FUNCTIONAL CHARACTERISTICS OF RENAL TRANSPORT MECHANISMS

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This review is to serve as a general progress report relating to the enzymatic components of the secretory and reabsorptive transport mechanisms of the nephron, particularly as they are influenced, stimulated or inhibited competitively.

Emphasis is to be placed on what are considered to be active processes of renal tubular secretion or reabsorption. Only such related renal physiology as is sufficient for the development of this thesis will be discussed. Consequently this is not to be primarily a resume of current progress in renal physiology, although much of the information to be presented is quite recent in its development. For reviews of collateral literature the reader is referred to the chapter on Kidney in the Annual Review of Physiology and to other excellent reviews and monographs (81, 127, 146, 165, 286, 330, 384, 393, 429, 430, 431, 437, 482, 495 496, 498–500, 533, 539, 585).

These active tubular mechanisms may be envisaged as complex enzymatic systems that, in addition to having specificity, are involved in a spatial transport of materials that is oriented directionally. Although this spatial transport of an agent from the extravascular or parenchymal boundary to the luminal border of the cell, or vice versa, involves macromolecular distances, it may be that this transfer is accomplished without a streaming of the enzymatic elements or the cellular particles with which they are identified or associated functionally.

DEFINITION OF TERMS

A brief review of renal physiology, as it relates to the elaboration of urine, will serve to permit the definition of certain terms repeatedly employed in this article. Essentially three processes are involved in the formation of urine by the kidney. They are 1) *glomerular filtration*, 2) *tubular secretion*, and 3) *tubular reabsorption*, both active and passive. These three processes have been presented diagrammatically in figure 1.

Glomerular filtration (figure 1, A) involves the passive ultrafiltration of a portion of the plasma water from the blood stream at the glomerular tuft. The composition of the fluid as it passes from the glomerular capsule and is presented to the most proximal cells of the tubule is ordinarily the same as that of the plasma from which it was filtered (427, 428, 436, 548), except for the absence of most of the proteins and certain other materials the molecular dimensions of which normally do not permit their filtration. Since this is a passive property of the membrane the force responsible for filtration is the algebraic sum of the hydrostatic, oncotic and intracapsular pressures.

Glomerular filtration rate (*GF*) (figure 1, A) can be determined most conveniently with the aid of a compound that 1) is not bound to plasma proteins, 2) is not secreted by the tubules, and 3) is not reabsorbed either actively or passively from the lumen of the tubule.

If there is neither secretion nor reabsorption of a compound it follows that the amount excreted is equal to the amount filtered. Inulin (136, 145, 153, 175, 186, 199, 438, 475, 476, 487) and less certainly endogenous creatinine (66, 85, 344, 403, 421, 486), thiosulfate (56, 59, 67, 90, 122, 170, 368, 401) and mannitol (20, 21, 108, 149, 153, 167, 367, 505) serve this purpose in man. Exogenous creatinine is the standard compound for such determinations in dogs (265, 390, 438, 439, 488), although the aforementioned compounds and others (102, 129, 158, 159, 161, 192–197, 209, 210, 301, 343, 434, 505, 541) likewise have been proposed for this purpose. Thus, if one determines the plasma concentration (P) of the agent (*i.e.*, inulin) in mg./cc. and the total amount excreted per minute (UV) (where U = urinary concentration in mg./cc. and V = urine volume/min.), the expression of the amount of

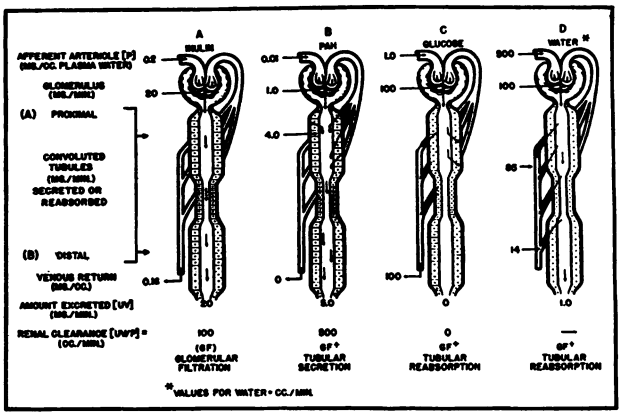


FIG. 1. A DIAGRAMMATIC REPRESENTATION OF THE NEPHRON

Its relation to (A) the glomerular filtration of inulin; (B) the tubular secretion of p-aminohippurate (PAH); (C) the reabsorption of glucose at low filtration loads; and (D) the reabsorption of water. Redrawn from Beyer: Pharmacological Basis of Penicillin Therapy, Charles C. Thomas, Springfield, Ill., 1950.

inulin excreted per unit time as a function of its plasma concentration (UV/P) is equivalent to the amount of plasma water that must have been filtered (*e.g.*, 100 cc./min. in example A, figure 1). This relationship of the total amount of a compound excreted per minute, UV, to its plasma concentration, P, is the basis of the concept of *renal clearance* (20, 153, 274, 290, 291, 354, 367, 428), and is illustrated for inulin in example A of figure 1.

Tubular secretion involves the active participation of the renal tubules in the elimination of a compound, in addition to the amount filtered at the glomerulus. Para-aminohippurate (PAH) is filtered by the glomeruli and is secreted by the tubules (89, 105, 153, 177, 212, 503). It is not bound to plasma protein, at least in the dog (34, 378). The avidity of PAH for its renal transport mechanism is so great that for practical purposes it may be considered to be extracted almost completely at low concentrations from the blood stream by the proximal tubules (79, 105, 212, 220, 229, 291, 369, 465, 466, 554). This is illustrated in example B, figure 1, in which the difference between the Arterial and the Venous concentration ((A-

V)/A × 100) indicates that extraction from the blood stream was complete (100%). In example B, figure 1, the clearance (UV/P) of PAH = 500 cc. Since extraction of the agent from the blood stream is essentially complete, it may be concluded for present purposes that *the clearance of PAH approximates the functional or effective renal plasma flow* (RPF). Clinically, clearance values are expressed in terms of a body surface area of 1.73 sq. M. Diodrast, like PAH, is secreted by the tubules and is suitable for the measurement of RPF (102, 103, 118, 212-214, 259, 289, 369, 503, 504).

Active tubular reabsorption involves the participation of the renal tubules in the extraction of a substance from the glomerular filtrate and its transfer from the lumen of the tubule to the blood stream. This may be illustrated classically by the almost complete reabsorption of filtered glucose and its almost complete normal absence from the urine (example C, figure 1).

Other useful terms may be derived from the data in figure 1. Examples A and B of that figure will serve this purpose.

Clearance ratio (*CR*) is the term given to the ratio of the clearance of one compound to that of another. Conventionally, if one of the two compounds measures glomerular filtration rate, the ratio is expressed with reference to it. For example, the clearance ratio of PAH/Inulin is 5.0 in figure 1, B. Depending on the agent studied, a clearance ratio may be greater than, less than or equal to 1.0, when the reference compound measures glomerular filtration rate. As the plasma concentration of a drug increases its clearance ratio may decrease, increase or remain constant. This will be discussed in more detail in the section on the *Interrelationship of Functional Units*.

Filtration Fraction (*FF*) is literally the fraction of the renal plasma flow that is filtered at the glomeruli. Since PAH clearance approximates renal plasma flow (figure 1, B) and inulin clearance equals glomerular filtration rate (figure 1, A), then inulin clearance/PAH clearance = GF/RPF = 100/500 (cc./min.) = 0.20. This figure of 0.20 (or more precisely 0.19) is that ascribed to the filtration fraction for man (212, 213). In the dog and the rabbit the filtration fraction is more nearly 0.30 (188, 446). This term applies only to the relationship of glomerular filtration to renal plasma flow. It is apt to be increased by afferent glomerular arteriolar dilatation or efferent vasoconstriction. It is said to be decreased by afferent arteriolar constriction or efferent arteriolar dilatation (103, 284, 287, 288, 326, 335, 425, 433, 435, 496).

Extraction (*E*), or *percentage extraction*, pertains to the difference between the renal arterial and venous blood, caused by the extraction of a drug by the kidney. The amount extracted is expressed as a fraction or a percentage of its arterial concentration. In the case of inulin (figure 1, A), its extraction (A-V)/A equals 0.20-0.16/.20 = 0.04/.20 = 0.20. The percentage extraction equals 0.20 × 100 or 20. If a compound measures glomerular filtration rate by clearance procedures and does not diffuse from blood cells into plasma, the fraction extracted from the blood stream must equal the filtration fraction or E = FF (379).

Extraction ratio (*ER*) is generally used to express the extraction of one compound in terms of that of a second substance, the clearance of which equals glomerular filtration rate. The extraction ratio for PAH may be calculated from the data in figure 1, B and A as follows: For PAH, E = (0.01 − 0)/0.01 = 1.0. The extraction of inulin, E = (0.2 − 0.16)/0.2 = 0.2. Then the extraction ratio, ER = E_{PAH}/E_{Inulin} or 1.0/0.2 = 5.0. In other strictly defined circumstances, as in this example, the extraction ratio should equal the clearance ratio, ER = CR. This is of value when one wishes to cross-check conventional clearance experiments by determining the over-all amount that left the renal blood stream. One should refer to other sources (184, 338, 379, 426, 490, 540, 541, 543) for more detailed and precise presentations of this general subject. In practice, this relationship for a given compound may be complicated by such factors as back diffusion, metabolism, adsorption on or absorption by the constituents of blood and a shift in these associations within the kidney.

The amount of water filtered at the glomeruli (figure 1, D) and reabsorbed by the tubules is not determined directly in conventional experiments. However, its filtration rate is equiva-

lent to the clearance of inulin, as discussed in a previous paragraph. The amount reabsorbed by the tubules is the difference between the glomerular filtration rate for inulin (figure 1, A) and the volume of urine eliminated per minute (V). Most of the water is reabsorbed by the proximal convoluted tubule, although a smaller amount is returned to the blood stream by the lower portion of the nephron (398, 483, 501, 548, 551, 566).

INTER-RELATIONSHIP OF FUNCTIONAL UNITS

The clearance of a compound that measures glomerular filtration does not vary with its plasma concentration or urine flow, as a generalization. From the previous discussion it follows that the extraction, E, of a compound, remains constant during changes in plasma concentration and urine flow, subject to the same limitations as obtain for clearance. For this relationship to exist, it follows that there is a linear relationship between plasma concentration and the amount filtered. This generalization (13, 57, 58, 86, 147, 175, 252, 354, 481, 502, 505, 538, 567) is valid only if adequate hydration is assured, if the concentration of the compound is not sufficient to alter renal blood flow or the permeability of the glomerular membranes, if the agent is not metabolized rapidly, if there is no contribution of presumably bound drug to glomerular filtration, and if there is no passive back diffusion of the chemical. It is not necessary to dwell on these limitations since there are satisfactory agents available for the measurement in question.

The clearance of a compound that is secreted by the renal tubules decreases, with increase in plasma concentration, to approach glomerular filtration rate as a limit, but it does not necessarily change with alterations in urine flow. This generalization is illustrated in figure 2, chart 1. However, it should be pointed out that a decrease in clearance with increase in plasma concentration may not be considered *a priori* evidence for the tubular secretion of a compound, in the absence of evidence that its extraction ratio and its clearance ratio exceed 1.0. Smith and his associates were among the first to demonstrate the above generalization of self-depression (504). This holds for such diverse agents as PAH, the pyridones and phenol red (215, 259, 260, 336, 378, 478, 490), exogenous creatinine in man (477), penicillin (14), and N^1-methylnicotinamide (39, 40), which represent compounds secreted by at least two distinct tubular secretory mechanisms.

The decrease in clearance of PAH with increase in plasma concentration is due to a progressive reduction in the percentage of drug that is extracted from the blood stream and is secreted by the tubules. Chart 2 of figure 2 illustrates that the amount filtered (F) increases in a linear manner over the whole range of PAH plasma concentrations. The absolute amount of drug secreted by the tubules (T) increases as the plasma concentration is raised until the secretory capacity of the cells is saturated (Tm). Beyond that point there is no increase in tubular secretion with increase in plasma concentration. Consequently, as one exceeds the Tm or tubular secretory capacity for a compound, the increase in the urinary elimination (UV) of the drug as the plasma concentration is elevated is determined by its rate of filtration (figure 2, chart 2).

Chart 3 of figure 2 illustrates that the percentage of PAH extracted by the tubules (T) falls off more rapidly than the total reduction in urinary elimination, with increase in the plasma concentration of the drug. The percentage of the total amount which is contributed by filtration (F) rises under these conditions. Beyond the point where the secretory capacity of the tubules is exceeded (Tm), the percentage of the total amount of drug eliminated that is extracted by the tubules decreases rapidly, and the percentage contributed by filtration increases correspondingly. The over-all percentage of drug extracted from the blood stream (E) falls with the decrease in the percentage extracted by the tubules, since it is at all times equal to the sum of the percentage of the drug extracted by the combination of tubular secretion and glomerular filtration.

As the plasma concentration of a compound which is actively reabsorbed by the tubules is increased, the clearance remains essentially zero until the reabsorptive capacity is exceeded. Beyond that point the clearance increases with rising plasma concentration (or, *more correctly*,

the amount filtered) to approach the difference between glomerular filtration rate and reabsorptive capacity as a limit. This principle was illustrated for glucose reabsorption by Shannon (484, 485) and has been shown to obtain for certain amino acids (51, 156, 157, 211, 391, 458, 587) ascorbic acid (460, 491), and certain electrolytes. However, no such clear-cut relationship exists for many other compounds that are reabsorbed by the renal tubules.

The several relationships between plasma concentration, or the amount filtered, and the

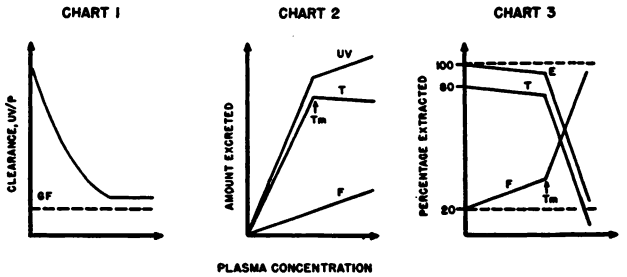


FIG. 2. CHARACTERISTICS OF A COMPOUND SECRETED BY THE RENAL TUBULES

Chart 1 illustrates that, as the plasma concentration of a compound secreted by the renal tubules is increased, there is a self-depression of its over-all clearance to approach glomerular filtration as a limit, but to exceed that limit by the increment of the UV value contributed by tubular secretion.

Chart 2 illustrates that, as the plasma concentration of a compound secreted by the tubules increases, the amount filtered (F) increases linearly. The amount secreted by the renal tubules (T) increases progressively until the capacity for secretion (Tm) is reached, beyond which point no additional secretion takes place as the plasma concentration is elevated. The total amount of the compound excreted per unit time (UV) increases as the sum of the amount filtered and the amount secreted by the tubules, to the limit of the functional capacity of the tubules (Tm). Beyond that point the amount of compound excreted, as the plasma concentration is increased, progresses as a linear function of the amount filtered per unit time.

Chart 3. As the plasma concentration of a compound secreted by the renal tubules increases, the percentage of the material extracted by the renal tubules (T) decreases and the percentage contributed by filtration (F) increases. Beyond the limit of the functional capacity of the tubules (Tm), the percentage extraction contributed by filtration increases rapidly as the plasma concentration rises and the percentage contributed by tubular secretion decreases commensurately. The overall extraction of the compound (E) decreases slowly at first, with increasing plasma concentration. Beyond the Tm for tubular secretion, the percentage extraction decreases rapidly to approach the percentage extracted by the glomeruli as a limit, but to remain in excess thereof by the increment contributed by tubular secretion.

elimination of compounds reabsorbed by the tubules are illustrated in figure 3. As shown in chart 1, figure 3, the excretion of glucose (UV) is negligible until its maximal rate of reabsorption (Tm) is exceeded. Beyond that point the rate of excretion parallels the rate of filtration (GF) and differs from it in magnitude by the amount of drug reabsorbed by the tubules.

The over-all extraction (E, chart 2, figure 3) of such a compound from the renal blood

stream is not demonstrable until the plasma concentration is increased sufficiently so that the amount filtered and presented to the tubules exceeds their reabsorptive capacity (Tm) for it. Thereafter, the over-all percentage extraction (E) of the compound increases as its plasma concentration is elevated. So long as reabsorption is not impaired the percentage extraction (E) of a compound like glucose can approach but cannot equal that of inulin (GF) at any non-toxic blood level.

Beyond the capacity (Tm) of the tubules to reabsorb a compound like glucose, its clearance increases to approach glomerular filtration rate (GF) as the plasma concentration is elevated. The same limitations obtain here as for the extraction of the compound and are illustrated in figure 3, chart 3.

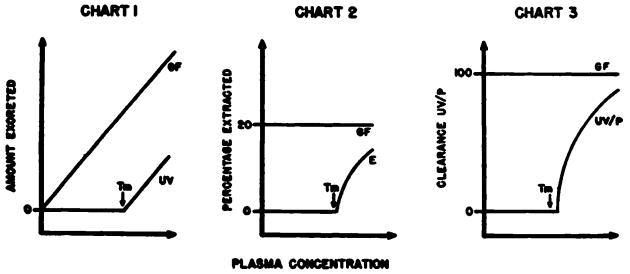


FIG. 3. CHARACTERISTICS OF A COMPOUND REABSORBED BY THE RENAL TUBULES

Chart 1 illustrates that, as the plasma concentration of such a compound increases, the amount filtered by the glomeruli (GF) increases in a linear manner. The amount of the compound which appears in the urine per unit time (UV) is negligible until the reabsorptive capacity of the tubules (Tm) is exceeded. Beyond the Tm, the amount which appears in the urine per unit time is a linear function of the amount filtered at the glomeruli.

Chart 2 illustrates that as the plasma concentration increases there is a negligible over-all difference between the amount of the compound which appears in renal arterial and renal venous blood. Beyond the tubular reabsorptive capacity (Tm) the over-all percentage extraction of the compound rises to approach the filtration fraction (percentage extraction of creatinine or inulin) as a limit, but remains less than that value by the increment reabsorbed by the tubules.

Chart 3. As the plasma concentration of such a compound increases, its clearance remains undeterminable until its tubular reabsorptive capacity (Tm) is exceeded. Beyond that point the clearance of the compound increases to approach glomerular filtration rate (GF) as a limit. Both the clearance and the percentage extraction of the compound remain less than their limiting values (GF) by the increment contributed by tubular reabsorption.

A three-component system for the filtration, secretion and reabsorption of a compound has been proposed. Barclay, Cooke and Kenny (8, 9) have discussed the theoretical excretion (clearance) pattern of such an agent. They theorize that at low plasma levels the clearance of such a compound may be considerably less than the glomerular filtration rate due to its reabsorption. As the plasma concentration of the agent is increased its clearance rises, as is characteristic of compounds that have a maximal reabsorptive capacity, to approach GF. Apparently as the plasma concentration of the drug is elevated progressively an element of tubular secretion becomes evident, for the clearance value may exceed GF to a considerable

extent. At still higher concentrations the "self-depression" of tubular secretion causes the clearance to fall toward or actually below GF, depending on the balance of the tubular reabsorptive and secretory capacities for the agent.

Barclay and his associates cite a number of examples of compounds that they believe to fulfill these requisites. Unfortunately, they have elected to recalculate and reinterpret the data of others on the clearance of urea (166, 316, 479, 481), sulfathiazole, sulfamethylthiodiazole, p-amino-benzoic acid and acetylsulfathiazole (18, 299, 312) to support the three-component thesis. To this they have added their own data on phosphate excretion (10). One could wish for examples that are less equivocal. The concept is attractive and it deserves critical investigation in other laboratories to establish its real merit. At present, the excretion of potassium by a three-component system of filtration, reabsorption and (at high levels) secretion is the most likely example but it does not fulfill all the limitations of the hypothesis (22, 271, 294, 318, 358-360, 371).

The functional capacity of the tubules to reabsorb or secrete a compound differs from one transport system to another and for any two compounds that are handled by the same mechanism. This can be illustrated by the Tm values for PAH, penicillin and diodrast which are secreted by the same tubular mechanism, for arginine and lysine which are reabsorbed by a common mechanism, and for the reabsorption of glucose by a separate mechanism (14, 51, 88, 212, 446, 484, 587).

The individual values for the functional capacity of the tubules to secrete or reabsorb a given compound are reproducible for a given animal, an animal species or a population of normal individuals within a species. Thus they are suitable as measurements of renal tubular function, just as creatinine and inulin are used for measuring the glomerular filtration rates of the dog and man, respectively.

Such measurements are generally regarded as *stress tests*, wherein they apply to the estimation of renal tubular function (212, 213, 259, 260, 290, 291, 417, 497, 500, 502, 504). Usually the value is referred to as the Tm of the compound, and is expressed in mg./min.

The measurement of a tubular secretory or reabsorptive capacity, as for PAH, or glucose, consists of the simultaneous measurement of glomerular filtration rate (GF) and the clearance of the compound at a high plasma concentration. The amount of PAH or glucose filtered per minute = the plasma concentration (in mg./cc.) times the glomerular filtration rate (in cc./min.). The difference between the amount of PAH excreted (UV) per minute and the amount filtered (P·GF) per minute [UV-(P·GF)] = the amount secreted per minute, PAH_{Tm}. The calculation of glucose Tm is simply the difference between the amount filtered (P·GF) and that which is excreted (UV) in the urine per minute, [(P·GF)-UV].

In principle, the measurement of the functional capacity of a renal transport mechanism is identical with that for the assay of an enzyme in terms of its function. Indeed, one can measure a single component of a complex system of enzymes simply by supplying an excess of its substrate and measuring the maximal rate of the reaction under conditions where the other components of the system are not limiting factors. The general subject of the relationship of enzymes to substrates for assay purposes has been discussed in some detail by Potter and his associates (150, 404, 406–410) and by others (455, 535, 536).

It is the opinion of the reviewer that in the measurement of a tubular functional capacity one simply defines the rate of reaction of the limiting component of a complex enzymatic process in terms of the amount of the substance that can be "transported" per unit time. This parallelism between the behavior of a renal tubular transport mechanism and a single component of an enzyme system will be shown to obtain for many of the properties of both.

FUNCTIONAL CHARACTERISTICS OF TUBULAR TRANSPORT SYSTEMS

The inhibition or stimulation of tubular secretory or reabsorptive processes will be discussed under the following seven headings:

1. Competition between two compounds for secretion by a common transport mechanism.
2. Competitive inhibition of a transport mechanism by a compound which is not secreted by that mechanism.
3. Inhibition by competition between systems for a common source of energy.
4. Inhibition of the phosphorylation mechanisms essential for secretion.
5. Alteration of the endocrinologic control of a secretory or reabsorptive function.
6. Inhibition of ion exchange mechanisms for electrolyte reabsorption.
7. Inhibition of respiratory systems essential for the over-all metabolism or viability of the cell.

1. *The competition of two or more compounds for secretion or reabsorption by the same transport mechanism* is the best known of these several inhibitory phenomena. It has been documented adequately by Smith (504), Shannon (480), and others (38, 47, 48, 122, 415). This type of competition is analogous to that which occurs between two compounds for oxidation by the same enzyme or enzyme system. For present purposes the concept will be presented in parallel for an enzyme system (figure 4) and for two renal transport systems (figure 5).

In either instance, when two compounds are presented for secretion (or oxidation), there is a mutual suppression of the rate at which either agent is handled, although the total amount of material secreted (or oxidized) may increase within the functional capacity of the system. The extent of depression of the secretion (or oxidation) of one substrate by another is inversely related to the amount (load) of each that is presented to the system, as influenced by their affinities for the common mechanism. In other words, the more important factors that are equated into the extent of such a competitive inhibition are: 1) the relative amounts of the substances presented to the system for secretion (or oxidation), and 2) the affinity of each substance for the secretory (or oxidative) process. The resultant of these factors in each instance determines the extent to which the system is "saturated" with either agent, thus limiting the amount of each that is secreted (or oxidized) per unit time. The term "saturation" as used herein bears the connotation of at least a two-component factor as it relates to a single substrate: 1) concentration, and 2) affinity.

