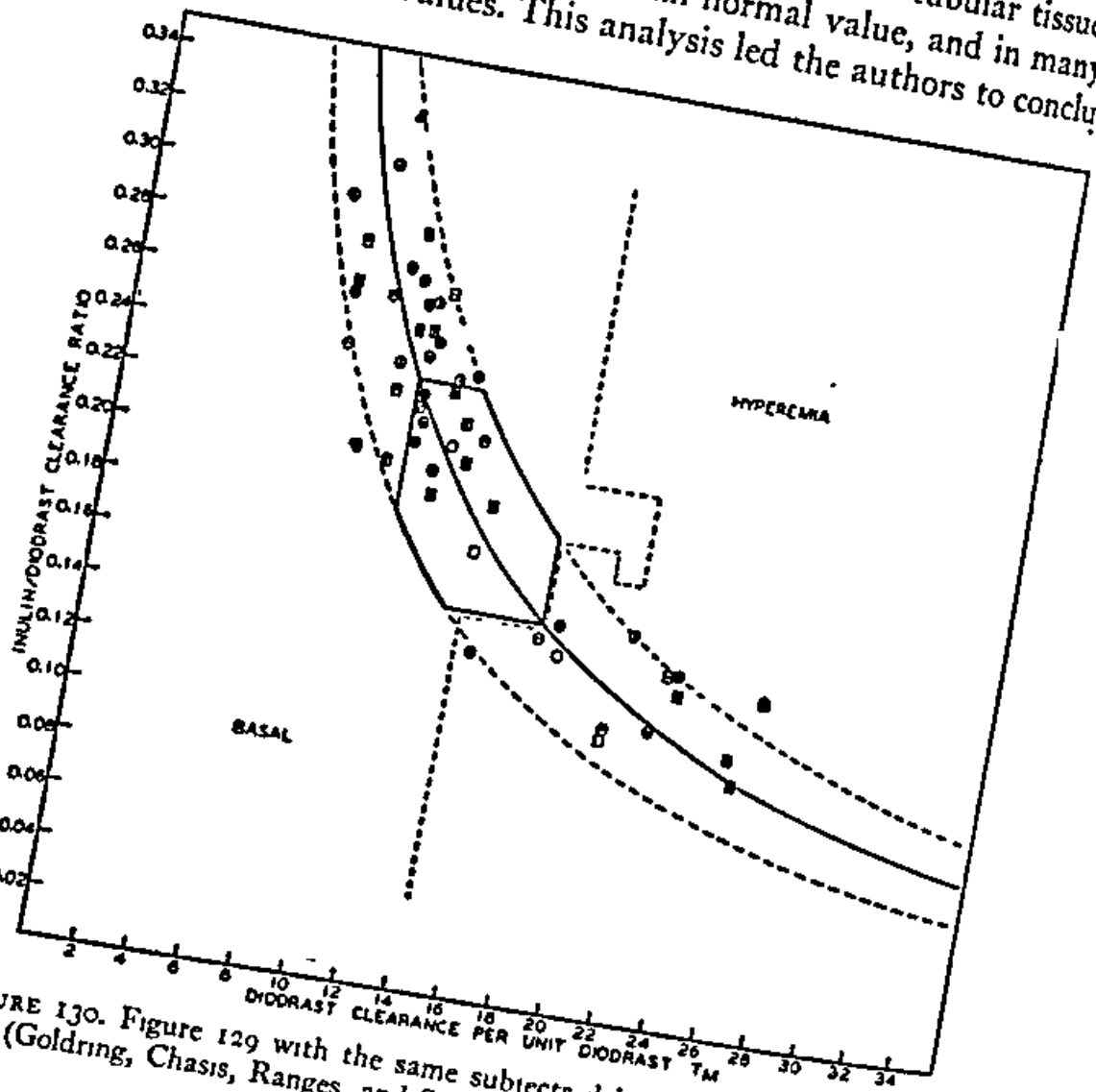

FIGURE 130. Figure 129 with the same subjects deleted as in figures 127 and 128. (Goldring, Chasis, Ranges, and Smith [186])

that some factor is operative in these subjects which tends to produce a relative ischemia of the residual functional tissue. (This ischemic factor may, of course, be operative in the subjects who were deleted because they showed a high C_{IN}/Tm_D ratio, but offset by such factors as were enumerated in defining that group.) Since all these subjects have an elevated mean blood pressure, the cause of this relative ischemia must be an increase in renal resistance.