Inhibition in this sense, then, is actually one of mass competition for secretion or oxidation and does not implicate any functional alteration of the transport mechanism per se. Under these circumstances there actually is not necessarily any real impairment of any renal function. Since there need be no alteration of function *per se*, it follows that the onset, extent and reversibility of the inhibition of secretion of one compound by another are determined by the relative saturation of the system with the two substrates. Onset of inhibition is as rapid as is the distribution of the inhibitor; extent of inhibition depends on the relative saturation of the system by the two substrates; and reversibility of the effect is de-

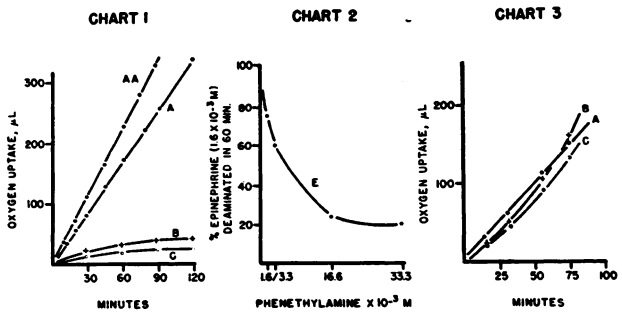


FIG. 4. ENZYMATIC CHARACTERISTICS OF THE COMPETITION BETWEEN TWO NATURAL SUBSTRATES FOR THE AMINE OXIDASE SYSTEM

Chart 1 illustrates the rate of oxidation of 0.0166 M epinephrine (A, AA). It may be seen that the amount of enzyme limits the rate of reaction since its concentration in the experiment illustrated by Curve AA is twice that present in the experiment represented by Curve A. Curve C represents the rate of oxidative deamination of 0.0166 M β-phenethylamine. Curve B represents the rate of oxidation of 0.0166 M epinephrine plus 0.0166 M β-phenethylamine in combination, and in the presence of the same amount of enzyme as was used in the experiments represented by Curves A and C.

Chart 2 represents the depression of the rate of oxidative deamination of epinephrine by increasing concentrations of β-phenethylamine.

Chart 3 represents the reversibility of the competitive inhibition of oxidation of epinephrine by β-phenethylamine (see text).

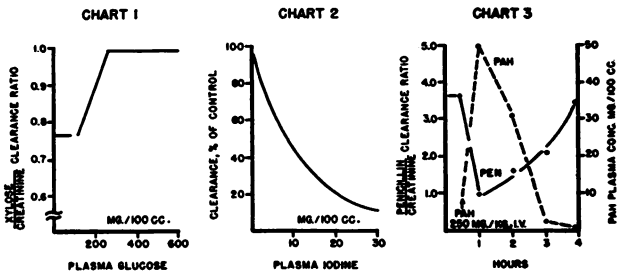


FIG. 5. ILLUSTRATING THE COMPETITION OF REABSORPTION OR SECRETION BETWEEN TWO COMPOUNDS THAT ARE HANDLED BY THE SAME TUBULAR TRANSPORT MECHANISM IN EITHER INSTANCE

Chart 1 illustrates the competitive inhibition of xylose tubular reabsorption by increasing plasma concentration of glucose. It may be seen that the reabsorption of xylose is depressed to the point that its clearance ratio approaches 1.0, indicating that very little of the compound is reabsorbed by the renal tubules under these conditions. Data of Shannon: Am. J. Physiol. **122**: 775, 1938.

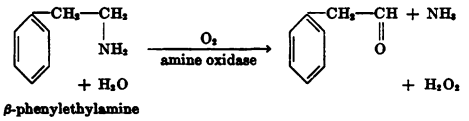
Chart 2 illustrates the depression of phenol red secretion by the renal tubules as the plasma iodine concentration of diodrast is elevated. Data of Smith, Goldring and Chasis: J. Clin. Invest. **17**: 263, 1938.

Chart 3 illustrates the reversibility of the depression of penicillin secretion by the renal tubules as the plasma concentration of p-aminohippurate (PAH) decreases.

termined by the rate at which the inhibitory agent is eliminated by excretion or metabolism. Moreover, when the system is saturated "completely"[1] by one compound, inhibition of transport of the other is "complete".[1] Therefore, a further increase in the load of the inhibitory agent is without additional effect. Finally, it should be understood that this type of inhibition holds only if two compounds are secreted, reabsorbed or oxidized by the same system. There is no cross-inhibition in the true sense of this term between compounds secreted, reabsorbed or oxidized by essentially different systems (39, 40, 51, 510–512).

Mass competition for transport (or inactivation) of this type and the several dependent properties recited above may be illustrated for tubular secretion and reabsorption, or for the oxidative deamination of dihydric-β-phenylethylamines. Perhaps it would be appropriate to present first the principles of competition between substrates for enzymatic oxidation and then to point out the similarity of these concepts to those for competition between agents for secretion or reabsorption by the kidney.

The enzyme system selected for the experiments illustrated in figure 4 has been named amine oxidase or monamine oxidase since it activates the oxidative deamination of a number of β-phenylethylamines according to the following general equation:



β-phenylethylamine

The characteristics of the system have been described in some detail elsewhere (2, 29, 36, 52, 222, 236, 239, 411, 518).

Chart 1 of figure 4 illustrates the character of the reaction involved in the oxidative deamination of epinephrine [N-methyl-β-(3,4 dihydroxyphenyl)-β-hydroxyethylamine (A and AA)], and β-phenylethylamine [phenethylamine (C)], and equimolar additions of the two amines (B), as recorded by the oxygen uptake of the system (28). It may be seen that when epinephrine and phenethylamine are combined in equimolar concentration (B) their additive rate of oxidation is intermediate between the rates of oxidation of the two agents presented individually to the system. Actually, the molar concentration of the two amines in combination (B) is twice that of either amine represented by curves A, AA and C. Since the concentration of the amines alone or in combination is sufficient to saturate the system (curves A and C), the amount of enzyme present limits the over-all rate of reaction.

This was demonstrated in a second manner, for when the amount of enzyme, to which the same amount of epinephrine was added, was twice (curve AA) that contained in the other vessel (A) it may be seen that the rate of oxidation of epinephrine was considerably increased, as compared to curve A. Thus the individual rate of oxidation is determined by the affinity of the amine for the system. The rate of reaction of the combination of amines reflects both their affinities for the system, when the amount of enzyme present is the limiting factor.

[1] The reason for qualifying the word "complete" is that theoretically this inhibition, like all the others mentioned herein that do not involve destruction of tissue, literally cannot be complete, although for practical purposes the increment by which the depression is not complete may lie within the analytical limitations of the methods employed.

Chart 2 of figure 4 demonstrates the inhibitory effect of increasing molar concentrations of phenethylamine on the rate of oxidative deamination of epinephrine. It may be seen that as the amount of phenethylamine is increased, deamination of epinephrine is depressed throughout the range of concentrations studied. The amount of epinephrine remaining at the end of 90 minutes was calculated from the O_2 uptake and was cross-checked by a colorimetric method which is specific for catecholethylamines (45).

The reversibility of the inhibition by phenethylamine was demonstrated in the following experiment. Epinephrine, phenethylamine and a combination of the two were added to amine oxidase preparations at a substrate final concentration of 0.0166 M in each instance, whether alone or in combination (0.0332 M total concentration in the latter instance). After an incubation period of one hour in an experiment analogous to that represented by chart 1, figure 4, the enzyme suspension was removed from the flasks, washed free of amine substrate and returned to clean vessels. The system was reconstituted, epinephrine was added to each flask in a final concentration of 0.0166 M and its rate of oxidation was recorded as represented in chart 3 of figure 7.

It may be seen that the enzyme survives these drastic conditions very well and that there is no residual effects that can be ascribed specifically to the phenethylamine. Thus it may be concluded that the inhibition of epinephrine oxidation by phenethylamine is a reversible reaction.

Figure 5 summarizes the analogous renal characteristics for competition between two compounds that are secreted (p-aminohippurate and penicillin, or phenol red and Diodrast) *and two that are reabsorbed* (glucose and xylose) *by the same transport mechanism in the particular instances.* Both glucose and xylose are reabsorbed by the same tubular mechanism (480). Consequently, they compete for reabsorption, as is illustrated in chart 1 of figure 5. Here it is shown that if the plasma concentration or the amount of xylose filtered remains relatively constant its reabsorption is decreased progressively as the plasma level of glucose, hence the amount filtered and presented for reabsorption, is elevated. As the reabsorption of xylose becomes decreased its clearance increases to approach that of creatinine. Under these conditions the xylose/creatinine clearance ratio approaches 1.0 as a limit.

Chart 2 of figure 5 illustrates the depression of phenol red secretion by diodrast (407). This is indicated by the progressive decrease in the phenol red clearance, expressed as per cent of its control value, as the plasma concentration of diodrast (iodine) is elevated.

Chart 3 of figure 5 illustrates the rapid onset and the reversibility of the PAH inhibition of penicillin secretion by the tubules. The depression of penicillin secretion is indicated by the decrease in the penicillin/creatinine clearance ratio. Insofar as can be determined, the onset of the PAH inhibition is immediate, the inhibition is maximal at a critical concentration of the inhibitor, and the reversibility of the inhibition is related to the rate at which PAH is eliminated from the body, as indicated by its falling plasma concentrations. These characteristics of the PAH-penicillin competition have been established in the laboratory (47) and confirmed in the clinic (32).

There are at least two tubular mechanisms for the reabsorption of amino acids (51, 587). This has been demonstrated by the competition of pairs of essential amino acids for reabsorption when administered simultaneously in large amounts.

One reabsorptive mechanism appears to be concerned with the basic amino acids. Competition for reabsorption could be demonstrated for arginine, histidine and lysine.

A second transport system is responsible for the reabsorption of monoaminomonocarboxylic acids, leucine and isoleucine. There is no cross-competition between the two different groups of amino acids.

A third mechanism may be concerned with glycine transport, since it was not possible in these experiments to demonstrate that its administration in large amounts interfered with the tubular reabsorption of amino acids of either of the above groups. Perhaps the data on which these interpretations rest are the more reliable since specific microbiological assays were employed for the estimation of the essential amino acids. Previously the nonspecific α-amino nitrogen analysis was the basis for the estimation of amino acid clearances or Tm (156, 211, 391).

This principle of competition for tubular secretion was made use of in the early days of the penicillin therapy of subacute bacterial endocarditis. Diodrast (415) and especially p-aminohippurate (32, 38, 47, 50) have been employed to increase the plasma concentration of penicillin by decreasing its secretion by the renal tubules. Because of the poor gastrointestinal absorption of PAH and its rapid excretion it was necessary to administer it in daily dosages of 100 to 200 grams by venoclysis (5, 31, 32, 306, 307, 351). Even at this tremendous dosage PAH did not interfere with other clinically measurable renal functions, in substantiation of laboratory studies relative to its pharmacologic (34) and toxicologic effects.

2. *Competitive inhibition of a transport mechanism by a compound that is not secreted by that system* is a relatively new concept in renal physiology, but its enzymologic counterpart has been recognized for some time. In both instances, which may be treated as one, the inhibitor is sufficiently related to compounds secreted (or oxidized) by the system that it has an affinity for the definitive component of the reaction process. However, the inhibitor is sufficiently different so that it is not secreted (or oxidized) by the mechanism involved. In other words, the compound has an affinity for, but it is refractory to, the action of the system (30, 35, 43, 268, 326–328).

Such a refractory compound can inhibit the secretion or oxidation of a natural substrate (*i.e.*, one which is secreted or oxidized, as the case may be). The completeness of the inhibition depends on the extent to which the system is saturated with the refractory agent. The saturation is the summation of the concentration and affinity of the inhibitor as compared to that of the natural substrate. In this instance, the refractory compound "blocks" secretion by displacing the normally secreted agent from the definitive component of the mechanism.

If a refractory compound displaces a natural substrate from a reaction there need not be any impairment of the reaction mechanism per se or of any other closely related system. It is important to understand this *displacement* aspect of the inhibition for it implies no essential alteration of function so far as the mechanism itself is concerned. Consequently, the onset, extent and reversibility of the inhibition are determined by the rate at which saturation of the system is at-

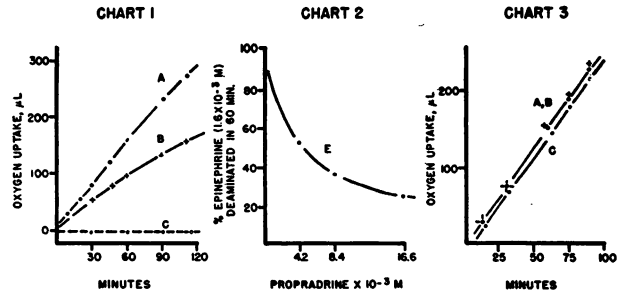


FIG. 6. DEMONSTRATING THE ENZYMATIC PRINCIPLES OF THE COMPETITION BETWEEN A NATURAL (EPINEPHRINE, A) AND A REFRACTORY (PROPADRINE, C) SUBSTRATE FOR THE AMINE OXIDASE SYSTEM

Chart 1 illustrates the rate of oxidative deamination of 0.0166 M epinephrine. Curve C illustrates the lack of oxidation of Propadrine, and Curve B illustrates the competitive inhibition of 0.0166 M epinephrine by 0.0166 M Propadrine.

Chart 2 illustrates that, as the concentration of Propadrine in combination with epinephrine is increased, the rate of oxidative deamination of the natural substrate (E) is depressed.

Chart 3 illustrates the reversibility of the inhibition of epinephrine deamination by the refractory substrate (see text).

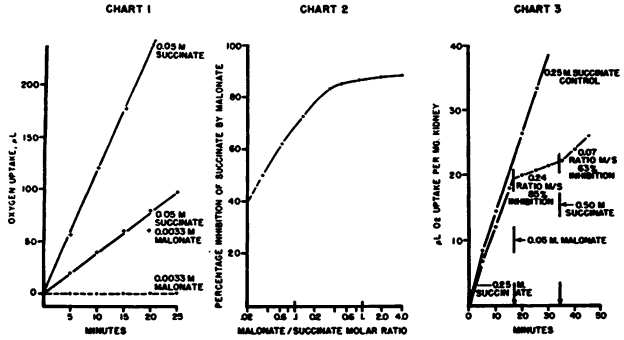


FIG. 7. THE COMPETITIVE INHIBITION OF SUCCINATE OXIDATION BY MALONATE

Chart 1 illustrates that whereas succinate is oxidized at a very rapid rate malonate is refractory to oxidation by the succinoxidase system. When succinate is presented with malonate to that system the rate of oxidation of the former substrate is markedly depressed.

Chart 2 illustrates the percentage inhibition of succinate oxidation by increasing malonate/succinate molar ratios.

Chart 3 illustrates the reversibility of the inhibition of succinate oxidation by malonate. It may be seen that, when 0.05 M malonate was added from the side arm into the reaction chamber of the vessel containing 0.25 M succinate plus the succinoxidase system, there was an 85% inhibition of the rate of oxidation of the natural substrate. When an additional 0.5 M succinate was added from the other side arm of the flask, the inhibition induced by malonate was reversed in agreement with the decreased malonate/succinate molar ratio but was not overcome completely, since malonate remained as a competitive substrate.

tained, its completeness, and the rate at which the refractory compound is metabolized or excreted. Since the compound must have a structure sufficiently similar to those secreted by the tubules in order to have an affinity for the mechanism concerned, the specificity of its action practically is assured. The characteristics of this displacement type of inhibition has been portrayed for the amine oxidase and the succinoxidase systems, and for the secretion of penicillin in figures 6, 7 and 8, respectively.

β-Phenylisopropanolamine (α-methyl-β-phenylethanolamine, Propadrine), like other α-alkyl-β-phenylethylamines, is refractory to oxidation by amine oxidase (28, 36, 64, 411),

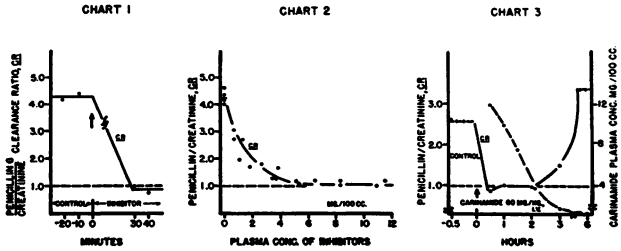


FIG. 8. ILLUSTRATING THE PRINCIPLES OF THE COMPETITIVE INHIBITION OF THE TUBULAR SECRETION OF A NATURAL SUBSTRATE (PENICILLIN) BY COMPOUNDS THAT ARE REFRACTORY TO SECRETION BY THAT MECHANISM

Chart 1 illustrates the rapidity of onset of the inhibition of tubular secretion of penicillin by Benemid. It may be seen that within the period allowed for distribution of the inhibitor the clearance ratio of the penicillin was decreased to or below 1.0, illustrating complete inhibition of its tubular secretion.

Chart 2 illustrates that, as the plasma concentration of a refractory inhibitor is increased, the amount of penicillin secreted by the tubules (as indicated by the penicillin/creatinine clearance ratio) decreases progressively until the clearance ratio is 1.0, indicating complete suppression of tubular secretion. Beyond that point there is no further depression of penicillin excretion by increasing plasma concentrations of the inhibitor. The closed circles represent experiments wherein Benemid was administered to two dogs. The open circles represent experiments wherein carinamide was administered to the same two dogs.

Chart 3 illustrates the reversibility of the inhibition of penicillin secretion by the tubules, as it relates to the falling plasma concentration of a single i.v. dose of carinamide.

as is illustrated by curve C, chart 1 of figure 6. However, it has sufficient affinity for the enzyme system that it can inhibit the rate of oxidation of epinephrine (A) when the two are presented to the enzyme in equimolar concentration (B). If the concentration of epinephrine added to a series of vessels containing the enzyme remains constant and the molarity of Propadrine is increased by definite increments, one can demonstrate the progressive depression of oxidation of the natural substrate (chart 2 of figure 6). The inhibition of epinephrine oxidation by the refractory substrate, Propadrine, is reversible as can be demonstrated by the experiment summarized in chart 3 of figure 6. The initial phase of the experiment was like that represented in chart 1 of figure 6, wherein 0.0062 M epinephrine

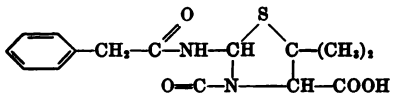
(A), 0.0082 M Propadrine (C), and a mixture of 0.0082 M epinephrine plus 0.0082 M Propadrine (B) were incubated with the amine oxidase for one hour. Thereafter the enzyme suspension was removed from the vessels, it was washed free of the amines and then was reconstituted in clean flasks. Epinephrine (0.0063 M, final concentration) was added to the side arm of each vessel; it was tipped into the reaction chamber after temperature equilibration, and its rate of oxidation was recorded.

From the data in chart 3 of figure 6, it may be seen that the enzyme suspensions to which Propadrine was added alone (C) or in combination (B) were as active after the removal of the amines as that which had been subjected to its natural substrate alone (A), within the limits of reproducibility of the method. The fact that the rate of oxidation of epinephrine in this experiment (chart 3) agrees so satisfactorily with that represented in curve A of chart 1 indicates that the over-all manipulations of the enzyme did not notably alter it.

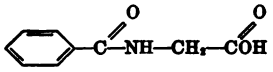
Similarly, it can be shown that whereas malonate is refractory to oxidation by the succinoxidase system, it does materially decrease the rate of oxidation of succinate when the two are added to the enzyme system simultaneously (31, 268; 412, 413) (chart 1 of figure 7). Moreover, the percentage inhibition of the oxidation by succinoxidase is determined by the molar ratio at which they are presented to the enzyme system (chart 2 of figure 7). Finally, the reversibility of this inhibition of succinate by malonate is presented in a manner that illustrates the ability of one substrate to displace the other from the enzyme system, as in chart 3 of figure 7. It is shown therein that the inhibition of succinate oxidation by malonate and the reversibility of that effect can be altered at will during a continuous experiment by adjusting the molar ratios of the two compounds so as to change the relative saturation of the system by the substrates.

The rapidity of onset, the relation of concentration of the inhibitor to its effect and the correlation of the elimination of the agent with the reversibility of the suppression of penicillin secretion by the tubules are presented in figure 8. Since carinamide (30, 35, 43) and Benemid[3], p-(di-n-propylsulfamyl)-benzoic acid (41, 48, 345, 532), are used here to illustrate the renal characteristics of competitive inhibition by displacement of a natural substrate by a refractory one, their chemical structures may be presented along with those of penicillin-G and p-aminohippurate, as follows:

"Natural" Substrates



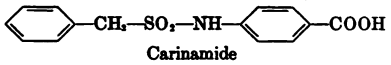
Penicillin-G



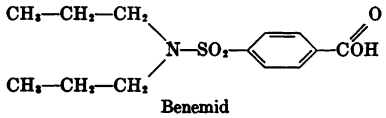
p-aminohippurate

[3] Benemid is the trademark that has been applied to p-(di-n-propyl-sulfamyl)-benzoic acid by Sharp and Dohme, Inc.

"Refractory" Substrates



Carinamide



Benemid

The rapidity of action of such a refractory substrate is illustrated by the effect of Benemid on the renal tubular secretion of penicillin, as represented by the depression of the penicillin/creatinine clearance ratio in chart 1 of figure 8. Complete inhibition of penicillin secretion occurs within the period of time allowed for the distribution of the agent. The decrease in penicillin/creatinine clearance ratio to less than 1.0 represents the effect of plasma binding of the antibiotic agent (132) on its glomerular filtration, in such a short term experiment.

When the concentration of penicillin is held fairly constant, it can be shown that as the plasma concentration of the refractory substrate is raised the tubular secretion of the antibiotic agent decreases progressively until its clearance is equivalent to that of creatinine (CR = 1.0) (chart 2, figure 8). Beyond that point there is no further depression of penicillin clearance regardless of the concentration of the refractory substrate, illustrating that its effect is on the tubular secretion of penicillin, not on its glomerular filtration. The fact that the penicillin/creatinine clearance ratio does not fall below 1.0 in these experiments is presumptive evidence that over a period of time the refractory substrate can displace penicillin from its binding to plasma protein. This may be analogous to the displacement of phenol red from its combination with plasma protein by diodrast or hippuran, thus increasing the free and filterable form of the dye, as was observed by Smith (506).

The reversibility of the action of the refractory substrate on the tubular secretion of penicillin is illustrated in chart 3 of figure 8. Carinamide has been selected for this demonstration for convenience, since it is eliminated much more rapidly than Benemid. By determining the penicillin/creatinine clearance ratio before and following a single large intravenous injection of carinamide, the inhibition of penicillin secretion can be demonstrated to diminish as the plasma concentration of the drug decreases, and to return to normal when carinamide no longer can be determined in the blood stream.

Here again one sees the effect of plasma binding on the depression of the penicillin/creatinine clearance ratio within an hour after carinamide was given. Over the course of time, penicillin was displaced from the protein and its clearance ratio rose to 1.0 and remained there until the plasma concentration of carinamide fell to a low level.

The apparent intestinal absorption and the maintenance of blood level of these

compounds reflect principally their rates of metabolism and excretion, since they are well absorbed and are distributed to a similar extent in the body. The tremendous differences that metabolism and excretion make in the appearance of the plasma curves of carinamide and Benemid may be illustrated by feeding equivalent amounts of the two drugs to patients or dogs. For example, if 60 mg. of carinamide/kilo of body weight is fed to a dog the maximal concentration of the drug may be expected to approximate 6 to 8 mg./100 cc., and a determinable amount may be expected to persist therein for about 4 hours. Following oral administration of the same per kilo dosage, the peak Benemid plasma concentration is 18 to 20 mg./100 cc. A determinable plasma concentration of the drug persists for well over 48 hours.

The carinamide/creatinine clearance ratio in the dog varies between 0.2 and 0.9, depending on its plasma concentration (44, 46, 379). However, the compound is so rapidly metabolized (46, 531) that the slope of its falling plasma concentration curve approximates that of mannitol (46), which in turn is determined by the glomerular filtration rate, at least conservatively (108, 149, 153, 167, 367, 505). The reabsorption of Benemid (48, 532) by the renal tubules is so great that the concentration of drug in the urine is insufficient for the measurement of renal clearance. This has been confirmed by renal arterial-venous extraction technics in the dog wherein any difference between those two plasma concentrations is well within the error of the methods. Although it is known that a metabolite of Benemid is excreted slowly, its rate of metabolism is so slow that the drug persists in the blood stream for as long as two days following a single oral dose administered to dogs (48, 321, 532).

The ability of compounds to inhibit differentially the mechanism for the tubular secretion of penicillin, phenol red, the hippurates and the pyridones is not related to their general toxicity, either between or within series of compounds. This lack of correlation between toxicity and ability to inhibit the tubular secretion of penicillin by the dog is illustrated in figure 9 for a series of related compounds. Here it may be seen that the toxicity increases (i.v. LD_{50} decreases) as the length of the alkyl chain is increased from C_2 to C_8. However, optimal inhibitory activity, as it relates to the tubular secretion of penicillin by the dog, is resident in the C_4-R structure within this series and decreases as the length of the chain is lengthened or shortened (37).

The competitive inhibition of secretion of a natural substrate by a refractory compound of this class has been shown to be a constant function that is independent of the molar concentration of the natural substrate (37). This has been demonstrated to obtain for the secretion of phenol red by frog or guinea pig renal cortex slices as it is inhibited by carinamide. The ratio of refractory to natural substrate was constant over the range of concentrations studied, but it was different for the two species. Moreover, the molar ratio undoubtedly differs for other combinations of natural and refractory substrates. In the case of penicillin therapy and ordinary clearance experiments, such as is represented in figure 8, this relationship is not seen, for technical reasons. Indeed the dosage of carinamide has been reported to be the same whether the dosage of penicillin

was in thousands or millions of units per day, administered orally or parenterally (31).

Reduction of the fundamental principles involved in this type of displacement inhibition to clinical practice may be illustrated by the therapeutic indications for carinamide and Benemid (31). Carinamide has proven to be a useful and safe agent for the enhancement of penicillin blood levels. The particular indications for the compound are in the treatment of subacute bacterial endocarditis, certain types of meningitis and other instances where it is necessary or

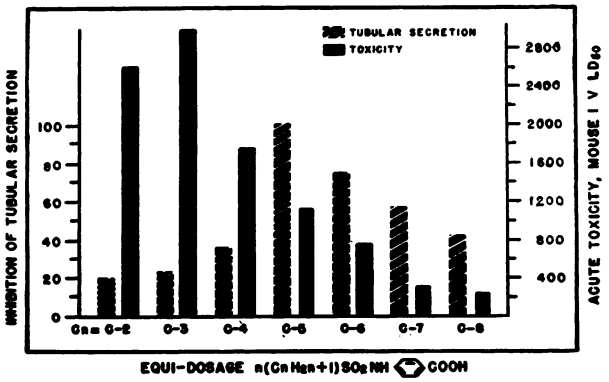


FIG. 9. ILLUSTRATING THE LACK OF A DIRECT RELATIONSHIP BETWEEN THE ABILITY OF A SERIES OF RELATED COMPOUNDS TO INHIBIT THE TUBULAR SECRETION OF PENICILLIN AND THEIR INHERENT TOXICITIES

Within the series, the toxicity of the compounds increases from C-2 to C-8, as represented by the decreasing LD_{50} (calculated lethal dose for 50 per cent of the mice injected) of the compounds administered intravenously to mice. It may be seen that the optimal activity of the compounds for the suppression of tubular secretion within this series is represented by the C-5 agent. As the number of carbon atoms in the alkyl chain is less than or greater than the C-5 compound, activity within the series diminishes. Data of Beyer, Painter and Wiebelhaus: Am. J. Physiol. 161: 259, 1950.

desirable to increase the concentration of penicillin in the body sufficiently to assure its diffusion into a relatively avascular area of infection. Similarly it should be combined with penicillin therapy when the infection is multilocular and when the direct instillation of the antibiotic agent into all parts of the infected area by injection cannot be assured. In these instances the attainment of a very high plasma concentration of penicillin assures a more uniform distribution of the agent throughout the involved area. Also, it is of use combined with oral penicillin therapy of diseases that are readily amenable to the action of the

antibiotic agent. The lack of renal toxicity of carinamide has been established by a number of studies (31, 33, 43), but none is so dramatic as its reported use in the therapy of certain types of nephritis for the apparently reversible inhibition of albuminuria, as described by Ek (164). The high rate of metabolism of the compound accounts for the necessity of administering it in dosages of 2 or 4 grams every 3 or 4 hours.

Although it is too early to discuss with assurance the indications for Benemid, the compound is unique. Apparently a daily dosage of 2 grams, divided and administered at 6 or 12 hour intervals, suffices to maintain an adequate plasma concentration in man. In addition to the aforementioned uses of carinamide, Benemid enhances the apparent plasma concentration of p-aminosalicylate (PAS), by decreasing the metabolism of the salicylate. This may constitute a real advantage in the maintenance of high plasma concentrations of PAS in the treatment of tuberculosis. Such concentrations are difficult to maintain, due to the gastric irritation which accompanies the ingestion of large PAS doses (69). It is anticipated that Benemid combined with penicillin will be a reliable and safe intermittent form of oral therapy. Present indications are that the drug is well tolerated and is safe for the customary duration of treatment of infectious diseases amenable to penicillin therapy.

3. *Inhibition by competition between transport systems for a common source of energy* is at present a little recognized interpretation of a repeatedly observed effect. It is difficult to approach the concept directly as it applies to renal physiology so that at present its substantiation is insecure.

It is likely that in some manner there are group commitments of energy by the cell for its several general functions. Clark and Barker (109) found no difference in the normally very small renal oxygen utilization of man between basal renal oxygen consumption and conditions wherein the transport mechanism for PAH secretion was saturated (Tm_{PAH}) or where water or mannitol diuresis was provoked. The constancy of renal oxygen uptake with alteration in "load" or "stress" has been observed by other investigators (91, 97, 543).

There is some evidence that in the kidney allocation of energy may be specific only in the sense of applying to a type of function, as growth, repair, specific processes of synthesis, certain transport mechanisms, etc. Thus, as two cellular functions, even diametrically opposite in their orientation (*i.e.*, tubular secretion and reabsorption) may share a common source and increment of energy, they necessarily compete for it. So long as the energy requirement for the secretion and reabsorption of substrates by the several systems does not exceed their allocation of energy at a given time there need be no apparent inhibition. If the load presented to any one transport mechanism be increased markedly, as would obtain when one measures the functional capacity or Tm of a single system, it follows that the function of other systems sharing the same increment of available energy would be depressed, since the sum of the commitments cannot exceed the energy momentarily available. Over the course of time the increment of energy for a specific group of functions may increase so that the inhibition of

collateral systems is not necessarily maintained. Inhibition by competition between systems for a common source of energy is illustrated in figures 10 and 11 with examples drawn from both enzymologic and renal function studies.

In figure 10 we have selected the rate of anaerobic glycolysis of glucose and fructose to illustrate that when two reactions, the transphosphorylation of these two compounds, compete for a limited source of energy the maximal rate at which they can both be gly-

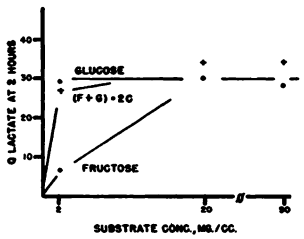


FIG. 10. ILLUSTRATING THAT THE AVAILABLE ENERGY FROM THE PHOSPHATE CYCLE LIMITS THE RATE OF ANAEROBIC GLYCOLYSIS OF GLUCOSE (-○-) AND FRUCTOSE (-●-)

The affinity of glucose for the system is greater than that of fructose, as illustrated by the $Q_{lactate}$ at the lowest concentration of substrate. When the two substrates are presented to the system so that the total molar concentration is twice that for either substrate alone, there is no increase in the rate of anaerobic glycolysis (+), within the limits of error of the method. Data of Meyerhof and Geliaskowa: Arch. Biochem. 12: 405, 1947.

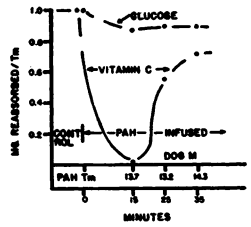


FIG. 11. ILLUSTRATING THE DEPRESSION OF REABSORPTION OF VITAMIN C, AND OF GLUCOSE TO A LIMITED EXTENT BY THE SIMULTANEOUS ADMINISTRATION OF P-AMINOHIPPURATE (PAH) IN AN AMOUNT SUFFICIENT TO DETERMINE ITS MAXIMAL SECRETORY CAPACITY (T_M).

Redrawn from Table 5 of the data of Selkurt: Am. J. Physiol., 142: 182, 1944

colyzed simultaneously does not exceed that for either studied by itself, within the error of the experiment. The data for this illustration are those of Meyerhof and Geliaskowa (341). Presumably, under the conditions of these experiments the availability of hexokinase was not necessarily a limiting factor.

The tubular reabsorptive capacity for ascorbic acid is low (174, 191, 414). Figure 11 illustrates the depression of glucose and ascorbic acid reabsorption

that can be induced by the saturation of the functional capacity of the tubules to secrete p-aminohippurate (PAH). This is a diagrammatic representation of an experiment by Selkurt (460). The depression of ascorbic acid reabsorption by PAH is profound at first, but it recovers partially in approximately one hour. He also demonstrated that glucose as well as hypertonic potassium chloride and sodium chloride could depress the reabsorption of ascorbic acid without influencing significantly the renal blood flow or glomerular filtration rate (467), but the mechanism of action may not be the same in this instance. He was not impressed by the depression of glucose reabsorption by PAH, for it was not always demonstrable and others (503) had not called attention to it previously. The mutual depression of glucose and PAH tubular functional capacities when determined simultaneously has since been noted in enough laboratories to establish its reality, although the inhibition is seldom of any considerable magnitude (163, 226, 253, 274).

The decrease in the capacity of one system by the simultaneous determination of another functional capacity of presumably the same cells has had no practical application in therapeutics. This relationship is of greatest consequence in the diagnostic determination of renal functional capacities (70, 163, 170, 192, 226, 253, 274). Because of these known, and probably other unrecognized, instances of depression of one Tm by the simultaneous determination of another it seems hazardous to measure at one time more than a single tubular functional capacity, when the absolute values are to be used diagnostically or interpretatively.

4. *Inhibition of the phosphorylation mechanisms that are essential for reabsorption or secretion* has been recognized by example for many years but it is still poorly understood. Since the over-all relation of phosphorylation to carbohydrate metabolism and to the reabsorptive or secretory transport mechanisms is discussed in another section of this review, it will be considered only in a general way here.

Von Mering first described the phenomenon of "phloridzin diabetes" (546). A few years later Minkowski (348) showed that the syndrome was primarily due to an alteration of renal function. Bilateral nephrectomy of phloridzinized dogs abolished the principal manifestations of the condition. This apparent selectivity of phloridzin for the inhibition of renal carbohydrate metabolism (549) probably is due to a concentration of the agent in the lumen of the tubules as a result of the reabsorption of water. This would tend to increase the diffusion of the glucoside into the tubular epithelium. Here, as in other tissues of the body, the compound inhibits the phosphorylation of glucose and for many years this effect has been presumed to account for the production of glycosuria, (112, 119, 120, 262, 263, 285, 313, 314, 365, 377, 508). It has no effect on glomerular filtration (390, 569).

More recently the mode of inhibition of glucose reabsorption by phloridzin has been reopened. Principally from the work of Shapiro (489) and of Meyerhof and Wilson (342) it appears that the oxidation of pyruvate and citrate and the utilization of that energy for the generation of high energy phosphate bonds

(the transphosphorylation of ADP to ATP associated with the breakdown of phosphopyruvate) is inhibited by one fifth to one tenth as much phloridzin as is required to inhibit glucose phosphorylation. Since the integrity of the phosphorylation systems has been found to be essential to certain other renal transport mechanisms one would anticipate that phloridzin should inhibit the secretion or reabsorption of other substances. Actually it has been shown to decrease the tubular secretion of diodone (569) and phenol red (37), the reabsorption of glucose and xylose (487), and the secretion of exogenous creatinine by man (477, 486).

There is more to the relationship of inhibition of transphosphorylation to the diminution of secretion or reabsorption than can be demonstrated with phloridzin alone. Loomis and Lipmann (309) demonstrated most clearly that 2,4-dinitrophenol "uncoupled" high energy phosphate bond generation from oxidative processes without necessarily inhibiting oxygen uptake. In the example cited by them the oxidation of glutamate served as the source of energy for the phosphorylation of adenosine. Handley (231), Taggart and Forster (525), Mudge and Taggart (361, 362) and our own studies (37) have demonstrated the inhibitory effect of dinitrophenol on the secretion of phenol red and PAH by the renal tubules. The former investigators have indicated that dinitrophenol does not decrease the tubular reabsorptive capacity (Tm) for glucose (231, 362). The explanation of the lack of an effect of dinitrophenol on glucose Tm does not seem to be self-evident from the data available.

5. *Alteration of the endocrinologic control of a secretory or reabsorptive function* introduces a regulatory type of effect that is important therapeutically and which holds promise of future potentialities. Very little is definitely known about this type of regulation or control, and it may be that the several aspects of the problem to be discussed actually will be found to have associations or fundamental dissimilarities not evident at present. Apparently, the problem is more difficult because not all species respond similarly with respect to the effect of hormones on renal functions, and neither do the hormones affect different tubular mechanisms at the same rate (135, 275).

The removal or intense irradiation of one kidney results in a hypertrophy and an increase in the various functional capacities of the contralateral organ. This "compensatory" growth of the opposite kidney appears to be under the control of the anterior pituitary for if hypophysectomy is performed prior to nephrectomy the remaining kidney fails to increase in size and functional capacity (134, 320, 564, 571–573, 575, 576, 584). In contrast, this "compensatory" hypertrophy of the contralateral kidney following nephrectomy still occurs after thyroidectomy or castration (320, 588).

If an anterior pituitary extract is administered to an hypophysectomized or even to a normal dog, the kidney increases in size and function to an extent that cannot be reproduced by the administration of thyroid or adrenal extracts (163 241). Thus there seems to be a renotrophic action of the anterior hypophysis that may be distinct from the adrenotrophic or the thyrotrophic factors (254, 320). This renotrophic action of anterior pituitary extract (570–576) is pro-

nounced when measured by the subsequent increase in diodrast Tm which may increase as much as 100 per cent. Under these circumstances the renal plasma flow and the glomerular filtration rate may not be increased very much in the normal animal.

In addition to its renotrophic (324, 576) effect, the anterior pituitary contributes to the control of water balance by exerting a diuretic influence antagonistic to that of the neuro- or posterior-hypophysis (12, 54, 570). Although the means by which this action is accomplished is obscure, nevertheless it is real. At least a portion of this effect may be mediated through the adrenotrophic action of the anterior lobe. In the hypophysectomized rat the diuretic response is delayed, and is similar when water or saline is administered *per os*. The administration of anterior lobe extracts does not necessarily improve the condition, but relatively small doses of adrenal cortical extract or desoxycorticosterone acetate almost completely restore to the hypophysectomized rat the ability to excrete water. Thus the altered ability to eliminate water following hypophysectomy may be due, at least in part, to the atrophy of the adrenal cortex in the absence of the adrenotrophic principle of the anterior pituitary (258, 574, 575).

It has been known for many years that the posterior pituitary elaborates an antidiuretic hormone, the secretion of which is controlled from the region of the supraoptic nucleus of the hypothalamus (73, 126, 178, 179, 238, 325, 357). This influence is mediated through the supraopticohypophyseal tract to the neurohypophysis (256, 257, 325, 383, 386–388). Interruption of the pathway results in the syndrome of diabetes insipidus. The administration of posterior pituitary extracts counteracts the effect of interruption of the innervation of the neurohypophysis or ablation of the crucial area of the supraoptic nuclei (7, 92, 95, 107, 126, 189, 237, 242, 246, 256, 300, 442, 558, 559). The antidiuretic principle has been demonstrated to be present in the urine of normal or dehydrated animals but not in the urine of dogs having diabetes insipidus (207, 230, 234, 235, 316).

Shannon has indicated that the diuresis of diabetes insipidus which follows transection of the supraopticohypophyseal tract is due to an impaired reabsorption of that increment of filtered plasma water that ordinarily is returned to the circulation by the distal tubules, together with an increase in the reabsorption of sodium by the proximal tubules (483). As a result of the increased reabsorption of sodium, extracellular fluid volume and glomerular filtration rate are increased (246, 442, 501). The administration of the antidiuretic principle increases the reabsorption of water by the distal segment of the nephron and decreases the reabsorption of sodium by the proximal convoluted tubules (248, 305, 483), according to present interpretation.

The antidiuretic action of morphine, certain barbiturates, acetylcholine, and certain other compounds has been attributed to a stimulation of the release of posterior antidiuretic principle by virtue of their action on the hypothalamus (139, 140, 201, 372, 386–388). If the nerve fibers connecting the hypothalamus with the neurohypophysis are intersected these agents have no effect on the subsequent diabetes insipidus.

Apparently the antidiuretic action of the cinchoninic acid derivatives de-

scribed by Marshall and Blanchard (332, 333) is not necessarily mediated through the hypothalamic-neurohypophyseal liberation of the antidiuretic principle. Certain of these compounds are effective antidiuretic agents in neurohypophysectomized dogs and in cases of diabetes insipidus. They do not necessarily affect glomerular filtration rate. The mode of action of the compounds on the kidney has not been worked out to date. Whereas these compounds seem to increase the reabsorption of water, they increase the excretion of uric acid (333) and decrease the tubular secretion of phenol red (138). It seems likely that the more active cinchoninic acid derivatives may stimulate the liberation of the antidiuretic principle of the posterior pituitary. If this should obtain, they would represent a most unusual group of compounds, for they are said to stimulate the liberation of the adrenocorticotrophic hormone of the anterior pituitary (62.)

In adrenal cortical insufficiency of pathological or surgical etiology the water and sodium excretion is essentially dissimilar to that noted in diabetes insipidus. In these subjects there is primarily a decreased reabsorption of sodium (206, 227, 445, 556) attended by a secondary adjustment of electrolyte and water balance. In adrenalectomized animals this is associated with a marked oliguria which leads to water intoxication when the administration of water is forced (198, 203–206). Administration of adrenal cortical extracts or desoxycorticosterone to such animals and to patients with Addison's disease increases the reabsorption of sodium and produces a concommitant readjustment of water balance (200, 206, 255, 520–523, 527–530).

Within the past few years the reemphasis on the concept of "forward failure" in the pathogenesis of peripheral edema of heart failure by Warren and Stead (555), the experimental production of hypertensive renal nephrosclerosis by Selye and his associates (469–472) by the excessive administration of desoxycorticosterone acetate and sodium chloride, and the demonstration of increased sodium and chloride reabsorption by the renal tubules when normal and decompensated patients exercise, by Newman and his associates (266, 366, 494), all have tended to accentuate the role of the kidney in the regulation of sodium excretion and the influence thereon of extra-renal factors, particularly the adrenal cortical hormones. Although a few other references (65, 240, 340, 352, 353, 529, 530) to this interrelationship of cardiac edema and sodium excretion have been included in the bibliography, the list is incomplete. The recent report by Sinclair-Smith, Kattus, Genest and Newman (494) is a particularly noteworthy contribution to this subject.

The role of the pituitary and adrenal cortical hormones in renal function, particularly water and electrolyte balance, is regulatory; homeostasis is maintained during adjustment to alterations in environment. Since these hormones apparently permit wide fluctuations in both water and salt excretion normally, it would seem that agents could be developed that would influence the safe alteration of sodium reabsorption or water retention, as in essential hypertension or cardiac decompensation. This might be accomplished by inhibiting moderately the action of the desoxycorticosterone-like principle of the adrenal cortex or the antidiuretic hormone of the posterior pituitary, depending on the primary effect desired.

In addition to the effects summarized above, the hormones of other endocrine glands exert a renotrophic action (60, 231, 275, 276, 292, 296, 320, 375, 376, 381, 468, 562) or decrease renal function (277, 529, 530, 537), as the case may be.

6. *Inhibition of ion exchange mechanisms for electrolyte reabsorption.* This principle combines certain enzymologic information with the newer knowledge of the role of the kidney in the maintenance of electrolyte balance. Perhaps these two elements of the concept might best be considered first separately, then as a whole.

Since plasma electrolytes are freely ultrafiltrable at the glomeruli it should be apparent that the kidney must conserve to the body its essential elements in order to maintain homeostasis of the internal milieu. It has been known for some time that this is accomplished in part by the formation and secretion of ammonia by the tubules (3, 282, 363, 542) to compensate in some measure for the reabsorption of sodium; by the excretion of strong acids, partially as such; and by the shift in urinary buffer, principally phosphate, from dibasic as it leaves the glomeruli to monobasic as it leaves the nephron (26).

Associated with the reabsorption of essential metabolites and electrolytes by the proximal convoluted tubules there occurs an "obligatory" reabsorption of 80 to 85 per cent of the plasma water filtered at the glomeruli (501, 548, 550, 551, 566). Since the tubules are freely permeable to water, osmotic equilibrium of proximal tubular urine with plasma is maintained during the reabsorption of critical substances. The remaining water that is reabsorbed is returned by the distal tubules (240, 483, 501, 566). This latter process is under the facultative control of the pituitary and the adrenal cortex, as discussed in the previous section and in the review by Harris (238).

It has been demonstrated that when an indicator dye such as phenol red is filtered at the glomeruli of the frog kidney, the pH of the glomerular fluid is the same as for plasma water. This has been confirmed by direct electrometric determinations (389). As the dye passes down the tubule its color does not change until the distal convoluted tubule is reached, at which point the change indicates an acidification of the urine (169, 356). In contrast to the acidification of urine in the distal tubules, phosphate, sulfate, bicarbonate, chloride, sodium and potassium appear to be reabsorbed entirely or for the most part in the proximal tubules, depending on the specific ion. Apparently phosphate and sulfate have definite Tm characteristics (6, 137, 173, 272, 310, 317, 395, 586). Bicarbonate and chloride are reabsorbed independently of their filtration rate but in amounts sufficient to maintain interdependently the normal sum of their plasma concentrations (202, 237, 311, 394, 418). The renal elimination of sodium is complicated by what may be a two-component system for reabsorption by both the proximal and the distal convoluted tubules (144, 151, 224, 266, 565, 567). Potassium is reabsorbed under most conditions but it may be secreted and reabsorbed under other circumstances (22, 113, 168, 271, 358–360, 371, 526, 583). Although the excretion of sodium and chloride has been generally thought to parallel each other, this is not necessarily the case (216) so long as ionic balance is maintained otherwise.

Three theories have been presented to account for the acidification of urine:

1) the phosphate reabsorption theory (26), 2) the carbonic acid filtration theory (473), and 3) the tubular ionic exchange theory (392). In an admirable series of papers Pitts and his associates have reported the examination of these theories and have documented well the tubular ion(ic) exchange theory (394, 396, 397, 399, 400, 402, 448, 451). The limitations of the ion exchange theory have been summarized by Menaker (339) and by Wesson, Anslow and Smith (566). Although it may be necessary to modify the details of this latter theory in time, it will be described in principle.

Figure 12 presents diagrammatically the tubular ion exchange theory of the acidification of urine, as redrawn from the illustration by Pitts (392). It is con-

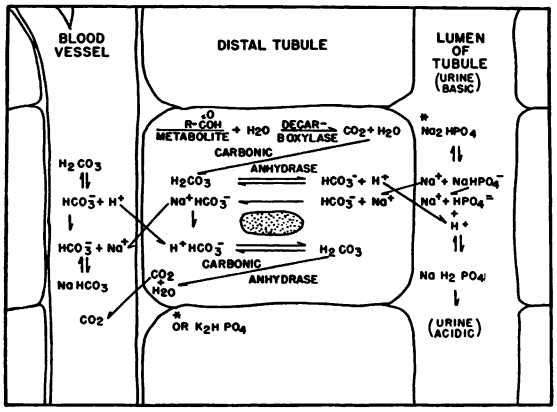


FIG. 12. A DIAGRAMMATIC REPRESENTATION OF THE BASIC CONCEPTS RELATING TO THE ION EXCHANGE THEORY FOR THE ACIDIFICATION OF URINE
Redrawn from Pitts: Science, 102: 81, 1945

ceived that by the decarboxylation of metabolites within the distal tubules carbon dioxide (CO_2) is released. The hydration of carbon dioxide to carbonic acid is catalyzed by carbonic anhydrase, which is abundantly present in the kidney (131). The carbonic acid dissociates to release H^+ ions. Since the tubular cell membrane is freely permeable to H^+ ions and presumably to Na^+ ions (liberated by the dissociation of the principal urinary buffer, Na_2HPO_4) a new equilibrium is set up resulting in an exchange of ions and an acidification of the urine, due to the dissociation of the resulting NaH_2PO_4. To be consistent, it must be supposed that this ion exchange is reciprocated at the blood vascular boundary of the cell, whereupon there would be an over-all return of sodium to the blood stream without a net change in the pH of the cell. The reabsorption of potassium could occur at least in part in this manner.

In the presence of carbonic anhydrase the reaction orientation ultimately would necessitate the splitting of H_2CO_3 and the diffusion of CO_2 into the blood stream. Very likely the carbonic anhydrase is more intimately associated with the membranous structure of the cell than is indicated in the diagram. In this theory the functional integrity of carbonic anhydrase is considered to be critical for the ion exchange. If it should be inhibited, the CO_2 built up would diffuse much more slowly and the reabsorption of sodium would be impaired.

Mann and Keilin reported that sulfanilamide was a specific inhibitor of carbonic anhydrase (327). Krebs and others have confirmed and extended this observation (130, 131, 281, 283). Höber repeated the phenol red experiment on the perfused frog kidney described by Montgomery and Pierce (356) and found that when sulfanilamide or its derivatives were added to the dye the normal yellow color of the acidic dye in the distal tubule was changed to pink, indicating that the urine was alkaline. This inhibitory effect of sulfanilamide on the acidification of urine, presumably by inhibiting carbonic anhydrase, was reversible (294). Pitts and his associates demonstrated an inhibitory effect of sulfanilamide on the acidification of urine and presented the experiments as evidence for the role of carbonic anhydrase in the ion exchange acidification of urine (395, 400, 402).

It is attractive to postulate that this relationship of carbonic anhydrase to the acidification of urine might be used to very practical advantage in the management of hypertensive or cardiac patients whose sodium retention exceeds their requirements. Thus an orally active, relatively non-toxic compound that inhibited renal tubular carbonic anhydrase would be a most attractive form of therapy for the promotion of an increased excretion of sodium in cases where its restricted intake is employed at present. The concentrating of the therapeutic agent in the lumen of the tubules by the reabsorption of water would present the inhibitor to those cells at a much higher concentration than would obtain for the rest of the body. One could take advantage of this concentration effect to attain efficacy and to minimise systemic toxicity. Schwartz has reported the clinical substantiation of this premise (457). However, the use of sulfanilamide for other than confirmation of this principle is contraindicated because of its systemic toxicity (19, 331, 334, 509, 517).

In this review a discussion of the action of diuretic agents must be limited primarily to their effects on the kidney, omitting the broader actions of many of these compounds. The simplest of these diuretic agents, water, is the most complicated from the standpoint of the interplay of many extrarenal factors. Its effects are intimately related to the interaction of the hypothalamus and the posterior pituitary, as has been reviewed by Pickford (385) and by Verney (544, 545), and to the functions of the adrenal cortex, as has been reviewed by Gaunt and others (206). These several interrelationships have been summarized in a previous section of this review. Also, the effects of the saline and the organic osmotic diuretic agents are especially influenced by the state of hydration of the subject. To a slightly less degree, the relationship of the extent of hydration to diuretic efficacy holds as well for the xanthine and the mercurial agents.

The diuresis produced by water and by alcohol is unique in that it is usually

accompanied by a decrease in chloride output. This has been interpreted as being influenced by the posterior pituitary antidiuretic principle or a closely related hormone (125, 162). Consistent with this interpretation are the several observations that the injection of posterior pituitary extracts most frequently induces a chloruresis accompanying the decrease in urine flow. (305, 385). The action of diuretic agents of the nature of ammonium chloride, ammonium sulfate, sodium sulfate, and urea usually is accompanied by an increase in chloride output, and an increased urinary acidity or an increased buffering power of the urine (160, 162). In a very general way, the efficacy of electrolytes as diuretic agents requires their usage in doses sufficient to increase their urinary output, thus the withholding from reabsorption of an osmotically equivalent amount of water. In a sense, this is the converse of the obligatory reabsorption of water with electrolytes by the proximal tubules, as was mentioned previously. Mannitol is an example of an organic osmotic diuretic agent which practically is not absorbed by the renal tubules. Actually it removes more than its osmotic increment of water, for diuresis induced by mannitol frequently is accompanied by an increased excretion of electrolytes (76, 83, 400, 424, 566). These osmotic diuretic compounds frequently increase the efficacy of the mercurial agents (171, 474).

The state of knowledge regarding the mode of action of xanthine diuretics still leaves much room for fundamental investigations. The majority opinion indicates that they decrease the tubular reabsorption of water, sodium and chloride ions, primarily.

Historically, much of the earlier evidence indicated that the action of these compounds was to increase the glomerular filtration rate due to their effects on the vascular system. However, Cushny and Lambie (128) pointed out that xanthine diuresis outlasted any increase in renal blood flow and this position was taken also by Walker and his associates (552). Biancardi (53) reported that in all cases of diuresis produced by theophylline the excretion of phenol red was no greater than in the control experiments; this suggests the desirability of repeating these earlier studies with the use of more modern methods of determining renal blood flow, etc.

Although it has been reported that the xanthine diuretics increase glomerular filtration rate (245, 452), the more generally accepted view is that they have no consistent effect on that renal function (68, 129). Recent evidence indicates that the xanthine diuretic agents inhibit the reabsorption of water, sodium and chloride (133, 273, 494).

The mercurials are the most reliable of present diuretic agents. They are the least specific of the compounds employed to inhibit a renal function. The diuretic action and toxicity of these compounds are directly related to the amount of mercury present and to its disassociation (228, 347). Reduced to elementary considerations, $HgCl_2$ is a strong diuretic agent. These generalizations are consistent with the earlier conclusions of Sollmann, Schreiber and Cole (507).

There can be little doubt that the kidney is the principal site of the diuretic effect of the mercurial agents. Direct evidence was obtained by Govaerts (221), who noted persistence of diuresis when a kidney from a mercury-intoxicated dog was anastomosed to the cervical vessels of a normal animal. Conversely, no

diuresis was seen when a normal kidney was anastomosed into the cervical vessels of a dog previously injected with a mercurial diuretic agent. Bartram (16) demonstrated unilateral diuresis when a small amount of a mercurial agent was injected slowly into a renal artery of a dog.

The principle over-all renal effect of the mercurial diuretic agents is to decrease the tubular reabsorption of water, chlorides and certain other electrolytes (27, 93, 151, 176, 219, 270, 349, 398, 444, 450). These diuretic compounds do not increase glomerular filtration rate (68, 129, 245, 452). In general mercurial agents combine with sulfhydryl groups, and this is responsible for their inhibitory effect on a number of essential cellular dehydrogenases (15, 24, 380, 557). That the diuretic effect of mercury is attributable to the inhibition of such enzymes seems likely since its renal effects, as well as its systemic toxicity, can be inhibited or reversed by the administration of the thiol, BAL, 2,3-dimercaptopropanol which has an unusually high affinity for the heavy metal (154, 172, 232, 519).

The seeming specificity of mercurial diuretic agents may be more directly related to factors other than a peculiar sensitivity of the distal tubular epithelium to them. Indeed, they have been shown to inhibit the proximal tubular secretion of PAH and the reabsorption of glucose (23, 87, 319, 422). In our experience with the secretion of phenol red by renal cortical tissue slices, the relationship between inhibition of phenol red secretion or of renal dehydrogenases and the molar concentration of mercury is not essentially different from that obtained in similar studies wherein the comparable dehydrogenases of other tissues are employed. In either instance mercurial inhibition of such dehydrogenase or secretory systems is difficultly reversible.

Probably the reason for the seemingly selective effect of a mercurial compound in producing diuresis is that it is filtered at the glomeruli and is concentrated by the obligatory reabsorption of water by the proximal tubules. Consequently, the agent is presented to the distal tubule at roughly eight to ten times its concentration in plasma and extracellular water. Further concentration by the additional reabsorption of water should bring the concentration of the agent up to the point where it could decrease the function of the distal convoluted tubules, even though the concentration presented to the proximal tubules by filtration of plasma water might be insufficient to inhibit their functions measurably. Since the foremost function of this distal segment of the nephron is the facultative reabsorption of water and some electrolytes, it is understandable that the principal effect of the agent is to produce diuresis with an increase in electrolyte excretion (151, 225, 483, 501, 566). Indeed, it has been suggested that the increase in urine flow follows the increased excretion of sodium (125, 151) or chloride (444).

7. *Inhibition of respiratory systems essential for the over-all metabolism or viability of the cell.* In the previous sections of this review we have dealt in general with the physiologically reversible alteration of the rate of an enzymatic reaction or the competitive inhibition by displacement of substrates from a definitive component of a system, the function of which has not been changed.

In this section we will deal briefly with inhibition of a toxic nature (315, 322,

364, 423, 439, 459, 580) or as it is seen in the terminal stages of disease. This pathological impairment of function may or may not be reversible, depending on the extent of damage. If the damage is repairable, the duration of its effect and the extent of the recovery of function will depend on the rate and completeness of the processes of repair.

From an enzymologic standpoint it may be stated, possibly overstated, that any compound which inhibits preferentially an enzymatic mechanism which is basic to the oxidative processes or the broad utilization of energy therefrom, may be expected to have a deleterious effect on the viability or morphology of the cell as well as on its transport systems. Even a short period of anoxia impairs renal transport mechanisms for organic compounds, electrolytes and water (80, 94, 97, 143, 148, 152, 280, 419, 420, 461–464). Compounds that strongly inhibit sulfhydryl-containing systems, such as many dehydrogenases, produce degeneration of the tubules and loss of function in a matter of minutes. An example of such an agent is tetrathionate (208). Mercurial agents inhibit sulfhydryl-containing enzymes (15, 24, 380, 557). The effect of sulfhydryl inhibitors in the form of organic mercurials can be used to advantage for the production of diuresis, but even in ordinary dosages their effect may be more widespread on transport mechanisms not directly related to water balance (23, 87, 176, 319, 373, 422). Their extrarenal toxicity is referable particularly to the heart (141, 142, 172, 233, 247, 267, 350, 519, 568). Moreover, many agents which are useful therapeutically may or may not impair renal functions temporarily (111, 121, 182, 183, 243, 374, 547).

Disease and the toxic products of bacterial or viral metabolism inhibit renal functions, nonspecifically as a rule. Thus it is well recognized that the duration of maintenance of repository penicillin blood levels is greater among ill than among ambulatory patients (534). In the early days of penicillin therapy it was noted that the highest penicillin blood levels from a given dose were obtained in patients having the greatest impairment of renal function (416).

The stress tests in the differential diagnosis of the arteriolar nephritis of hypertension, subacute and chronic glomerulonephritis, etc. define functionally the impairment of tubular capacity in comparison with renal blood flow or glomerular filtration (1, 11, 61, 74–78, 84, 96, 104, 106, 114, 116, 117, 134, 187, 190, 214, 293, 323, 328, 382, 494, 560, 563). The decrease in functional capacity may be disseminated or focal, from the standpoint of individual cells or nephrons.

ENZYMATIC ASPECTS OF A TUBULAR SECRETORY MECHANISM

In previous sections of this review the concepts of functional capacities for secretion or reabsorption by the renal tubules were presented together with a consideration of how the secretion or reabsorption of compounds could thereby be influenced. In this presentation, the belief was stated that whereas a single transport mechanism may share many enzymatic components with other systems in the cell, a secretory or reabsorptive function gains singularity by the interaction of a definitive (terminal) component in a chain of reactions.

The purpose of this section is to examine present knowledge concerning the enzymatic components of the transport mechanism responsible for the tubular secretion of hippurates, penicillin, phenol red and pyridones, and to present a working hypothesis for that over-all enzymatic transport system. The previous review of this subject by Shannon (482) may be consulted for the earlier approaches to this problem, as summarized in his theory of tubular secretion or reabsorption.

It was the classical work of Richards, Starling, Marshall, Chambers, Van Slyke, and Smith, together with their collaborators, that effected the ultimate reconciliation of the filtration-reabsorption theory of Ludwig with the Heidenhain theory of urine secretion. In large measure, the initiation of that work was stimulated by Cushny's monograph (127). All this has given us our present basic concepts of glomerular ultrafiltration, tubular secretion and tubular reabsorption as they participate in the over-all clearance of compounds. The historical development of these concepts has been presented interestingly in several of the review articles cited in the introductory remarks of this report.

Credit for the establishment of tubular secretion as a fundamental renal function goes to Marshall and his associates for their excellent work (329, 336, 337). Richards and Barnwell (432) noted that phenol red passed into the lumen of the frog's renal tubules under conditions that excluded glomerular filtration but the observation was interpreted in a manner that did not necessarily implicate tubular secretion of the dye.

Later, Chambers and his associates (98–100) maintained fragments of the metanephric avian kidney in tissue culture and showed that these could secrete phenol red or certain other sulfonated dyes into their lumen, in amounts sufficient to distend the tubule and to decrease the apparent concentration of dye in the surrounding medium. They showed that cold (see also Bickford, 55), anoxia, cyanide, hydrogen sulfide and sodium iodoacetate inhibited the secretion of the dye. These observations were extended to the metanephric kidney as well. Previously, Richards and Barnwell (432) had noted that cyanide inhibited the appearance of phenol red in the frog kidney under conditions that precluded filtration of the dye. Starling and Verney (513) and, later, Bayliss and Lundsgaard (17) found that the addition of cyanide to the kidney perfusion fluid markedly increased urine flow and produced a glycosuria, the composition of the urine being similar to that of a plasma ultrafiltrate.

In his review of renal tubular secretion Shannon reiterated his views of tubular transport mechanism in general terms that applied particularly to the reabsorption of glucose (482, 485). This hypothesis may be introduced to give perspective to the considerations that are to follow. He has stated that . . .

"In the case of an excreted substance one may assume, first, that in the sequence of reactions that result in its transfer, the solute enters into reversible combination with some cellular element which is present in a constant but limited amount, and second, that the decomposition of this complex limits the further progress of the solute toward the tubule lumen. Thus there are required two consecutive reactions, as follows,

$$A + B \rightleftarrows AB \rightarrow Ts + B$$

where *A* is the solute at the proximal side of the reaction (in the interstitial fluid around the tubule cells), *B* is the cellular element, *AB* the complex formed reversibly by these two, and *Ts* the solute on the distal side of the limiting reaction. In order to arrive at a maximal rate of excretion under these circumstances the second reaction must be a first order process, its rate slow in relation to the rate of attainment of equilibrium in the first."

This statement has been presented, for in a sense it is an over-simplification of the following discussion.

Some recent progress has been made toward the definition of the transport mechanism for the secretion of phenol red and p-aminohippurate (PAH). In large measure this work was stimulated by Forster's description of a method for studying the secretion of phenol red by frog kidney slices (185), and by Dearborn's use of the technic (138) in Marshall's laboratory. Taggart and Forster (525) have employed the isolated tubules of the flounder for the study of phenol red transport. Mudge and Taggart (361, 362) have employed conventional clearance technics, using diodrast and p-aminohippurate in the dog. Cross and Taggart have studied the ability of rabbit renal slices to concentrate p-aminohippurate (123).

We have employed for our studies the secretion of phenol red by frog and mammalian kidney slices (37), certain enzymologic technics, and conventional clearance procedures plus differential analyses, using solvent extraction or chromatographic methods for the separation of metabolites. Considering the diversity of the methods employed in the several laboratories over the course of time, the agreement of results and interpretation, insofar as they are comparable, lends assurance to their general validity.

From the beginning of the use of isolated renal tissues for the study of phenol red secretion there has been agreement that cyanide inhibits that over-all mechanism (17, 37, 98–101, 123, 370, 432). It is well established that cyanide blocks $Fe^{++} \rightleftharpoons Fe^{+++}$ catalyzed systems, particularly the cytochromes, and so inhibits oxidative respiration (269, 516). That oxidative reactions are involved in phenol red secretion is easily demonstrated for none of the dye appears in the lumen of the tubules when an atmosphere of nitrogen is substituted for oxygen in an otherwise optimal set-up (37, 98–101, 123). We have employed 95% O_2–5% CO_2 in a bicarbonate-phosphate buffer in the mammalian renal slice technic (37).

That oxidation is essential for phenol red or PAH secretion can be demonstrated further by employing phenylhydrazine which blocks oxidases (25, 63), $HgCl_2$ and quinone which block dehydrogenases (24, 408), dehydroacetic acid which blocks the succinoxidase system (492), and other inhibitors (37, 55, 98–101, 123), all of which depress phenol red secretion at concentrations that materially decrease the respiration of the tissue. The sites of action of these several inhibitors on oxidases and dehydrogenases are well established and the literature relating to their substantiation is cited in the above references.

Although respiration is essential to phenol red and p-aminohippurate secretion, oxidation in the absence of phosphorylation is insufficient to complete the secretory process. It has been shown that in the presence of dinitrophenol, which

uncouples oxidation from phosphorylation (124, 223, 309), neither phenol red nor PAH is secreted by either the amphibian or the mammalian proximal tubules, although it causes no inhibition of the oxygen uptake of the tissue (37, 123, 231, 361, 362, 525).

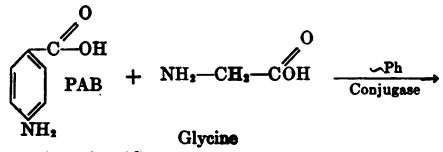
This correlation between dinitrophenol inhibition of tubular secretion and the coupling of oxidation-phosphorylation cycles indicated that energy-rich phosphate bonds somehow participated in the cellular transport of phenol red. The prompt and complete reversibility of the dinitrophenol inhibition of secretion indicated that phosphate bond energy was concerned with more than the maintenance of viability of the tubules (37, 525).

The importance of transphosphorylation reactions in phenol red and PAH secretion was indicated also by the inhibitory effect of phloridzin thereon (37). Although its effects are multiple it seems certain that phloridzin inhibits phosphorylation reactions (119, 120, 262, 263, 274, 285, 313, 314, 377, 489, 508). Thus evidence based on this inhibitor is contributory, if not definitive. To this point the cumulative evidence indicates that both oxidation and phosphorylation mechanisms must remain intact if secretion is to take place, and that high energy phosphate bonds are essential to the secretion of phenol red and PAH.

High-energy phosphate bonds serve as a source of energy for phenol red and PAH secretion. It is possible to inhibit the utilization of that energy for secretion with the aid of carinamide or Benemid. At concentrations that do not inhibit oxygen uptake (37, 48, 49), or the coupling of oxidation with phosphorylation (524), or the utilization of energy from the phosphate cycle for such reactions as the phosphorylation of glucose (577, 578), both Benemid and carinamide inhibit phenol red and PAH secretion. Thus it appears that these compounds inhibit an enzyme that requires high-phosphate-bond energy for the completion of its reaction. In this sense, then, these compounds inhibit the definitive enzyme of a coupled system.

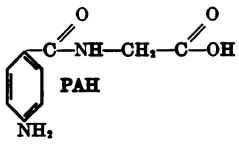
The nature of the definitive enzyme that is inhibited by these compounds remains uncertain. Experiments by Cross and Taggart implicate acetate, which has a striking stimulatory effect on PAH accumulation in the rabbit kidney slice, as a possible rate-limiting cellular component of the PAH transport mechanism (123). Our own studies suggest that the definitive mechanism is a "conjugase", analogous in its energy requirement to the coupled systems described for the conjugation of p-aminobenzoic acid with glycine to form PAH (110), and the sulfate conjugation of phenols (4). In neither instance does conjugation proceed in the absence of a source of energy from the phosphate cycle. At present it seems quite possible that the implication of acetate and the conjugation system may be two aspects of the same over-all reaction.

The similarity of the requirements of the phenol red secretory system to those of the conjugation reactions just mentioned caused us to determine the effects of carinamide and Benemid on the system described by Cohen and McGilvery (110) for the conjugation of PAB with glycine to form PAH, which may be written as follows:



Glycine

(p-aminobenzoic acid)



(p-aminohippuric acid)

It was observed that this reaction went essentially to completion in the presence of liver or kidney as the source of conjugase plus the reconstituted phosphorylation system as the source of energy (~Ph).

We have found that carinamide and Benemid are potent inhibitors of this glycine conjugation reaction (49, 578). This inhibition occurs without a decrease in the over-all oxygen uptake of the system and without affecting the phosphorylation processes that serve as a source of energy. This latter point was confirmed by demonstrating that these compounds did not inhibit the transphosphorylation of glucose in the presence of phosphorylase. Thus it seems evident that carinamide and Benemid inhibit the definitive conjugase component of this over-all synthesis of PAH.[3]

More recent chromatographic evidence indicates that neither carinamide nor Benemid inhibits the conjugation of PAB to form its glucuronide when that compound is administered to dogs (42, 71, 82, 181, 346, 579). From these studies on glucuronide formation, plus those related to the synthesis and secretion of PAH, a relationship between glycine conjugation and tubular secretion suggests itself. Since neither PAB reabsorption nor its glucuronide formation is inhibited by these compounds, it is attractive to relate these two conjugative reactions with the orientation of tubular secretion and reabsorption.

Figure 13 presents a working diagram wherein conjugative reactions are correlated with the over-all cellular processes of PAB reabsorption and PAH secretion. For schematic reasons both reactions have been illustrated as though

[3] This reaction of PAB with glycine is not strictly analogous to peptide bond formation because of the absence of the α-amino group adjacent to the carboxyl group which takes place in the amide linkage. The resulting compound is not a dipeptide since the α-amino nitrogen is not repeated in the molecule. Thus the reaction is a catabolic one representing the inactivation of PAB. The dissimilarity of this conjugation reaction to peptide synthesis has been confirmed in a very practical way, since in neither of the chronic toxicity studies nor in the prolonged clinical usage of either carinamide or Benemid has any alteration of nitrogen metabolism been noted.

they occurred in the same cell. While this may be true, it is not implicit in the statement of the hypothesis.

This scheme for the tubular reabsorption of PAB or the secretion of PAH rests on a triad of postulates. 1) So far as the cells are concerned both tubular processes of secretion and reabsorption are really secretory, the secretory processes being oriented in the opposite directions within the cells. This implies that the compounds diffuse into the cell in either instance and that energy is ex-

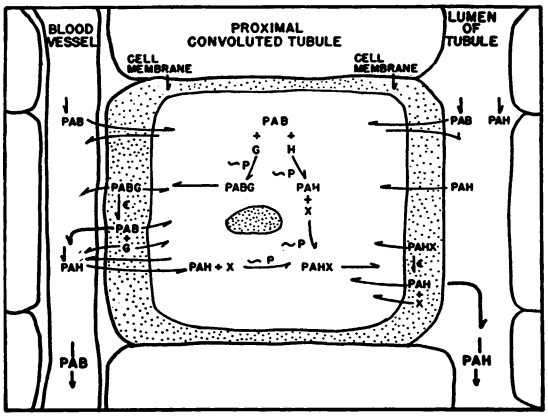


FIG. 13. A diagrammatic representation of the over-all reactions in the formation of p-aminohippurate (PAH) by the conjugation of glycine with p-aminobenzoate (PAB) in the proximal cells of the renal tubule; together with the formation and cleavage of the intermediary metabolites, PABG and PAHX, formed in the course of the active "reabsorption" of PAB and secretion of PAH, respectively. Arrows indicate the general direction of the diffusion gradient for the several compounds.

pended by the cell only in their over-all elimination therefrom. 2) In the case of either PAB or PAH another labile conjugate is formed within the cell (PAB $\xrightarrow{\sim Ph}$ PABG; PAH $\xrightarrow{\sim Ph}$ PAHX) through the expenditure of high phosphate-bond energy, which permits the building up of a concentration of the intermediary metabolite within the cell that will enable it to diffuse toward the cell boundaries under its own gradient. 3) Direction or orientation is given to the cellular secretory process by the concentration of an enzyme at the parenchymal or the luminal border which is capable of splitting the specific conjugate (PABG or PAHX), thus releasing the original compound (PAB or PAH) within the interstices of the membrane or in close proximity thereto in sufficient concentration to permit the diffusion of the agent into the surrounding medium.

1) The initial step of diffusion of PAB or PAH into the cells of the proximal convoluted tubules is easily demonstrated. Cross and Taggart (123) found that when slices from the kidney of the rabbit were suspended in a buffered solution of PAB the ratio of its concentrations in the medium and in the cells was 1.0, indicating a uniform diffusion of this compound. We have found that this same ratio holds for the distribution of PAH when its active secretion by the tubules is inhibited by Benemid or carinamide. In each instance these data indicate that the cell membrane is permeable to PAB and PAH and that in the first step no energy is required for the transport of the compounds.

2) On the other hand, evidence was presented in previous paragraphs that both the conjugation of PAB (*i.e.*, with glycine) (110) and the secretion of phenol red (37, 525) or PAH required high phosphate-bond energy. The principal source of such energetic systems has been identified with the chromatin material within the cells (250, 251, 405, 407, 453–456). Presumably, then, these conjugative reactions occur in, on, or at the chromatin particles. At those points within the cell the concentration of PABG and PAHX should be the greatest, hence these agents could diffuse toward the boundaries of the cell, as determined by their over-all gradients.

3) The orientation of the cellular "secretion" of PAB and PAH is in opposite directions by virtue of the over-all tubular reabsorption of PAB and tubular secretion of PAH (34, 503). Thus the cleavage of the PABG metabolite probably occurs at the interstitial border and the PAHX very likely occurs at the luminal border of the cell. Although the nature of either intermediary metabolite is unknown, the requirements for the synthesis of both appear to be somewhat similar. It is attractive to look for two basically similar enzymes which differ in their specificity and which are oriented at opposite borders of the cell. One does not have to look far for two enzymes.

It has been known for some time that the renal cortex is one of the three richest sources of phosphatases (72, 261–264, 443, 449, 581, 582). The distribution of the phosphatases was found by Gomori (217, 218) to be limited to the proximal convoluted tubules of the nephron and this is easily confirmed. There are essentially two phosphatases. The alkaline phosphatase is restricted to the luminal membrane and the brush border of the cells. Acid phosphatase is more diffusely represented, but it is concentrated to the greatest extent on the interstitial side of the cell.

Whether or not the two phosphatases are responsible for the cleavage of the two hypothetical metabolites, they do fulfill the general requirements mentioned for similarity, specificity and opposite spatial orientation. It would seem plausible that the cell would make use of an over-all phosphorylation-phosphorolytic reaction for the complex process of secretion. The first (phosphorylation) would be an energonic one requiring a source of high phosphate-bond energy (264), and the second (phosphorolysis) would require a lower expenditure of energy than would a hydrolytic process (264). In our experience carinamide does not inhibit either of the phosphatases of the kidney or the liver. Although it cannot be considered conclusive, this lack of an effect of carinamide on phosphatases is at

least consistent with the impression gained from the glycine conjugation experiments that both it and Benemid inhibit the secretion of PAH by decreasing the formation of the intermediary metabolite and not by inhibiting its cleavage.

Thus carinamide and Benemid may be considered tentatively to act on the definitive conjugase of the reaction involved in the synthesis of PAH from PAB or of PAHX from PAH. It is probable that this is the reaction, with its full complement of enzymatic commitments for oxidation and phosphorylation, that limits the over-all expression of Tm. This hypothesis, summarized in figure 13, is presented with the assurance that it may need to be revised in detail as it is examined intensively. The principle that has been presented seems attractive, since it considers the vitalistic functions of orientation and the spatial transport of materials in conventional terms of diffusion gradients, coupled conjugative reactions and the hydrolysis or phosphorolysis of conjugates.

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REFERENCES

1. Aas, K., and Blegen, E.: The renal blood flow and the glomerular filtration rate in congestive heart failure and some other clinical conditions; the effect of exercise and hypoxemia; a preliminary report. Scandinav. J. Clin. & Lab. Investigation, 1: 22–32, 1949.
2. Alles, G. A., and Heegaard, E. V.: Substrate specificity of amine oxidase. J. Biol. Chem., 147: 487–508, 1943.
3. Archibald, R. M.: Enzymatic determination of glutamine. J. Biol. Chem., 154: 643–656, 1944.
4. Arnolt, R. I., and deMeio, R. H.: The conjugation of phenol and its action on the respiration of tissues in vitro. An. Asoc. quím. argent., 30: 40, 1942.
5. Avery, N. L., Jr., Major, M. C., Mayer, O. B., and Nelson, R. C.: Massive doses of penicillin in the treatment of subacute bacterial endocarditis. Ann. Int. Med., 24: 900–904, 1946.
6. Ayer, J. L., Schiess, W. A., and Fitts, R. F.: Independence of phosphate reabsorption and glomerular filtration in the dog. Am. J. Physiol., 151: 168–173, 1947.
7. Bailey, P., and Bremer, F.: Experimental diabetes insipidus. Arch. Int. Med., 28: 773–803, 1921.
8. Barclay, J. A., Cooke, W. T., and Kenney, R. A.: Evidence for a three-component system of renal excretion. Acta med. Scandinav., 128: 500–508, 1947.
9. Barclay, J. A., Cooke, W. T., and Kenney, R. A.: Concept of renal thresholds. Acta med. Scandinav., 128: 578–583, 1947.
10. Barclay, J. A., Cooke, W. T., and Kenney, R. A.: The renal excretion of inorganic phosphate in man and dog. Acta med. Scandinav., 134: 107–116, 1949.
11. Barclay, A. E., Daniel, P., Franklin, K. J., Prichard, M. M. L., and Trueta, J.: Records and findings obtained during studies of the renal circulation in the rabbit with special reference to vascular short-circuiting and functional cortical ischaemia. J. Physiol., 105: 27P–28P, 1946.
12. Barnes, B. O., Regan, J. F., and Bueno, J. G.: Is there specific diuretic hormone in anterior pituitary? Am. J. Physiol., 105: 559–561, 1933.
13. Barnett, H. L., Hare, K., McNamara, H., and Hare, R.: Measurement of glomerular filtration rate in premature infants. J. Clin. Investigation, 27: 691–699, 1948.
14. Barnett, H. L., McNamara, H., Schultz, S., and Tompsett, R.: Renal clearances of sodium penicillin G, procaine penicillin G and inulin in infants and children. Pediatrics, 3: 418–423, 1949.
15. Barron, E. S. G., and Singer, T. P.: Studies on biological oxidations; sulfhydryl enzymes in carbohydrate metabolism. J. Biol. Chem., 157: 221–240, 1945.
16. Bartram, E. A.: Experimental observations on effect of various diuretics when injected directly into one renal artery of dog. J. Clin. Investigation, 11: 1197–1219, 1932.
17. Batlins, L. E., and Lundegaard, E.: Action of cyanide on isolated mammalian kidney. J. Physiol., 74: 279–293, 1932.
18. Becker-Christensen, P., and Schou, P.: Experimental studies on the excretion of sulfathiazole by the kidneys with normal and greatly increased diuresis (sulphate diuresis). Acta Pharmacol., 1: 357–368, 1945.
19. Beckman, W. W., Rossmiesl, E. C., Pettengill, R. B., and Bauer, W.: Study of effects of sulfanilamide on acid-base metabolism. J. Clin. Investigation, 19: 635–644, 1940.

20. Berger, E. Y., Farber, S. J., and Earle, D. P.: Comparison of the constant infusion and urine collection techniques for the measurement of renal function. J. Clin. Investigation, 27: 710–716, 1948.
21. Berger, E. Y., Farber, S. J., and Earle, D. P.: Renal excretion of mannitol. Proc. Soc. Exper. Biol. & Med., 64: 62–66, 1947.
22. Berliner, R. W., and Kennedy, T. J., Jr.: Renal tubular secretion of potassium in the normal dog. Proc. Soc. Exper. Biol. & Med., 67: 542–545, 1948.
23. Berliner, R. W., Kennedy, T. J., Jr., and Hilton, J. G.: Salyrgan and renal tubular secretion of para-aminohippurate in dog and man. Am. J. Physiol., 154: 537–541, 1948.
24. Bersheim, F.: The Interaction of Drugs and Cell Catalysts. Burgess Publishing Co., Minneapolis, 1946.
25. Bersheim, F.: Note on the action of copper and phenylhydrazine on certain dehydrogenases. J. Biol. Chem., 133: 685–690, 1940.
26. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice. pp. 639–633, The Williams & Wilkins Co., Baltimore, 1950.
27. Beutner, R., Landay, J., and Lieberman, A.: Evidence for local effect of mercurial diuretics. Proc. Soc. Exper. Biol. & Med., 44: 130–133, 1940.
28. Beyer, K. H.: The relation of molecular configuration to the rate of deamination of sympathomimetic amines by aminase. J. Pharmacol. & Exper. Therap., 79: 85–96, 1943.
29. Beyer, K. H.: Sympathomimetic amines: the relation of structure to their action and inactivation. Physiol. Rev., 26: 169–197, 1946.
30. Beyer, K. H.: New concept of competitive inhibition of the renal tubular excretion of penicillin. Science, 105: 94–96, 1947.
31. Beyer, K. H.: Pharmacological Basis of Penicillin Therapy. Chapter VII, Charles C. Thomas, Springfield, Ill., 1950.
32. Beyer, K. H., Flippin, H., Verwey, W. F., and Woodward, R.: The effect of para-aminohippuric acid on plasma concentration of penicillin in man. J. Am. M. A., 126: 1007–1009, 1944.
33. Beyer, K. H., McKinney, S. E., Tillson, E. K., and Green, C. W.: 4′-Carboxyphenylmethanesulfonanilide (caronamide): its toxicologic effects. J. Pharmacol. & Exper. Therap., 91: 263–271, 1947.
34. Beyer, K. H., Mattis, P. A., Patch, E. A., and Russo, H. F.: Para-aminohippuric acid; its pharmacodynamic actions. J. Pharmacol. & Exper. Therap., 84: 136–146, 1945.
35. Beyer, K. H., Miller, A. K., Russo, H. F., Patch, E. A., and Verwey, W. F.: The inhibitory effect of caronamide on the renal elimination of penicillin. Am. J. Physiol., 149: 355–366, 1947.
36. Beyer, K. H., and Morrison, H. S.: Relation of structure to deamination of sympathomimetic amines. Indust. & Engin. Chem. (Indust. Ed.), 37: 142–145, 1945.
37. Beyer, K. H., Painter, R. H., and Wiebelhaus, V. D.: Enzymatic factors in the renal tubular secretion of phenol red. Am. J. Physiol., 144: 289–297, 1945.
38. Beyer, K. H., Peters, L., Woodward, R., and Verwey, W. F.: The Enhancement of the physiological economy of penicillin in dogs by the simultaneous administration of para-aminohippuric acid. J. Pharmacol. & Exper. Therap., 82: 310–323, 1944.
39. Beyer, K. H., Russo, H. F., Gass, S. R., Miller, K. B., and Aman, A. A.: The renal tubular excretion of N-methylnicotinamide by the dog. Am. Physiol. Soc. (Proc.), 155: 426–427, 1948.
40. Beyer, K. H., Russo, H. F., Gass, S. R., Wilhotte, K. M., and Pitt, A. A.: The renal tubular elimination of N¹-methylnicotinamide. Am. J. Physiol., 160: 311–320, 1950.
41. Beyer, K. H., Russo, H. F., Gass, S. R., et al.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid): its effect on certain renal transport mechanisms of the dog. To be published.
42. Beyer, K. H., Russo, H. F., Patch, E. A., Peters, L., and Sprague, K. L.: The formation and excretion of acetylated sulfonamides. J. Lab. & Clin. Med., 31: 65–71, 1946.
43. Beyer, K. H., Russo, H. F., Patch, E. A., Tillson, E. K., and Shaner, G.: Certain pharmacologic properties of 4′-carboxyphenylmethanesulfonanilide (caronamide), including its effect on the renal clearance of compounds other than penicillin. J. Pharmacol. & Exper. Therap., 91: 272–287, 1947.
44. Beyer, K. H., Russo, H. F., Tillson, E. K., Gass, S. R., and Schuchardt, G. S.: Carinamide (4′-carboxyphenylmethanesulfonanilide): its renal clearance and binding on plasma protein. Am. J. Physiol., 159: 181–193, 1949.
45. Beyer, K. H., and Shapiro, S. H.: The excretion of conjugated epinephrine related compounds. Am. J. Physiol., 144: 321–330, 1945.
46. Beyer, K. H., Tillson, E. K., Russo, H. F., Schuchardt, G. S., and Gass, S. R.: The absorption and elimination of caronamide (4′-carboxyphenylmethanesulfonanilide). J. Pharmacol. & Exper. Therap., 94: 167–177, 1948.
47. Beyer, K. H., Verwey, W. F., Woodward, R., Peters, L., and Mattis, P. A.: The enhancement of the plasma concentration of penicillin in dogs by the simultaneous administration of para-aminohippuric acid. Am. J. M. Sc., 209: 608–621, 1945.
48. Beyer, K. H., Wiebelhaus, V. D., Russo, H. F., Peck, H. M., and McKinney, S. E.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid)—an antiestabolite: its pharmacological properties. Federation Proc., 9: 258–259, 1950.
49. Beyer, K. H., Wiebelhaus, V. D., Tillson, E. K., Russo, H. F., and Wilhotte, K. M.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid): the inhibition of glycine conjugative reactions. Proc. Soc. Exper. Biol. & Med., In press.

50. Bryer, K. H., Woodward, R., Peters, L., Verwey, W. F., and Mattis, P. A.: The prolongation of penicillin retention in the body by means of para-aminohippuric acid. Science, 100: 107–108, 1944.
51. Bryer, K. H., Wright, L. D., Skeggs, H. R., Russo, H. F., and Shanker, G. A.: Renal clearance of essential amino acids: their competition for reabsorption by the renal tubules. Am. J. Physiol., 151: 209–210, 1947.
52. Bhagvat, K., Blaschko, H., and Richter, D.: Amine oxidase. Biochem. J., 33: 1338–1341, 1939.
53. Biancardi, S.: Further studies on the diuretic mechanism of theophylline. Boll. Soc. ital. biol. sper., 11: 672–673, 1936.
54. Biasotti, A.: Thyroïde et action diurétique de l'extrait ante-hypophysaire. Abstr., Compt. rend. Soc. de biol., 115: 330–330, 1934.
55. Bickford, R. G., and Winton, F. R.: The influence of temperature on the isolated kidney of the dog. J. Physiol., 89: 196–219, 1937.
56. Bing, J., and Effersøe, P.: Comparative tests of the thiosulphate and creatinine clearance in rabbits and cats. Acta physiol. Scandinav., 15: 231–236, 1948.
57. Berring, T.: Measurement of glomerular filtration rate. Scandinav. J. Clin. & Lab. Investigation, 1: 343, 1949.
58. Berring, T.: Renal excretion of urea. Scandinav. J. Clin. & Lab. Investigation, 1: 343, 1949.
59. Brønnebor, M., Dalgaard-Mikkelsen, S., and Raaschou, F.: Does the filtration (thiosulfate clearance) differ at different pH values in the urine? Scandinav. J. Clin. & Lab. Investigation, 1: 347, 1949.
60. Blackman, S. S., Jr., Thomas, C. B., and Howard, J. E.: The effect of testosterone propionate on the arterial blood pressure, kidneys, urinary bladder and livers of growing dogs. Bull. Johns Hopkins Hosp., 74: 321–334, 1944.
61. Blake, W., Wegria, R., Keating, R., and Ward, H.: Effect of increased renal venous pressure on renal function. Am. J. Physiol., 137: 1–13, 1949.
62. Blanchard, K. C., Dearborn, E. H., Maren, T. H., and Marshall, E. K., Jr.: Stimulation of the anterior pituitary by certain cinchoninic acid derivatives. Bull. Johns Hopkins Hosp., 86: 83–88, 1950.
63. Blaschko, H.: The mechanism of catalase inhibitions. Biochem. J., 29: 2302–2312, 1935.
64. Blaschko, H., Richter, D., and Schlossman, H.: The oxidation of adrenaline and other amines. Biochem. J., 31: 2187–2196, 1937.
65. Blegen, E.: Kidney function in heart failure, Scandinav. J. Clin. & Lab. Investigation, 1: 298–304, 1948.
66. Blegen, E., Haugen, H. N., and Aas, K.: Endogenous "creatinine" clearance. Scandinav. J. Clin. & Lab. Investigation, 1: 191–200, 1949.
67. Blegen, E., Øening, K., and Aas, K.: The renal clearance of thiosulfate in man, Scandinav. J. Clin. & Lab. Investigation, 1: 102–106, 1949.
68. Blumgart, H. L., Gilligan, D. R., Levy, R. C., Brown, M. G., and Volk, M. C.: Action of diuretics: action of diuretics in normal persons. Arch. Int. Med., 54: 40–61, 1934.
69. Boger, W. P., Gallagher, M. E., and Pitts, F. W.: The effect of a new benzoic acid derivative on penicillin and para-aminosalicylic acid (PAS). J. Phila. Gen. Hosp., 1: 51–57, 1950.
70. Bonnheim, R. W., Dill, L. V., and Dana, E. S.: The effect of diodrast on the normal uric acid clearance. J. Clin. Investigation, 23: 776–782, 1944.
71. Borgström, B.: Detoxification of benzoic acid by glucuronic acid under normal conditions and in liver disease. Acta med. Scandinav., 133: 7–18, 1949.
72. Bourne, G.: The distribution of alkaline phosphatase in various tissues. Quart. J. Exper. Physiol., 32: 1–19, 1943.
73. Bourquin, H.: Studies on diabetes insipidus. Am. J. Physiol., 96: 66–77, 1931.
74. Bradley, S. E.: Medical progress; modern concepts of renal structure and function in chronic Bright's disease. New England J. Med., 231: 421–426, 452–458, 1944.
75. Bradley, S. E.: Medical progress; the pathogenesis of renal insufficiency. New England J. Med., 233: 496–504, 530–535, 1945.
76. Bradley, S. E.: Management of patient with chronic diffuse glomerulonephritis. M. Clin. North America, 29: 1184–1199, 1945.
77. Bradley, S. E.: Medical progress; biochemical abnormalities during renal insufficiency. New England J. Med., 235: 755–758, 791–796, 1946.
78. Bradley, S. E., and Blake, W. D.: Pathogenesis of renal dysfunction during congestive heart failure. Am. J. Med., 6: 470–480, 1949.
79. Bradley, S. E., Currey, J., and Bradley, G. P.: Unpublished data. Cited by Bradley, S. E. in ref. 74.
80. Brandt, J. L., and Gruhn, J. G.: Effect of renin on proteinuria and PAH clearance at low plasma levels. Am. J. Physiol., 153: 456–463, 1948.
81. Braun Menendez, E.: Kidney. Ann. Rev. Physiol., 6: 365–394, 1944.
82. Bray, H. G., Ryman, B. E., and Thorpe, W. V.: Fate of certain organic acids and amides in the rabbit; o- and m-hydroxybenzoic acids and amides. Biochem. J., 43: 561–567, 1948.
83. Bridger, C. E., Smatherss, S. E., Cotterman, C. W., Dameron, J. T., and Little, J. W.: The diuretic effect of gelatin solutions. Am. J. Physiol., 142: 246–253, 1944.
84. Briggs, A. P., Fowell, D. M., Hamilton, W. F., Remington, J. W., Wheeler, N. C., and Winslow, J. A.: Renal and circulatory factors in the edema formation of congestive heart failure. J. Clin. Investigation, 27: 810–817, 1948.
85. Brod, J., and Sirota, J. H.: The renal clearance of endogenous "creatinine" in man. J. Clin. Investigation, 27: 645–654, 1948.
86. Brun, C.: The influence of renal function tests on the function of the kidney. Scandinav. J. Clin. & Lab. Investigation, 1: 344, 1949.

87. Brun, C., Hilden, T., and Raaschou, F.: On the effects of mersalyl on the renal function. Acta pharmacol. et toxicol., 3: 1–12, 1947.
88. Bryner, S., Clark, W. H., Randall, E., and Rantz, L. A.: Renal tubular excretory capacity for penicillin in health and in subacute bacterial endocarditis. Am. J. Med., 5: 203–209, 1948.
89. Bucht, H.: Examination of the renal plasma flow by means of para-aminohippuric acid (PAH) using one intramuscular injection. Scandinav. J. Clin. & Lab. Investigation, 1: 126–130, 1949.
90. Bucht, H.: On the tubular excretion of thiosulfate and creatinine under the influence of caronamide. Scandinav. J. Clin. & Lab. Investigation, 1: 270–276, 1949.
91. Bucht, H., Werkö, L., and Josephson, B.: The oxygen consumption of the human kidney during heavy tubular excretory work. Scandinav. J. Clin. & Lab. Investigation, 1: 277–280, 1949.
92. Burgess, W. W., Harvey, A. M., and Marshall, E. K., Jr.: Site of antidiuretic action of pituitary extract. J. Pharmacol. & Exper. Therap., 49: 237–240, 1933.
93. Carey, R. L.: On the potency and toxicity of a new mercurial diuretic: sodium N-(beta-hydroxymercuri-gamma-methoxypropyl)-3-pyridone-5-carboxylate. J. Am. Pharm. A. (Scient. Ed.), 36: 139–144, 1947.
94. Caldwell, F. T., Rolf, D., and White, H. L.: Effects of acute hypoxia on renal circulation in man. J. Appl. Physiol., 1: 807–800, 1949.
95. Campbell, J. R., and Blumgart, H. L.: Treatment of diabetes insipidus with pituitary posterior lobe extract applied intranasally. Am. J. M. Sc., 176: 769–782, 1928.
96. Cargill, W. H.: The measurement of glomerular and tubular plasma flow in the normal and diseased human kidney. J. Clin. Investigation, 28: 533–535, 1949.
97. Cargill, W. H., and Hickam, J. B.: The oxygen consumption of the normal and the diseased human kidney. J. Clin. Investigation, 28: 536–532, 1949.
98. Chambers, R., Beck, L. V., and Belkin, M.: Secretion in tissue cultures; inhibition of phenol red accumulation in chick kidney. J. Cell. & Comp. Physiol., 6: 435–450, 1935.
99. Chambers, R., and Cameron, G.: Intracellular hydrion concentration; the secreting cells of the mesonephros in the chick. J. Cell. & Comp. Physiol , 2: 99–103, 1932.
100. Chambers, R., and Kempton, R. T.: Indications of function of the chick mesonephros in tissue culture with phenol red. J. Cell. & Comp. Physiol., 3: 131–167, 1933.
101. Chambers, R., and Kempton, R. T.: Elimination of neutral red by frog's kidney. J. Cell. & Comp. Physiol. 10: 199–221, 1937.
102. Chapman, D. W., and Peoples, S. A.: Sulfathiazole as a substitute for inulin in determining the glomerular filtration rate. J. Clin. Investigation, 26: 1177, 1947.
103. Chasis, H., Ranges, H. A., Goldring, W., and Smith, H. W.: The control of renal blood flow and glomerular filtration in normal man. J. Clin. Investigation, 17: 603–607, 1938.
104. Chasis, H., and Redish, J.: Effective renal blood flow in the separate kidneys of subjects with essential hypertension. J. Clin. Investigation, 20: 655–661, 1941.
105. Chasis, H., Redish, J., Goldring, W., Ranges, H. A., and Smith, H. W.: The use of sodium p-aminohippurate for the functional evaluation of the human kidney. J. Clin. Investigation, 24: 583–588, 1945.
106. Chesley, L. C., Connell, E. J., Chesley, E. R., Kate, J. D., and Gliesen, C. S.: The diodrast clearance and renal blood flow in toxemias of pregnancy. J. Clin. Investigation, 19: 219–224, 1940.
107. Christie, C. D., and Stewart, G. N.: Study of some cases of diabetes insipidus with special reference to detection of changes in blood when water is taken or withheld. Arch. Int. Med., 29: 555–566, 1922.
108. Clark, J. K., and Barker, H. G.: Is mannitol metabolised? Proc. Soc. Exper. Biol. & Med., 69: 153–153, 1948.
109. Clark, J. K., and Barker, H. G.: Effect of work on renal oxygen utilization. Federation Proc., 8: 26, 1949.
110. Cohen, P. P., and McGilvery, R. W.: Peptide bond synthesis; the formation of p-aminohippuric acid by rat liver slices. J. Biol. Chem., 166: 261–272, 1946.
111. Coller, F. A., Rees, V. L., Campbell, K. N., Iob, V. L., and Moyer, C. A.: Effects of ether and cyclopropane anesthesia upon the renal function in man. Ann. Surg., 118: 717–727, 1943.
112. Colowick, S. P., Welch, M. S., and Cori, C. F.: Phosphorylation of glucose in kidney extract. J. Biol. Chem., 133: 339–373, 1940.
113. Conway, E. J., Fitzgerald, O., and Macdougald, T. C.: Potassium accumulation in the proximal convoluted tubules of the frog's kidney. J. Gen. Physiol., 29: 305–334, 1946.
114. Cooper, A. M., Eckhardt, R. K., Falcon, W. W., and Davidson, C. S.: Investigation of the aminoaciduria in Wilson's disease (hepatolenticular degeneration): demonstration of a defect in renal function. J. Clin. Investigation, 29: 265–278, 1950.
115. Corcoran, A. C., Masson, G., Rehting, R., and Page, I. H.: Measurement of renal functions in rats. Am. J. Physiol., 154: 170–178, 1948.
116. Corcoran, A. C., and Page, I. H.: Renal blood flow in experimental renal hypertension. Am. J. Physiol., 135: 361–371, 1942.
117. Corcoran, A. C., and Page, I. H.: Differential diagnosis of terminal glomerulonephritis and malignant hypertension; renal aspects. Ann. Int. Med., 21: 747–764, 1944.
118. Corcoran, A. C., Smith, H. W., and Page, I. H.: The removal of diodrast from blood by the dog's explanted kidney. Am. J. Physiol., 134: 333–337, 1941.
119. Cori, G. T., Colowick, S. P., and Cori, C. F.: The activity of the phosphorylating enzyme in muscle extract. J. Biol. Chem., 127: 771–782, 1939.
120. Cori, G. T., and Cori, C. F.: Kinetics of enzymatic synthesis of glycogen from glucose-1-phosphate. J. Biol. Chem., 135: 733–755, 1940.

121. Craig, F. N., Visscher, F. E., and Houck, R.: Renal function in dogs under ether or cyclopropane anesthesia. Am. J. Physiol., 142: 106–118, 1945.
122. Crawford, B.: Depression of the exogenous creatinine/inulin or thiosulfate clearance ratios in man by diodrast and p-aminohippuric acid. J. Clin. Investigation, 27: 171–175, 1948.
123. Cross, R. J., and Taggart, J. V.: Renal tubular transport: accumulation of p-aminohippurate by rabbit kidney slices. Am. J. Physiol., 161: 181–190, 1950.
124. Cross, R. J., Taggart, J. V., Covo, G. A., and Green, D. E.: Studies on the cytophorase system; the coupling of oxidation and phosphorylation. J. Biol. Chem., 177: 655–677, 1949.
125. Crutchfield, A. J., and Wood, J. E.: Urine volume and total renal sodium during water diuresis. Ann. Int Med., 28: 28–40, 1948.
126. Curtis, G. M.: Production of experimental diabetes insipidus. Arch. Int. Med., 34: 801–836, 1924.
127. Cushny, A. R.: The Secretion of the Urine. Longmans, Green, & Co., New York, 1917.
128. Cushny, A. R., and Lambie, C. G.: The action of diuretics. J. Physiol., 55: 276–286, 1921.
129. Davenport, L. F., Fulton, M. N., VanAuken, H. A., and Parsons, R. J.: The creatinine clearance as a measure of glomerular filtration in dogs with particular reference to the effect of diuretic drugs. Am. J. Physiol., 108: 99–106, 1934.
130. Davenport, H. W.: Inhibition of carbonic anhydrase by thiophene-2-sulfonamide and sulfanilamide. J. Biol. Chem., 158: 567–571, 1945.
131. Davenport, H. W., and Wilhelmi, A. E.: Renal carbonic anhydrase. Proc. Soc. Exper. Biol. & Med., 48: 52–56, 1941.
132. Davis, B. D.: The binding of sulfonamide drugs by plasma proteins; a factor in determining the distribution of drugs in the body. J. Clin. Investigation, 22: 753–762, 1943.
133. Davis, J. O., and Shock, N. W.: The effect of theophylline ethylene diamine on renal function in control subjects and in patients with congestive heart failure. J. Clin. Investigation, 28: 1459–1468, 1949.
134. Dean, A. L., and Abels, J. C.: Study by the newer renal function tests of an unusual case of hypertension following irradiation of one kidney and the relief of the patient by nephrectomy. J. Urol., 52: 497–501, 1944.
135. Dean, A. L., Abels, J. C., and Taylor, H. C.: The effects of certain hormones on the renal function of man. J. Urol., 53: 647–651, 1945.
136. Dean, R. F. A., and McCance, R. A.: Inulin, diodane, creatinine and urea clearances in newborn infants. J. Physiol., 106: 431–439, 1947.
137. Dean, R. F. A., and McCance, R. A.: Phosphate clearances in infants and adults. J. Physiol., 107: 183–186, 1948.
138. Dearborn, E. H.: Inhibition of the appearance of phenol red in frog kidney tubules *in vitro*. Proc. Soc. Exper. Biol. & Med., 70: 105–106, 1949.
139. de Bodo, R. C.: The antidiuretic action of morphine and its mechanism. J. Pharmacol. & Exper. Therap., 82: 74–85, 1944.
140. de Bodo, R. C., and Prescott, K. F.: The antidiuretic action of barbiturates (phenobarbital, amytal, pentobarbital) and the mechanism involved in this action. J. Pharmacol. & Exper. Therap., 85: 223–233, 1945.
141. De Graff, A. C., and Lehman, R. A.: The acute toxicity of mercurial diuretics. J. Am. M. A., 119: 998–1001, 1942.
142. De Graff, A. C., and Nadler, J. E.: A review of the toxic manifestations of mercurial diuretics in man. J. Am. M. A., 119: 1006–1011, 1942.
143. Derobert, L., Desclaux, P., Hadengue, A., and Le Breton: L'intoxication par le dinitrophénol 1:2:4 (thermol); essai thérapeutique (1ère note). Ann. de méd. lég., 29: 263–268, 1948.
144. Dicker, S. E.: Renal excretion of sodium and potassium in rats. J. Physiol., 107: 8–13, 1948.
145. Dicker, S. E., and Heller, H.: The mechanism of water diuresis in normal rats and rabbits as analysed by inulin and diodone clearances. J. Physiol., 103: 449–460, 1945.
146. Dock, W.: Kidney. Ann. Rev. Physiol., 9: 225–254, 1947.
147. Dole, V. P.: Back-diffusion of urea in the mammalian kidney. Am. J. Physiol., 139: 504–513, 1943.
148. Dole, V. P., Emerson, K., Phillips, R. A., Hamilton, P., and Van Slyke, D. D.: The renal extraction of oxygen in experimental shock. Am. J. Physiol., 145: 337–345, 1946.
149. Dominguez, R., Corcoran, A. C., and Page, I. H.: Mannitol: kinetics of distribution, excretion and utilization in human beings. J. Lab. & Clin. Med., 32: 1192–1202, 1947.
150. DuBois, K. P., and Potter, V. R.: The assay of animal tissues for respiratory enzymes; adenosinetriphosphatase. J. Biol. Chem., 150: 185–195, 1943.
151. Duggan, J. J., and Pitts, R. F.: Studies on diuretics; the site of action of mercurial diuretics. J. Clin. Investigation, 29: 365–371, 1950.
152. Duquenois, P.: A suicide by oral ingestion of 2,4-dinitrophenol. Ann. de méd. lég., 30: 86–91, 1949.
153. Earle, D. P., and Berliner, R. W.: A simplified clinical procedure for measurement of glomerular filtration rate and renal plasma flow. Proc. Soc. Exper. Biol. & Med., 52: 262–264, 1946.
154. Earle, D. P., Jr., and Berliner, R. W.: Effect of 2,3-dimercaptopropanol on diuresis. Am. J. Physiol., 151: 215–220, 1947.
155. Earle, D. P., Jr., Taggart, J. V., and Shannon, J. A.: Glomerulonephritis; a survey of the functional organization of the kidney in various stages of diffuse glomerulonephritis. J. Clin. Investigation, 23: 119–137, 1944.
156. Eaton, A. G., Ferguson, F. P., and Byer, F. T.: The renal reabsorption of amino acids in dogs: valine, leucine and isoleucine. Am. J. Physiol., 145: 491–499, 1946.

167. Eckhardt, R. D., and Davidson, C. S.: Urinary excretion of amino acids following the rapid injection of a solution of amino acids in man. J. Clin. Investigation, 27: 737–736, 1948.
168. Epperson, P.: Comparative determinations of the creatinine and thiosulfate clearances in kittens. Scandinav. J. Clin. & Lab. Investigation, 1: 346, 1949.
169. Epperson, P.: Comparative investigations into the inulin, creatinine and thiosulfate clearances of rabbits after ingesting sodium benzoate. Scandinav. J. Clin. & Lab. Investigation, 1: 343, 1949.
160. Eggleton, M. G.: Some factors affecting the acidity of urine in man. J. Physiol., 106: 456–465, 1947.
161. Eggleton, M. G., and Hare, Y. A.: Sodium thiosulfate clearance in the cat. J. Physiol., 110: 96–109, 1949.
162. Eggleton, M. G., and Smith, I. G.: The effect of ethyl alcohol and some other diuretics on chloride excretion in man. J. Physiol., 104: 435–443, 1946.
163. Eiler, J. J., Althausen, T. L., and Stockholm, M.: The effect of thyroxin on the maximum rate of transfer of glucose and diodrast by the renal tubules. Am. J. Physiol., 140: 699–707, 1944.
164. Ek, J.: Is urinary protein excreted by the renal tubular epithelium? Scandinav. J. Clin. & Lab. Investigation, 2: 72–78, 1950. cf. Josephson, B., and Ek, J.: *Ibid.* 2: 176, 1950.
165. Ekehorn, G.: Principles of renal function. Acta med. Scandinav., Supp. 36: 1–717, 1931.
166. Ekehorn, G.: Excretion of urinary waste-products under abnormal conditions with special regard to tubular functions. Acta med. Scandinav., 122: 134–190, 1945.
167. Elkinton, J. R.: The volume of distribution of Mannitol as a measure of the volume of extracellular fluid, with a study of the mannitol method. J. Clin. Investigation, 26: 1068–1077, 1947.
168. Elkinton, J. R., Tarail, R., and Peters, J. P.: Transfers of potassium in renal insufficiency. J. Clin. Investigation, 26: 878–888, 1949.
169. Ellenbeck, P.: Site of acidification of urine in frog's and rat's kidney. Quart. J. Exper. Physiol., 30: 305–316, 1940.
170. Elliot, S. R., II, and Scott, H. W., Jr.: Effect of para-aminohippuric acid on sodium thiosulfate determinations in renal clearance studies. Bull. Johns Hopkins Hosp., 83: 213–224, 1948.
171. Ephrigin, C. B., Myers, D. B., and Fulton, M. N.: The modifying effect of various inorganic salts on the diuretic action of salyrgan. Arch. Int. Med., 57: 714–738, 1936.
172. Faban, A., and Marbek, G.: Influence of sulfhydryl compounds on diuresis and renal and cardiac circulatory changes caused by mersalyl. J. Pharmacol. & Exper. Therap., 92: 73–83, 1948.
173. Farnsworth, E. B.: Renal reabsorption of chloride and phosphate in normal subjects and in patients with essential arterial hypertension. J. Clin. Investigation, 25: 897–905, 1946.
174. Faulkner, J. M., and Taylor, F. H. L.: Observations on the renal threshold for ascorbic acid in man. J. Clin. Investigation, 17: 69–75, 1938.
175. Ferguson, M. H., Olbrich, O., Robson, J. S., and Stewart, C. P.: The use of inulin clearance as a measure of glomerular filtration. Quart. J. Exper. Physiol., 35: 251–280, 1950.
176. Ferrannini, A., and Fontana, G.: Action of mercurial diuretics on the elimination of uric acid in normal persons and in those with liver disease. Boll. soc. ital. biol. sper., 14: 567–568, 1939.
177. Finkelstein, N., Alimenosa, L. M., and Smith, H. W.: The renal clearances of hippuric acid and pyridone derivatives. Am. J. Physiol., 133: P276–P277, 1941.
178. Fisher, C., and Ingram, W. R.: Effect of interruption of supraopticohypophyseal tracts on antidiuretic, pressor and oxytocic activity of posterior lobe of hypophysis. Endocrinology, 20: 763–768, 1936.
179. Fisher, C., Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-hypophyseal System. Edwards Bros., Ann Arbor, 1938.
180. Fisher, S. H., Troast, L., Waterhouse, A., and Shannon, J. A.: The relation between chemical structure and physiological disposition of a series of substances allied to sulfanilamide. J. Pharmacol. & Exper. Therap., 79: 372–381, 1943.
181. Fishman, W. H.: Studies on β-glucuronidase; the increase in β-glucuronidase activity of mammalian tissues induced by feeding glucuronidogenic substances. J. Biol. Chem., 136: 229–236, 1940.
182. Fishman, W. H., and Govier, W. H.: The changes in rat kidney cocarboxylase associated with injurious effects of *dl*-serine. Science, 101: 277–279, 1945.
183. Flink, E. B.: Blood transfusion studies; the relationship of hemoglobinemia and of the pH of the urine to renal damage produced by injection of hemoglobin solution into dogs. J. Lab. & Clin. Med., 32: 223–261, 1947.
184. Forster, R. P.: An examination of some factors which alter glomerular activity in the rabbit kidney. Am. J. Physiol., 150: 332–333, 1947.
185. Forster, R. P.: Use of thin kidney slices and isolated renal tubules for direct study of cellular transport kinetics. Science, 108: 65–67, 1948.
186. Forster, R. P.: The use of inulin and creatinine as glomerular filtrate measuring substances in the frog. J. Cell. & Comp. Physiol., 12: 213–223, 1938.
187. Forster, R. P., and Mabs, J. P.: Effect of experimental neurogenic hypertension on renal blood flow and glomerular filtration rates in intact denervated kidneys of unanesthetised rabbits with adrenal glands demedullated. Am. J. Physiol., 150: 534–540, 1947.
188. Forster, R. P., and Mabs, J. R.: Renal function in the rabbit as influenced by the administration of water, anesthetics and diuretics. Federation Proc., 5: 39, 1946.
189. Fraser, A. M.: Action of oxytocic hormone of pituitary gland on urine secretion. J. Physiol., 101: 236–251, 1942.
190. Friedman, B., Moschkowitz, L., and Marrus, J.: Unilateral renal disease and renal vascular changes in relation to hypertension in man. J. Urol., 68: 5–15, 1942.
191. Friedman, G. J., Sherry, S., and Ralli, E. P.: Mechanism of excretion of vitamin C by human kidney at low and normal plasma levels of ascorbic acid. J. Clin. Investigation, 19: 685–689, 1940.

192. Friedman, M.: Observations concerning the effects of (1) sodium salicylate and of (2) sodium salicylate and glycine upon the production and excretion of uric acid and allantoin in the rat. Am. J. Physiol., 152: 303-308, 1948.
193. Friedman, M., and Byers, S. O.: Observations concerning the causes of the excess excretion of uric acid in the Dalmatian dog. J. Biol. Chem., 175: 727-735, 1948.
194. Friedman, M., and Byers, S. O.: Effect of sodium salicylate upon the uric acid clearance of the Dalmatian dog. Am. J. Physiol., 154: 167-169, 1948.
195. Friedman, M., and Byers, S. O.: Clearance of allantoin in the rat and dog as a measure of glomerular filtration rates. Am. J. Physiol., 151: 193-197, 1947.
196. Friedman, M., Byers, S. O., and Abrahm, P. M.: Allantoin clearance as a measure of glomerular filtration in man. Proc. Soc. Exper. Biol. & Med., 64: 322-323, 1947.
197. Friedman, M., Byers, S. O., and Abrahm, P. M.: Renal clearance of allantoin as a measure of glomerular filtration rate. Am. J. Physiol., 155: 278-281, 1948.
198. Friedman, S. M., MacKenzie, K. R., and Friedman, C. L.: Renal function in the adrenalectomized rat. Endocrinology, 43: 129-138, 1948.
199. Friedman, S. M., Polley, J. R., and Friedman, C. L.: The clearance of inulin and sodium p-aminohippurate in the rat. Am. J. Physiol., 150: 340-353, 1947.
200. Friedman, S. M., Polley, J. R., and Friedman, C. L.: The effect of desoxycorticosterone acetate on blood pressure, renal function and electrolyte pattern in the intact rat. J. Exper. Med., 87: 330-338, 1948.
201. Fuco, N. W.: The antidiuretic action of yohimbine. Endocrinology, 34: 142-145, 1944.
202. Gabrilove, J. L.: Chloride excretion during glycosuria in patients with diabetes. J. Clin. Investigation, 25: 256-260, 1946.
203. Gaudino, M., and Levitt, M. F.: Influence of the adrenal cortex on body water. J. Clin. Investigation, 28: 1487-1497, 1949.
204. Gaunt, R.: Water diuresis and water intoxication in relation to the adrenal cortex. Endocrinology, 34: 400-415, 1944.
205. Gaunt, R.: Endocrine factors in water diuresis and water intoxication. Tr. New York Acad. Sc., 6: 179-187, 1944.
206. Gaunt, R. (Ed.): The adrenal cortex. Ann. New York Acad. Sc., 50: 809-678, 1949.
207. Gilman, A., and Goodman, L.: Secretory response of posterior pituitary to need for water conservation. J. Physiol., 90: 113-124, 1937.
208. Gilman, A., Philips, F. S., Koelle, E. S., Allen, R. P., and St. John, E.: The metabolic reduction and nephrotoxic action of tetrathionate in relation to a possible interaction with sulfhydryl compounds. Am. J. Physiol., 147: 115-126, 1946.
209. Gilman, A., Philips, F. S., and Koelle, E. S.: The renal clearance of thiosulfate with observations on its volume distribution. Am. J. Physiol., 146: 348-357, 1946.
210. Gilman, A., Philips, F. S., and Koelle, E. S.: The renal clearance of thiosulfate in the dog. Federation Proc., 5: 33, 1946.
211. Gomyoda, E., Little, J. D., Grim, W. M., and Dunbar, P.: The renal amino acid clearance in the normal dog. Am. J. Physiol., 140: 668-686, 1944.
212. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease. Commonwealth Fund, New York, 1944.
213. Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W.: Relations of effective renal blood flow and glomerular filtration to tubular excretory mass in normal man. J. Clin. Investigation, 19: 789-799, 1940.
214. Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W.: Effective renal blood flow in subjects with essential hypertension. J. Clin. Investigation, 20: 637-653, 1941.
215. Goldring, W., Clark, R. W., and Smith, H. W.: The phenol red clearance in normal man. J. Clin. Investigation, 15: 221-228, 1936.
216. Goldsteiner, J. W., and Stowe, C. H.: The relative independence of sodium and chloride excretion. J. Clin. Endocrinol., 9: 365-371, 1949.
217. Gomori, G.: Distribution of acid phosphatase in tissues under normal and under pathologic conditions. Arch. Path., 32: 189-199, 1941.
218. Gomori, G.: Microtechnical demonstration of phosphatase in tissue sections. Proc. Soc. Exper. Biol. & Med., 42: 23-26, 1939.
219. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. The MacMillan Co., New York, 1941.
220. Goodwin, W. E., Sloan, R. D., and Scott, W. W.: The "trueta" renal vascular "shunt"; an experimental demonstration of neurovascular control of the renal circulation in the rabbit, dog, and monkey. J. Urol., 61: 1010-1027, 1949.
221. Govaerts, P.: Origine rénale ou tissulaire de la diurèse par un composé mercuriel organique. Compt. rend. Soc. de biol., 99: 647-649, 1928.
222. Govier, W. M., Grelis, M. E., Yanz, N. S., and Beyer, K. H.: Studies on the mechanism of action of sympathomimetic amines; the oxidation of tyramine by rat liver homogenates. J. Pharmacol. & Exper. Therap., 97: 149-158, 1946.
223. Green, D. E., Loomis, W. F., and Auerbach, V. H.: Studies on the cytochrome system; the complete oxidation of pyruvic acid to carbon dioxide and water. J. Biol. Chem., 172: 339-408, 1948.
224. Green, D. M., and Farah, A.: Influence of sodium load on sodium excretion. Am. J. Physiol., 158: 444-456, 1949.

225. Griggs, D. E., and Johns, V. J.: Influence of mercurial diuretics on the excretion of sodium, potassium and chlorides. California Med., 69: 133–137, 1948.
226. Grimmell, L. J., Chertack, M. M., Rehfuss, H. L., Kendrick, A. B., and Forrest, R. A.: Effect of hyperglycemia on the clearances of inulin and para-aminohippuric acid. Proc. Central Soc. Clin. Research, 21: 64, 1948.
227. Grollman, A.: The Adrenals. The Williams & Wilkins Co., Baltimore, 1936.
228. Haas, H. T. A.: Mercurial diuretics. Pharmacie, 2: 1–8, 1947.
229. Hagenbeen, N. R., Keiding, R., and Schmidt, V.: Clearance determinations after oral administration of parahippuric acid. Scandinav. J. Clin. & Lab. Investigation, 2: 12–13, 1950.
230. Hall, C. A., Frame, B., and Dreil, V. A.: Renal excretion of water and antidiuretic substances in patients with hepatic cirrhosis and rats with dietary liver injury. Endocrinology, 44: 76–82, 1949.
231. Handley, C. A.: Effect of thyroxine and dinitrophenol on renal functions. Federation Proc., 9: 281–282, 1950.
232. Handley, C. A., and LaForge, M.: Effects of thiols on mercury diuresis. Proc. Soc. Exper. Biol. & Med., 65: 74–75, 1947.
233. Handley, C. A., Sigafoos, R. B., Telford, J., and LaForge, M.: Effect of chronic administration of mercurial diuretics on glomerular filtration in the dog. Proc. Soc. Exper. Biol. & Med., 72: 201–203, 1949.
234. Hare, K., Hickey, R. C., and Hare, R. S.: The renal excretion of an antidiuretic substance by the dog. Am. J. Physiol., 134: 240–244, 1941.
235. Hare, K., Melville, E. V., Chambers, G. H., and Hare, R. S.: Assay of antidiuretic material in blood and urine. Endocrinology, 36: 323–331, 1945.
236. Hare, M. L. C.: Tyramine oxidase; new enzyme system in liver. Biochem. J., 22: 968–979, 1928.
237. Hare, R. S., Hare, K., and Phillips, D. M.: The renal excretion of chloride by the normal and by the diabetes insipidus dog. Am. J. Physiol., 149: 234–248, 1943.
238. Harris, G. W.: Neural control of the pituitary gland. Physiol. Rev., 28: 139–179, 1948.
239. Hartung, W. H.: Inactivation and detoxication of pressor amines. Ann. Rev. Biochem., 15: 503–516, 1946.
240. Hatman, J. M., Shumway, N. P., Dumke, P., and Miller, M.: Experimental hyposthenuria. J. Clin. Investigation, 18: 195–212, 1939.
241. Heinbecker, P., Rolf, D., and White, H. L.: Effects of extracts of hypophysis, thyroid, and adrenal cortex on some renal functions. Am. J. Physiol., 139: 543–549, 1943.
242. Heller, H.: Action of antidiuretic principle of posterior pituitary extracts on urine excretion of anaesthetised animals. J. Physiol., 98: 406–418, 1940.
243. Herrin, R. C.: Factors affecting the tests of kidney function. Physiol. Rev., 21: 529–562, 1941.
244. Herrin, R. C., and Nicholes, H. J.: The influence of vitamin A upon urea and inulin clearance in the dog. Am. J. Physiol., 125: 786–801, 1939.
245. Herrmann, G., and Dicherd, G. M.: Further studies on the mechanism of diuresis with special reference to the action of some newer diuretics. J. Lab. & Clin. Med., 22: 767–779, 1937.
246. Hickey, R. C., and Hare, K.: The renal excretion of chloride and water in diabetes insipidus. J. Clin. Investigation, 23: 768–775, 1944.
247. Hines, L. E.: The effect of diuresis by mercurials on the clinical course of congestive heart failure. J. Am. M. A., 110: 303–306, 1938.
248. Hjort, A. M.: Antidiuretic effect of pituitary oxytocic and pressor principles on water diuresis in man. Endocrinology, 12: 496–500, 1928.
249. Höber, R.: Effects of some sulfonamides on renal secretion. Proc. Soc. Exper. Biol. & Med., 49: 87–90, 1942.
250. Hogeboom, G. H.: Succinic dehydrogenase of mammalian liver. J. Biol. Chem., 142: 739–740, 1940.
251. Hogeboom, G. H., Claude, A., and Hotchkiss, R. D.: The distribution of cytochrome oxidase and succinoxidase in the cytoplasm of the mammalian liver cell. J. Biol. Chem., 165: 615–629, 1946.
252. Holden, R. F., Jr., and Bulger, H. A.: The nature of volume effects in renal clearances. Am. J. Physiol., 145: 633–645, 1946.
253. Houck, C. R.: Mutual depression of reabsorption and excretory maxima in renal tubules. Proc. Soc. Exper. Biol. & Med., 63: 396–401, 1946.
254. Ingle, D. J.: Metabolic functions of the endocrine system. Ann. Rev. Physiol., 7: 537–566, 1945.
255. Ingle, D. J., and Sheppard, R.: Effect of two adrenal steroids and insulin on the excretion of sodium and chloride. Federation Proc., 3: 21, 1944.
256. Ingram, W. R., Fisher, C., and Ranson, S. W.: Experimental diabetes insipidus in monkey. Arch. Int. Med., 57: 1067–1080, 1936.
257. Ingram, W. R., Ladd, L., and Benbow, J. T.: Excretion of antidiuretic substance and its relation to hypothalamicohypophyseal system in cats. Am. J. Physiol., 127: 544–551, 1939.
258. Joseph, S., Schweiker, M., Ulmer, N. Z., and Gaunt, R.: The anterior pituitary and its relation to the adrenal cortex in water diuresis. Endocrinology, 35: 338–346, 1944.
259. Josephson, B.: The saturation of the diodrast excretion of the renal tubular cells. Acta med. Scandinav., Supp. 186: 239–249, 1947.
260. Josephson, B.: Examination of "diodrast" clearance and tubular excretory capacity in man by means of two single injections of "diodrast" (umbudil). Acta med. Scandinav., 128: 515–537, 1947.
261. Kalckar, H. M.: Phosphorylation in kidney tissue. Enzymologia, 2: 47–53, 1937.
262. Kalckar, H. M.: Significance of phosphorylation in kidney tissue. Skandinav. Arch. f. Physiol., 77: 46–47, 1937.
263. Kalckar, H. M.: Nature of phosphoric esters formed in kidney extracts. Biochem. J., 33: 631–641, 1939.
264. Kalckar, H. M.: The nature of energetic coupling in biological synthesis. Chem. Rev., 28: 71–178, 1941

265. KAPLAN, B. I., AND SMITH, H. W.: Excretion of inulin, creatinine, xylose and urea in the normal rabbit. Am. J. Physiol., 113: 354-360, 1935.
266. KATTUS, A. A., SINCLAIR-SMITH, B., GEHRET, J., AND NEWMAN, E. V.: The effect of exercise on the renal mechanism of electrolyte excretion in normal subjects. Bull. Johns Hopkins Hosp., 84: 344-365, 1949.
267. KAUFMAN, R. E.: Immediate fatalities after intravenous mercurial diuretics. Ann. Int. Med., 28: 1060-1067, 1948.
268. KEILIN, D., AND HARTREE, E. F.: Succinic dehydrogenase-cytochrome system of cells; intracellular respiratory system catalysing aerobic oxidation of succinic acid. Proc. Roy. Soc., London, s. B., 129: 277-306, 1940.
269. KEILIN, D., AND MANN, T.: Hematin compound of peroxidase. Proc. Roy. Soc., London, s. B., 122: 119-133, 1937.
270. KEITH, N. M.: The action and use of diuretics with especial reference to mercurial compounds. J. Am. M. A., 107: 2047-2051, 1936.
271. KEITH, N. M., AND OSTERBERG, A. E.: The excretion of potassium by the kidney. Am. J. Physiol., 129: 305-306, 1940.
272. KEMPNER, W., LESSEUR, J. M., NEWBORG, B., AND WHICKER, C. F.: Sulfate and phosphate excretion in urine of patients on rice diet. Am. J. M. Sc., 216: 667-688, 1948.
273. KIRSTEIN, L.: Studies on the diuretic effect of injectable xanthine derivatives. Acta. med. Scandinav., 128: 122-137, 1947.
274. KLOPP, C., YOUNG, N. F., AND TAYLOR, H. C.: Probable errors in simultaneous measurement of separate kidney functions. J. Clin. Investigation, 24: 117-121, 1945.
275. KLOPP, C., YOUNG, N. F., AND TAYLOR, H. C.: Effects of testosterone and of testosterone propionate on renal functions in man. J. Clin. Investigation, 24: 188-191, 1945.
276. KOCHAKIAN, C. D.: Comparison of renotrophic with androgenic activity of various steroids. Am. J. Physiol., 142: 315-325, 1944.
277. KOCHAKIAN, C. D.: Effect of estrogens on the body and organ weights and the arginase and "alkaline" and "acid" phosphatases of the liver and kidney of castrated male mice. Am. J. Physiol., 151: 126-129, 1947.
278. KOCHAKIAN, C. D., AND DOHERTY, P.: Enzyme studies on the "endocrine kidney." Proc. Soc. Exper. Biol. & Med., 67: 61-62, 1948.
279. KOCHAKIAN, C. D., AND VAIL, V. N.: Effect of adrenalectomy, adrenal cortex extract, and adrenal cortex extract plus testosterone propionate on phosphatases of rat tissues. J. Biol. Chem., 156: 779-780, 1944.
280. KOLNTSKY, S., AND GUSTAFSON, G. E.: The effects of temporary cessation of renal blood flow in rats. J. Clin. Investigation, 26: 1072-1078, 1947.
281. KREBS, H. A.: Inhibition of carbonic anhydrase by sulfonamides. Biochem. J., 43: 525-533, 1948.
282. KREBS, H. A.: Metabolism of amino-acids; synthesis of glutamic acid and ammonia, and enzymic hydrolysis of glutamine in animal tissues. Biochem. J., 29: 1951-1969, 1935.
283. KREBS, H. A., AND ROUGHTON, F. J. W.: Carbonic anhydrase as a tool in studying the mechanism of reactions involving carbonic acid, carbon dioxide or bicarbonate ion. Biochem. J., 43: 550-555, 1948.
284. KUHN, J. P., FUTCHER, P. H., AND GOLDMAN, M. L.: Unilateral adrenalectomy, unilateral splanchnic nerve resection and homolateral renal function. Am. J. Physiol., 154: 229-240, 1948.
285. LAMBRECHTS, A.: Phlorhizin et muscles du chien in vivo et in vitro. Compt. rend. Soc. de biol., 118: 1248-1250, 1935.
286. LAMPORT, H.: Kidney. Ann. Rev. Physiol., 7: 331-364, 1945.
287. LAMPORT, H.: The relative changes in afferent and efferent arteriolar resistance in the normal human kidney. J. Clin. Investigation, 20: 545-548, 1941.
288. LAMPORT, H.: Formulae for afferent and efferent arteriolar resistance in the human kidney: an application to the effects of spinal anesthesia. J. Clin. Investigation, 20: 535-544, 1941.
289. LANDIS, E. M., ELSOM, K. A., BOTT, P. A., AND SHIELS, E. H.: Simultaneous plasma clearances of creatinine and certain organic compounds of iodine in relation to human kidney function. J. Clin. Investigation, 15: 397-409, 1936.
290. LANDOWNE, M., AND ALVING, A. S.: A clinical method of determining the specific renal functions of glomerular filtration, maximal tubular excretion or reabsorption (and "effective blood flow"), using a single injection of a single substance. Proc. Central Soc. Clin. Research, 18: 5-6, 1945.
291. LANDOWNE, M., AND ALVING, A. S.: A method of determining the specific renal functions of glomerular filtration, maximal tubular excretion (or reabsorption), and "effective blood flow" using a single injection of a single substance. J. Lab. & Clin. Med., 32: 931-942, 1947.
292. LATTIMER, J. K.: The action of testosterone propionate upon the kidneys of rats, dogs, and man. J. Urol., 48: 778-794, 1942.
293. LAUSON, H. D., BRADLEY, S. E., AND COURNAND, A.: Renal circulation in shock. J. Clin. Investigation, 23: 381-402, 1944.
294. LEAF, A., CAMARA, A. A., AND ALBERTSON, B.: Renal tubular secretion of potassium in man. J. Clin. Investigation, 28: 1526-1533, 1949.
295. LEHR, D., TERRANOVA, R., AND BOYD, L. J.: The action of some central nervous system depressants upon watersalyrgan diuresis (an experimental study). Urol. & Cutan. Rev., 47: 661-669, 1943.
296. LEVEDAHL, B. H., AND SAMUELS, L. T.: The effect of testosterone and methyltestosterone on guanidoacetic acid, creatine, and creatinine in plasma and urine. J. Biol. Chem., 176: 337-346, 1948.
297. LEVVY, G. A., AND STOREY, I. D. E.: The measurement of glucuronide synthesis by tissue preparations. Biochem. J., 44: 395-399, 1949.

208. Lewis, R. A., Thorn, G. W., Koepf, G. F., and Dorrance, S. S.: Role of adrenal cortex in acute anoxia. J. Clin. Investigation, 21: 33–46, 1942.

209. Lindahl, O., and Josephson, B.: Kidney function and renal clearances of some sulfanilamide derivatives. Acta med. Scandinav., 120: 196–236, 1945.

210. Lindhooom, G. A.: Beobachtungen bei einem Fall von Diabetes insipidus et mellitus. Deutsches Arch. f. klin. Med., 175: 74–89, 1933.

201. Lippman, R. W.: Endogenous and exogenous creatinine clearances in the rat. Am. J. Physiol., 151: 211–214, 1947.

202. Lipschitz, W. L., and Burding, E.: Mechanism of biological formation of conjugated glucuronic acids. J. Biol. Chem., 129: 353–358, 1939.

203. Lipschitz, W. L., and Hadidian, Z.: Amides, amines and related compounds as diuretics. J. Pharmacol. & Exper. Therap., 81: 84–94, 1944.

204. Lipschitz, W. L., Hadidian, Z., and Kerpscar, A.: Bioassay of diuretics. J. Pharmacol. & Exper. Therap., 79: 97–110, 1943.

205. Little, J. M., Wallace, S. L., Weatley, E. C., and Anderson, G. A.: Effect of pitressin on the urinary excretion of chloride and water in the human. Am. J. Physiol., 151: 174–185, 1947.

206. Loewe, L., Rosenblatt, P., and Altura-Werber, E.: A refractory case of subacute endocarditis due to Veillonella gazogenes clinically arrested by a combination of penicillin, sodium para-aminohippurate and heparin. Am. Heart J., 32: 337–338, 1946.

207. Loewe, L., Rosenblatt, P., Altura-Werber, E., and Kozak, M.: The prolonging action of penicillin by p-aminohippuric acid. Proc. Soc. Exper. Biol. & Med., 58: 298–300, 1945.

208. Loomis, T. A., Koepf, G. F., and Hubbard, R. S.: The excretion of sulfanilamide and acetylsulfanilamide by the human kidney. Am. J. Physiol., 141: 158–163, 1944.

209. Loomis, W. E., and Lipmann, F.: Reversible inhibition of the coupling between phosphorylation and oxidation. J. Biol. Chem., 173: 807–808, 1948.

210. Lotspeich, W. D.: Renal tubular reabsorption of inorganic sulfate in the normal dog. Am. J. Physiol., 151: 311–318, 1947.

211. Lotspeich, W. D., Swan, R. C., and Pitts, R. F.: The renal tubular reabsorption of chloride. Am. J. Physiol., 148: 445–448, 1947.

212. Lundquist, F.: Renal tubular secretion of sulfonamides and p-aminobenzoic acid. Acta pharmacol. et toxicol. 1: 307–324, 1945.

213. Lundsgaard, E.: Die Wirkung von Phlorrhizin auf die Glucoseresorption. Biochem. Ztschr., 264: 221–223, 1933.

214. Lundsgaard, E.: Inhibition of esterification processes as the cause of the phlorhizin action. Biochem. Ztschr., 264: 209–220, 1933.

215. Lyman, C. L., and Guzman Barron, E. S.: Studies on biological oxidations; oxidations and carbohydrate synthesis in nephritic kidney slices. J. Biol. Chem., 133: 293–306, 1940.

216. McCance, R. A.: The excretion of urea, salts and water during periods of hydropaenia in man. J. Physiol., 104: 196–209, 1945.

217. McCance, R. A., and von Fenck, M. A.: The titratable acidity, pH, ammonia and phosphates in the urines of very young infants. Arch. Dis. Childhood, 22: 200–209, 1947.

218. McCance, R. A., and Widdowson, E. M.: Alkalosis with disordered kidney functions; observations on case. Lancet, 2: 347–349, 1937.

219. McDonald, R. K., and Miller, J. H.: Effect of mercury on renal tubular transfer of p-aminohippurate and glucose in man. Proc. Soc. Exper. Biol. & Med., 72: 406–410, 1949.

220. MacKay, E. M.: Degree of compensatory renal hypertrophy following unilateral nephrectomy; influence of testosterone propionate. Proc. Soc. Exper. Biol. & Med., 45: 216–217, 1940.

221. McKinney, S. E., and Peck, H. M.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid): toxicologic and pathologic studies. To be published.

222. MacNider, W. De B., Trott, J. C., and Bruce, M. D.: Concerning the inability of 2,3 dithiopropanol (BAL) to prevent or to modify the acute renal injury induced by uranium nitrate. J. Pharmacol. & Exper. Therap., 92: 262–275, 1948.

223. McQuarrie, I., and Ziegler, M. M.: Disturbances in electrolyte metabolism of patients with nephrotic syndrome. Postgrad. Med., 6: 281–291, 1949.

224. McQuarrie-Williams, M., and Thompson, K. W.: Effect of ablation of hypophysis upon weight of kidney of rat. Yale J. Biol. & Med., 12: 531–541, 1940.

225. Magoun, H. W., Fisher, C., and Ranson, S. W.: Neurohypophysis and water exchange in monkey. Endocrinology, 26: 161–174, 1939.

226. Malup, N. S.R: Role of renal innervation in renal tubular function. Am. J. Physiol., 139: 103–108, 1943.

227. Mann, T., and Keilin, D.: Sulfanilamide as a specific inhibitor of carbonic anhydrase. Nature, 146: 164–165, 1940.

228. Marshall, D., and Hoffman, W. S.: The nature of the altered renal function in lower nephron nephrosis. J. Lab. & Clin. Med., 33: 1468, 1948.

229. Marshall, E. K., Jr.: The secretion of phenol red by the mammalian kidney. Am. J. Physiol., 99: 77–86, 1931.

230. Marshall, E. K., Jr.: The comparative physiology of the kidney in relation to theories of renal secretion. Physiol. Rev., 14: 133–180, 1934.

231. Marshall, E. K., Jr.: Bacterial chemotherapy; pharmacology of sulfanilamide. Physiol. Rev., 19: 240–289, 1939.

332. Marshall, E. K., Jr.: Further observations on the antidiuretic effect of cinchoninic acid derivatives. Bull. Johns Hopkins Hosp., 86: 86–101, 1950.

333. Marshall, E. K., Jr., and Blanchard, K. C.: Antidiuretic effect of 3-hydroxycinchoninic acid derivatives. J. Pharmacol. & Exper. Therap., 95: 186–190, 1949.

334. Marshall, E. K., Jr., Cutting, W. C., and Emerson, K.: Toxicity of sulfanilamide. J. Am. M. A., 110: 253–257, 1938.

335. Marshall, E. K., and Kolls, A. C.: Studies on nervous control of kidney in relation to diuresis and urinary secretion. Am. J. Physiol., 49: 302–343, 1919.

336. Marshall, E. K., Jr., and Crane, M. M.: Secretory function of renal tubules. Am. J. Physiol., 70: 455–485, 1924.

337. Marshall, E. K., Jr., and Vickers, J. L.: The mechanism of the elimination of phenolsulphonephthalein by the kidney; proof of secretion by convoluted tubules. Bull. Johns Hopkins Hosp., 34: 1–6, 1923.

338. Mason, M. F., Blalock, A., and Harrison, T. R.: The direct determination of the renal blood flow and renal oxygen consumption of the unanesthetised dog. Am. J. Physiol., 118: 667–678, 1937.

339. Menaker, W.: Buffer equilibria and reabsorption in the production of urinary acidity. Am. J. Physiol., 154: 174–184, 1948.

340. Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure; evidence of "forward failure" as primary cause of edema. J. Clin. Investigation, 26: 389–400, 1946.

341. Meyerhof, O., and Gellhorn, N.: The rate of anaerobic glycolysis of various benzoes in mammalian tissues. Arch. Biochem., 12: 405–424, 1947.

342. Meyerhof, O., and Wilson, J. R.: Studies on glycolysis of brain preparations. Arch. Biochem., 17: 183–189, 1948.

343. Miller, B. F., and Winkler, A.: The ferrocyanide clearance in man. J. Clin. Investigation, 15: 489–493, 1936.

344. Miller, B. F., and Winkler, A. W.: Renal excretion of endogenous creatinine in man; comparison with exogenous creatinine and inulin. J. Clin. Investigation, 17: 31–40, 1938.

345. Miller, C. S., Ziegler, C., and Sprague, J. M.: The synthesis of p-(di-n-propylsulfamyl)-benzoic acid (Benemid) and related compounds. To be published.

346. Mills, G. T.: The glucuronidase content of animal tissues and the role of the spleen in the metabolism of conjugated glucuronic acids. Biochem. J., 49: 253–255, 1946.

347. Milnor, P., Burch, R., Ray, T., Tremewoot, S., and Berberian, G.: Considerations of renal, hepatic and extremital arteriovenous differences in concentration of radiomercury of a mercurial diuretic. J. Clin. Investigation, 29: 72–86, 1950.

348. Minkowski, O.: Untersuchungen über Diabetes Mellitus nach Extirpation des Pankreas. Arch. f. exper. Path. u. Pharmakol., 31: 85, 1893.

349. Modell, W., and Gold, H.: Comparison of the diuretic action of sodium dehydrocholate and mercupurin in man. J. Clin. Investigation, 24: 384–387, 1945.

350. Modell, W., and Knop, S.: Acute toxicity of mercurial diuretics. Proc. Soc. Exper. Biol. & Med., 55: 80–83, 1944.

351. Mokotoff, R., Brams, W., Katz, L. N., and Howell, K. M.: The treatment of bacterial endocarditis with penicillin; results of 17 consecutive unselected cases. Am. J. M. Sc., 211: 396–416, 1946.

352. Mokotoff, R., and Ross, G.: Renal blood flow and sodium excretion studies in congestive heart failure. J. Clin. Investigation, 26: 1190–1191, 1947.

353. Mokotoff, R., Ross, G., and Leiter, L.: Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. J. Clin. Investigation, 27: 1–9, 1948.

354. Möller, E., McIntosh, J. F., and Van Slyke, D. D.: Studies of urea excretion; relationship between urine volume and the rate of urea excretion by normal adults. J. Clin. Investigation, 6: 427–465, 1928.

355. Montgomery, H.: Quantitative studies of composition of glomerular urine; reaction of glomerular urine of frogs and Necturi. J. Biol. Chem., 116: 749–761, 1935.

356. Montgomery, H., and Pierce, J. A.: Site of acidification of urine within renal tubule in Amphibia. Am. J. Physiol., 118: 144–153, 1937.

357. Motzfeldt, K.: Experimental studies on the relation of the pituitary body to renal function. J. Exper. Med. 25: 153–183, 1917.

358. Mudge, G. H., Ames, A., III, Foulks, J., and Gilman, A.: Effect of drugs on renal secretion of potassium in the dog. Am. J. Physiol., 161: 151–158, 1950.

359. Mudge, G. H., Foulks, J., and Gilman, A.: The renal excretion of potassium. Proc. Soc. Exper. Biol. & Med., 67: 545–547, 1948.

360. Mudge, G. H., Foulks, J., and Gilman, A.: Renal secretion of potassium in the dog during cellular dehydration. Am. J. Physiol., 161: 159–166, 1950.

361. Mudge, G. H., and Taggart, J. V.: Effect of acetate on the renal excretion of p-aminohippurate in the dog. Am. J. Physiol., 161: 191–197, 1950.

362. Mudge, G. H., and Taggart, J. V.: Effect of 2,4-dinitrophenol on renal transport mechanisms in the dog. Am. J. Physiol., 161: 173–180, 1950.

363. Mylon, E., and Heller, J. H.: Renal glutaminase. Am. J. Physiol., 154: 542–548, 1948.

364. Mylon, E., and Smith, E. R.: Mechanisms concerned in necrosis effected by unsaturated fatty acid. Arch. Path., 45: 21–34, 1948.

365. Nash, T. P., Jr.: Phlorhizin diabetes. Physiol. Rev., 7: 385–420, 1927.

366. Newman, E. V.: Function of the kidney and metabolic changes in cardiac failure. Am. J. Med., 7: 490–496, 1949.

367. Newman, E. V., Bordley, J., III, and Winternitz, J.: The interrelationships of glomerular filtration rate (mannitol clearance), extracellular fluid volume, surface area of the body and plasma concentration of mannitol; definition of extracellular fluid clearance determined by following plasma concentration after single injection of mannitol. Bull. Johns Hopkins Hosp., 75: 253–268, 1944.
368. Newman, E. V., Gilman, A., and Philips, F. S.: The renal clearance of thiosulfate in man. Bull. Johns Hopkins Hosp., 79: 229–242, 1946.
369. Newman, E., Kattus, A., Genecin, A., Genest, J., Calkins, E., and Murphy, J.: Observations on the clearance method of determining renal plasma flow with diodrast, para-aminohippuric acid (PAH) and para-acetylaminohippuric acid (PACA). Bull. Johns Hopkins Hosp., 84: 135–168, 1949.
370. Nicholson, T. F.: Renal function as affected by experimental unilateral kidney lesions; the effect of cyanide. Biochem. J., 45: 112–118, 1949.
371. Nohr, M.: Untersuchungen über das Verhalten des Kaliums im Organismus; ueber Schwankungen der Kaliumsalzen und bei verschiedenen Diuresformen und ihre Beziehung zur Kaliumausscheidung im Harn. Skandin. Arch. f. Physiol., 55: 211–230, 1930.
372. O'Connor, W. J.: The effect of section of the supraoptico-hypophyseal tracts on the inhibition of water-diuresis by emotional stress. Quart. J. Exper. Physiol., 33: 149–161, 1946.
373. Okui, T.: Comparative studies on the action of fraxinin and of several other diuretics as well as of gout remedies on urine and uric acid elimination. Tôhoku J. Exper. Med., 32: 235–252, 1938.
374. Orth, O. S., and Stoteman, J. W.: Constancy of urea clearances in dogs following surgical anesthesias with cyclopropane, ether and chloroform. Proc. Soc. Exper. Biol. & Med., 39: 403–406, 1938.
375. Ortiz, E. A.: Demonstration of a cyclic change in the histochemistry of the kidney synchronised with the estrous cycle in the rat. Endocrinology, 36: 92–97, 1945.
376. Ortiz, K. A., and Ortiz, J. G.: The specificity of sex hormones on the tissue aldehyde shift in the rat kidney and of fuchsin sulfurous acid reagent on aldehydes. J. Pharmacol. & Exper. Therap., 87: 306–312, 1946.
377. Ostern, P., Gutekr, J. A., and Terszakowic, J.: Über die Bildung des Hexose-monophosphorsäure-esters, und dessen Umwandlung in Fructose-diphosphorsäure-ester im Muskel. Ztschr. f. physiol. Chem., 243: 9–37 1936.
378. Peck, H. M.: The renal extraction and clearance of p-aminohippurate and phenol red. To be published.
379. Peck, H. M., Tillson, E. K., Waller, W. S., and Beyer, K. H.: The renal extraction and excretion of carinamide (4'-carboxyphenylmethanesulfonanilide). J. Lab. & Clin. Med., 35: 87–96, 1950.
380. Peters, R. A., Stocken, L. A., and Thompson, R. H. S.: British antilewisite (BAL). Nature, 156: 616–619, 1945.
381. Pfeiffer, C. A., Emmel, V. M., and Gardner, W. U.: Renal hypertrophy in mice receiving estrogens and androgens. Yale J. Biol. & Med., 12: 493–501, 1940.
382. Pfeiffer, J. B., and Ripley, H. S.: Measurement of renal blood flow and glomerular filtration during variations in blood pressure related to changes in emotional state and life situation. J. Clin. Investigation, 26: 1193, 1947.
383. Phillips, D. M., and Hare, K.: Antidiuretic potency of the neurohypophysis of the cat following pituitary-stalk section. Endocrinology, 37: 30–33, 1945.
384. Phillips, R. A.: Kidney. Ann. Rev. Physiol., 11: 493–526, 1949.
385. Pickford, M.: Control of the secretion of antidiuretic hormone from the pars nervosa of the pituitary gland. Physiol. Rev., 25: 573–595, 1945.
386. Pickford, M.: The inhibitory action of acetylcholine on water diuresis in the dog. J. Physiol., 92: 16P–17P, 1938.
387. Pickford, M.: The inhibitory effect of acetylcholine on water diuresis in the dog and its pituitary transmission. J. Physiol., 95: 226–238, 1939.
388. Pickford, M., and Ritchie, A. E.: Experiments on the hypothalamic-pituitary control of water excretion in dogs. J. Physiol., 104: 105–128, 1945.
389. Pierce, J. A., and Montgomery, H.: Microquinhydrone electrode: its application to determination of pH of glomerular urine of Necturus. J. Biol. Chem., 110: 763–775, 1935.
390. Pitts, R. F.: The clearance of creatinine in the phlorizinized dog. Am. J. Physiol., 109: 543–549, 1934.
391. Pitts, R. F.: A comparison of the renal reabsorptive processes for several amino acids. Am. J. Physiol., 140: 535–547, 1944.
392. Pitts, R. F.: The renal regulation of acid-base balance with special reference to the mechanism for acidifying the urine. Science, 102: 49–54, 81–85, 1945.
393. Pitts, R. F.: Kidney. Ann. Rev. Physiol., 8: 199–230, 1946.
394. Pitts, R. F.: The excretion and reabsorption of bicarbonate by the normal human kidney. J. Clin. Investigation, 26: 1189–1194, 1947.
395. Pitts, R. F., and Alexander, R. S.: Renal reabsorptive mechanism for inorganic phosphate in normal and acidotic dogs. Am. J. Physiol., 142: 648–663, 1944.
396. Pitts, R. F., and Alexander, R. S.: Nature of renal tubular mechanism for acidifying urine. Am. J. Physiol., 144: 239–254, 1945.
397. Pitts, R. F., Ayer, J. L., and Schiess, W. A.: The renal regulation of acid-base balance in man; the reabsorption and excretion of bicarbonate. J. Clin. Investigation, 28: 35–44, 1949.
398. Pitts, R. F., and Duggar, J. J.: Studies on diuretics; the relationship between glomerular filtration rate, proximal tubular absorption of sodium and diuretic efficacy of mercurials. J. Clin. Investigation, 29: 372–379, 1950.

399. PITTS, R. F., AND LOTSPEICH, W. D.: Bicarbonate and the renal regulation of acid base balance. Am. J. Physiol., 147: 138–154, 1946.
400. PITTS, R. F., AND LOTSPEICH, W. D.: Factors governing the rate of excretion of titratable acid in the dog. Am. J. Physiol., 147: 481–492, 1946.
401. PITTS, R. F., AND LOTSPEICH, W. D.: Use of thiosulfate clearance as a measure of glomerular filtration rate in acidotic dogs. Proc. Soc. Exper. Biol. & Med., 64: 234–237, 1947.
402. PITTS, R. F., LOTSPEICH, W. D., SCHIESS, W. A., AND AYER, J. L.: The regulation of acid-base balance in man; the nature of the mechanism for acidifying the urine. J. Clin. Investigation, 27: 48–56, 1948.
403. POPPER, H.: Glomerulusinsuffizienz und tubuläre Funktionsstörung. Klin. Wchnschr., 16: 1454–1460, 1937.
404. POTTER, V. R.: Studies on the mechanism of hydrogen transport in animal tissues; the succinoxidase system. J. Biol. Chem., 141: 775–787, 1941.
405. POTTER, V. R.: Coupling between phosphorylation and oxidation of the 4-carbon acids in rat kidney homogenates. Arch. Biochem., 6: 439–453, 1945.
406. POTTER, V. R.: The assay of animal tissues for respiratory enzymes; the malic dehydrogenase system. J. Biol. Chem., 165: 311–334, 1946.
407. POTTER, V. R.: The assay of animal tissues for respiratory enzymes; further studies on oxidative phosphorylation. J. Biol. Chem., 169: 17–37, 1947.
408. POTTER, V. R., AND DUBOIS, K. P.: Studies on mechanism of hydrogen transport in animal tissues; inhibitor studies with succinic dehydrogenase. J. Gen. Physiol., 26: 391–404, 1943.
409. POTTER, V. R., AND ELVEHJEM, C. A.: A modified method for the study of tissue oxidations. J. Biol. Chem., 114: 495–504, 1936.
410. POTTER, V. R., AND ELVEHJEM, C. A.: The effect of inhibitors on succinoxidase. J. Biol. Chem., 117: 341–349, 1937.
411. PUGH, C. E. M., AND QUASTEL, J. H.: Oxidation of amines by animal tissues. Biochem. J., 31: 2306–2331, 1937.
412. QUASTEL, J. H., AND WHETHAM, M. D.: Dehydrogenations produced by resting bacteria. Biochem. J., 19: 520–531, 1925.
413. QUASTEL, J. H., AND WHEATLEY, A. H. M.: Biological oxidations in the succinic acid series. Biochem. J., 26: 117–128, 1931.
414. RALLI, E. P., FRIEDMAN, G. J., AND RUBIN, S. H.: The mechanism of the excretion of vitamin C by the human kidney. J. Clin. Investigation, 17: 765–770, 1938.
415. RAMMELKAMP, C. H., AND BRADLEY, S. E.: Excretion of penicillin in man. Proc. Soc. Exper. Biol. & Med., 53: 30–32, 1943.
416. RAMMELKAMP, C. H., AND KEEFER, C. S.: Absorption, excretion, and distribution of penicillin. J. Clin. Investigation, 23: 425–437, 1943.
417. RANGES, H. A., CHASIS, H., GOLDRING, W., AND SMITH, H. W.: The functional measurement of the number of active glomeruli and tubules in the kidneys of normal and hypertensive subjects. Am. J. Physiol., 126: 608, 1939.
418. RAPAPORT, S., BRODSKY, W. A., AND WEST, C. D.: Excretion of solutes and osmotic work of the 'resting' kidney of hydropenic man. Am. J. Physiol., 157: 357–363, 1949.
419. RASKA, S. B.: The metabolism of the kidney in experimental renal hypertension; the concentration of cytochrome C and the activities of the cytochrome oxidase and of the succinic dehydrogenase systems in the kidney of dogs with experimental renal hypertension; the inhibitory effect of renin and of kidney tissue preparations from hypertensive dogs on the respiratory enzymes. J. Exper. Med., 82: 227–240, 1945.
420. RASKA, S. B.: The metabolism of the ischemic kidney; the respiration and the oxidase activity of the ischemic kidney. J. Exper. Med., 78: 75–89, 1943.
421. RENBERG, P. B.: Studies on kidney function; the rate of filtration and reabsorption in the human kidney. Biochem. J., 20: 447–460, 1926.
422. REINECKE, R. M., RUDOLPH, G. G., AND BRYSON, M. J.: Effect of ureteral ligation, phloridzin and mercury bichloride on the gluconeaic function of the kidney. Am. J. Physiol., 151: 199–201, 1947.
423. REINER, J. M.: Effect of enzyme inhibitors on transformation of enzymes in the living cell. Proc. Soc. Exper. Biol. & Med., 63: 81–84, 1946.
424. RELMAN, A. S., GOODYER, A. V. N., AND PETERSON, E. R.: Effect of mannitol on salt excretion during water diuresis. J. Appl. Physiol., 1: 601–605, 1949.
425. REUBI, F. C., AND SCHRODER, H. A.: Can vascular shunting be induced in the kidney by vasoactive drugs? J. Clin. Investigation, 20: 114–122, 1940.
426. RHOADS, C. P., ALVING, A. S., HILLER, A., AND VAN SLYKE, D. D.: The functional effect of explanting one kidney and removing the other. Am. J. Physiol., 109: 320–325, 1934.
427. RICHARDS, A. N.: Kidney function. Am. J. M. Sc., 163: 1–19, 1922.
428. RICHARDS, A. N.: The nature and mode of regulation of glomerular function. Am. J. M. Sc., 170: 781–802, 1925.
429. RICHARDS, A. N.: Processes of urine formation in the amphibian kidney. Harvey Lectures, 30: 93–118, 1934–35.
430. RICHARDS, A. N.: Physiology of the kidney. Bull. New York Acad. Med., 14: 5–30, 1938.
431. RICHARDS, A. N.: Processes of urine formation. Proc. Roy. Soc., London, s. B., 126: 398–432, 1938.
432. RICHARDS, A. N., AND BARNWELL, J. B.: Experiments concerning question of secretion of phenolsulphonephthalein by renal tubule. Proc. Roy. Soc., London, s. B., 102: 73–91, 1927.
433. RICHARDS, A. N., BARNWELL, J. B., AND BRADLEY, R. C.: The effect of small amounts of adrenalin upon the glomerular blood vessels of the frog's kidney perfused at a constant rate. Am. J. Physiol., 79: 410–418, 1927.

434. Richards, A. N., Bott, P. A., and Wiehfall, B. B.: Experiments concerning the possibility that inulin is secreted by the renal tubules. Am. J. Physiol., 123: 281–306, 1938.
435. Richards, A. N., and Schmidt, C. F.: A description of the glomerular circulation in the frog's kidney and observations concerning the action of adrenalin and various other substances upon it. Am. J. Physiol., 71: 178–206, 1924.
436. Richards, A. N., and Walker, A. M.: Quantitative studies of the glomerular elimination of phenol red and indigo carmine in frogs. J. Biol. Chem., 87: 479–496, 1930.
437. Richards, A. N., and Walker, A. M.: Urine formation in the amphibian kidney. Am. J. M. Sc., 190: 737–746, 1935.
438. Richards, A. N., Wiehfall, B. B., and Bott, P. A.: Renal excretion of inulin, creatinine and xylose in normal dogs. Proc. Soc. Exper. Biol. & Med., 32: 73–75, 1934.
439. Richards, A. N., Wiehfall, B. B., and Bott, P. A.: Inulin and creatinine clearances in dogs, with notes on some late effects of uranium poisoning. J. Biol. Chem., 116: 749–755, 1936.
440. Richardson, H. L., Kennedy, J. C., and West, E. S.: Diuretic and other effects of intravenous sorbitol and sucrose; removal of edema fluid by the combined action of these substances and salyrgan. Northwest Med., 42: 89–93, 1943.
441. Riggs, T. R., and Hogsted, D. M.: Some factors affecting the acetylation of p-aminobenzoic acid in the rat. J. Biol. Chem., 179: 669–675, 1949.
442. Robert, F.: Über die Einwirkung von Hypophysin und seinen Fraktionen auf den Wasser-Salzstoffwechsel. Arch. f. exper. Path. u. Pharmakol., 164: 367–382, 1932.
443. Rossmon, R.: The Significance of Phosphoric Esters in Metabolism. New York University Press, New York, 1933.
444. Rost, C. C., and Pfeiffer, C.: Relative increase in chloride excretion in dog after graduated doses of mercurial diuretics. Am. J. Physiol., 135: 801–804, 1942.
445. Rommelaf, J. C., Sartorius, O., and Pitts, R. F.: Excretion and reabsorption of sodium and water in the adrenalectomized dog. Am. J. Physiol., 159: 134–136, 1949.
446. Russo, H. F., Cimenera, J., Gabe, S. R., and Beyer, K. H.: A statistical study of normal renal functions of the dog. To be published.
447. Russo, H. F., Gabe, S. R., Schuchardt, G. S., Tillson, E. K., and Beyer, K. H.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid): its absorption and elimination by the dog. To be published.
448. Sartorius, O. W., Rommelaf, J. C., and Pitts, R. F.: The renal regulation of acid-base balance in man; the nature of the renal compensations in ammonium chloride acidosis. J. Clin. Investigation, 28: 423–430, 1949.
449. Schales, O., and Mann, G. E.: Reversible inactivation of alkaline kidney phosphatase. J. Biol. Chem., 175: 487–488, 1948.
450. Schaumann, O., and Schmidt, L.: Über die Beeinflussung der Wirkung von Oxytocin und Vasopressin auf die Salzdiurese durch Salyrgan. Arch. f. exper. Path. u. Pharmakol., 205: 367–375, 1948.
451. Schiess, W. A., Ayer, J. L., Lotspeich, W. D., and Pitts, R. F.: The renal regulation of acid-base balance in man; factors affecting the excretion of titratable acid by the normal human subject. J. Clin. Investigation, 27: 57–64, 1948.
452. Schmitz, H. L.: Studies on the action of diuretics; the effect of euphyllin and salyrgan upon glomerular filtration and tubular reabsorption. J. Clin. Investigation, 11: 1075–1097, 1932.
453. Schneider, W. C.: Action of ribonuclease on the succinoxidase system. J. Biol. Chem., 164: 241–247, 1946.
454. Schneider, W. C.: Intracellular distribution of enzymes; the distribution of succinic dehydrogenase, cytochrome oxidase, adenosinetriphosphatase and phosphorus compounds in normal rat tissues. J. Biol. Chem., 165: 585–593, 1946.
455. Schneider, W. C., and Potter, V. R.: The assay of animal tissues for respiratory enzymes; succinic dehydrogenase and cytochrome oxidase. J. Biol. Chem., 149: 217–227, 1943.
456. Schneider, W. C., and Potter, V. R.: Biocatalysts in cancer tissue; succinic dehydrogenase and cytochrome oxidase. Cancer Research, 3: 353–357, 1943.
457. Schwartz, W. B.: The effect of sulfanilamide on salt and water excretion in congestive heart failure. New England J. Med., 240: 173–177, 1949.
458. Schwimmer, B. S.: Urinary excretion of amino acids by the rat. Proc. Soc. Exper. Biol. & Med., 66: 315–319, 1947.
459. Scott, J. K.: Pathologic anatomy of acute experimental beryllium poisoning. Arch. Path., 45: 354–350, 1948.
460. Selkurt, E. E.: The influence of glucose renal tubular reabsorption and p-aminohippuric acid tubular excretion on the simultaneous clearance of ascorbic acid. Am. J. Physiol., 142: 183–190, 1944.
461. Selkurt, E. E.: The changes in renal clearance following complete ischemia of the kidney. Am. J. Physiol., 144: 395–403, 1945.
462. Selkurt, E. E.: Comparison of renal clearances with direct renal blood flow under control conditions and following renal ischemia. Am. J. Physiol., 145: 376–386, 1946.
463. Selkurt, E. E.: Renal blood flow and renal clearance during hemorrhagic shock. Am. J. Physiol., 145: 699–709, 1946.
464. Selkurt, E. E.: The relation of renal blood flow to effective arteriol pressure in the intact kidney of the dog. Am. J. Physiol., 147: 537–549, 1946.
465. Selkurt, E. E., Hall, P. W., and Spencer, M. P.: Response of renal blood flow and clearance to graded partial obstruction of the renal vein. Am. J. Physiol., 157: 40–46, 1949.
466. Selkurt, E. E., Hall, P. W., and Spencer, M. P.: Influence of graded arterial pressure decrement on renal clearance. Am. J. Physiol., 159: 369–378, 1949.

467. Selkurt, E. E., Talbot, L. J., and Houck, C. R.: The effect of the administration of estrogen on the mechanism of ascorbic acid excretion in the dog. Am. J. Physiol., 140: 360-368, 1943.
468. Selye, H.: Effect of testosterone on kidney. J. Urol., 42: 637-641, 1939.
469. Selye, H.: Textbook of Endocrinology. Acta Endocrinologica, University of Montreal, Montreal, 1947.
470. Selye, H.: The alarm reaction and the diseases of adaptation. Ann. Int. Med., 29: 403-415, 1948.
471. Selye, H., Hall, C. E., and Rowlby, E. M.: Malignant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride. Canad. M. A. J., 49: 33-62, 1943.
472. Selye, H., Stone, H., Nielsen, K., and Leblond, C. P.: Studies concerning the effects of various hormones upon renal structure. Canad. M. A. J., 52: 571-583, 1945.
473. Sendroy, J., Jr., Sehlig, S., and Van Slyke, D. D.: Studies of acidosis; carbon dioxide tension and acid-base balance of human urine. J. Biol. Chem., 104: 479-500, 1934.
474. Shaffer, C. F.: The diuretic effect of ascorbic acid; preliminary report on its use in cardiac decompensation. J. Am. M. A., 124: 709-701, 1944.
475. Shannon, J. A.: The excretion of inulin by the dogfish, Squalus acanthias. J. Cell. & Comp. Physiol., 5: 301-310, 1934.
476. Shannon, J. A.: The excretion of inulin by the dog. Am. J. Physiol., 112: 405-413, 1935.
477. Shannon, J. A.: The renal excretion of creatinine in man. J. Clin. Investigation, 14: 403-410, 1935.
478. Shannon, J. A.: The excretion of phenol red by the dog. Am. J. Physiol., 113: 609-610, 1935.
479. Shannon, J. A.: Glomerular filtration and urea excretion in relation to urine flow in the dog. Am. J. Physiol., 117: 306-325, 1936.
480. Shannon, J. A.: The tubular reabsorption of xylose in the normal dog. Am. J. Physiol., 122: 775-781, 1938.
481. Shannon, J. A.: Urea excretion in the normal dog during forced diuresis. Am. J. Physiol., 122: 783-787, 1938.
482. Shannon, J. A.: Renal tubular excretion. Physiol. Rev., 19: 63-83, 1939.
483. Shannon, J. A.: Control of renal excretion of water; effect of variations in state of hydration on water excretion in dogs with diabetes insipidus; rate of liberation of posterior pituitary antidiuretic hormone in dog. J. Exper. Med., 76: 371-390, 1942.
484. Shannon, J. A., Farber, S., and Troast, L.: The measurement of glucose Tm in the normal dog. Am. J. Physiol., 133: 753-761, 1941.
485. Shannon, J. A., and Fisher, S.: The renal tubular reabsorption of glucose in the normal dog. Am. J. Physiol., 122: 765-774, 1938.
486. Shannon, J. A., and Rangee, H. A.: On the renal tubular excretion of creatinine in normal man. J. Clin. Investigation, 20: 169-176, 1941.
487. Shannon, J. A., and Smith, H. W.: The excretion of inulin, xylose and urea by normal and phlorizinized man. J. Clin. Investigation, 14: 393-401, 1935.
488. Shannon, J. A., and Winton, F. R.: The renal excretion of inulin and creatinine by the anesthetised dog and the pump-lung-kidney preparation. J. Physiol., 98: 97-108, 1940.
489. Shapiro, B.: The mechanism of phloridzin glucosuria. Biochem. J., 41: 151-154, 1947.
490. Sherman, H. L.: Renal elimination of phenol red in dog. J. Physiol., 87: 237-253, 1936.
491. Sherry, S., Friedman, G. J., Paley, K., Berkman, J., and Ralli, E. P.: The mechanism of the excretion of vitamin C by the dog kidney. Am. J. Physiol., 130: 376-380, 1940.
492. Shideman, F. E., Woods, L. A., and Stevens, M. H.: Dehydroacetic acid (DHA); detoxication and effects on renal function. To be published.
493. Sims, E. A. H., and Selden, D. W.: Reabsorption of creatine and guanidoacetic acid by the renal tubules. Am. J. Physiol., 157: 14-20, 1949.
494. Sinclair-Smith, B., Kattus, A. A., Genest, J., and Newman, E. V.: The renal mechanism of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive cardiac failure; the effects of exercise, rest and aminophyllin. Bull. Johns Hopkins Hosp., 84: 369-394, 1949.
495. Smith, H. W.: The Physiology of the Kidney. Oxford University Press, New York, 1937.
496. Smith, H. W.: The physiology of the renal circulation. Harvey Lect., 35: 106-223, 1939-40.
497. Smith, H. W.: Note on the interpretations of clearance methods in the diseased kidney. J. Clin. Investigation, 20: 631-635, 1941.
498. Smith, H. W.: Lectures on the Kidney. Porter Lectures, University of Kansas Press, Lawrence, 9th Series, Revised, 1943.
499. Smith, H. W.: Renal physiology between two wars. J. Mt. Sinai Hosp., 10: 41-68, 1943.
500. Smith, H. W.: The application of saturation methods to the study of glomerular and tubular function in the human kidney. J. Mt. Sinai Hosp., 10: 80-108, 1943.
501. Smith, H. W.: Excretion of water. Bull. New York Acad. Med., 23: 177-195, 1947.
502. Smith, H. W., Chasis, H., Goldring, W., and Ranges, H. A.: Glomerular dynamics in the normal human kidney. J. Clin. Investigation, 19: 751-764, 1940.
503. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M.: The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Investigation, 24: 388-404, 1945.
504. Smith, H. W., Goldring, W., and Chasis, H.: The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. J. Clin. Investigation, 17: 263-278, 1938.
505. Smith, W. W., Finkelstein, N., and Smith, H. W.: Renal excretion of hexitols (sorbitol, mannitol, and dulcitol) and their derivatives (sorbitan, isomannide and sorbide) and of endogenous creatinine-like chromogen in dog and man. J. Biol. Chem., 135: 231-250, 1940.

506. Smith, W. W., and Smith, H. W.: Protein binding of phenol red, diodrast and other substances in plasma. J. Biol. Chem., 124: 107–113, 1938.
507. Sollman, T., Schreiber, N. E., and Cole, H. N.: Comparative diuretic response to clinical injections of various mercurials. Arch. Int. Med., 58: 1067–1086, 1936.
508. Sorkin, S., Levine, R., and Lehmann, W.: Utilization of carbohydrate by the phlorhizinized dog. Proc. Soc. Exper. Biol. & Med., 39: 443–447, 1938.
509. Southworth, H.: Acidosis associated with administration of para-amino-benzene-sulfonamide (prontylin). Proc. Soc. Exper. Biol. & Med., 36: 58–61, 1937.
510. Sperber, I.: The excretion of some organic bases and some phenols and phenol derivatives. Scandinav. J. Clin. & Lab. Investigation, 1: 245–246, 1949.
511. Sperber, I.: The excretion of piperidine, guanidine, methylguanidine, and N¹-methylnicotinamide in the chicken. Kgl. Lantbruks Högskol. Ann., 16: 49–64, 1949.
512. Sperber, I.: The mechanism of renal excretion of some 'detoxication products' in the chicken. Abstr. 17th International Physiological Congress, p. 217–218, 1947.
513. Starling, E. H., and Verney, E. B.: Secretion of urine as studied on the isolated kidney. Proc. Roy. Soc., London, s. B., 97: 321–363, 1925.
514. Stieglitz, E. J.: Studies in uric acid clearance. U. S. Pub. Health Reports, 57: 1306–1310, 1942.
515. Storey, I. D. E.: The influence of bicarbonate upon glucuronide synthesis. Biochem. J., 44: xli, 1949.
516. Stotz, E., Altschul, A. M., and Hogness, T. R.: Cytochrome C-cytochrome oxidase complex. J. Biol. Chem., 124: 745–754, 1938.
517. Strauss, M. B., and Southworth, H.: Urinary changes due to sulfanilamide administration. Bull. Johns Hopkins Hosp., 63: 41–45, 1938.
518. Sumner, J. B., and Somers, G. F.: Chemistry and Methods of Enzymes. Academic Press, Inc., New York, 1943.
519. Sussman, R. M., and Schack, J. A.: BAL inhibition of mercurial diuresis in congestive heart failure. Proc. Soc. Exper. Biol. & Med., 66: 247–248, 1947.
520. Swingle, W. W., Parkins, W. M., Taylor, A. R., and Hays, H. W.: A study of water intoxication in the intact and adrenalectomized dog and the influence of adrenal cortical hormones upon fluid and electrolyte distribution. Am. J. Physiol., 119: 567–586, 1937.
521. Swingle, W. W., and Pfiffner, J. J.: Experiments with an active extract of suprarenal cortex. Anat. Rec., 44: 225–236, 1929.
522. Swingle, W. W., and Remington, J. W.: Role of adrenal cortex in physiological processes. Physiol. Rev., 24: 99–127, 1944.
523. Swingle, W. W., Remington, J. W., Hays, H. W., and Collings, W. D.: Effectiveness of primary doses of desoxycorticosterone acetate in protecting the adrenalectomized dog against water intoxication. Endocrinology, 28: 531–534, 1941.
524. Taggart, J. V.: Unpublished data. Personal communication. Also cited by Mudge, G. H., and Taggart, J. V., in ref. 363.
525. Taggart, J. V., and Forster, R. P.: Renal tubular transport; effect of 2,4-dinitrophenol and related compounds on phenol red transport in the isolated renal tubules of the flounder. Am. J. Physiol., 161: 167–172, 1950.
526. Tarail, R., and Elkinton, J. R.: Potassium deficiency and the role of the kidney in its production. J. Clin. Investigation, 26: 99–113, 1949.
527. Thorn, G. W.: Clinical use of extracts from adrenal cortex and of synthetic products having similar actions. J. Am. M. A., 125: 10–15, 1944.
528. Thorn, G. W.: The Diagnosis and Treatment of Adrenal Insufficiency. Charles C. Thomas, Springfield, Ill., 1949.
529. Thorn, G. W., and Emersson, J. K.: The role of gonadal and adrenal cortical hormones on the production of edema. Ann. Int. Med., 14: 767–769, 1940.
530. Thorn, G. W., Engel, L. L., and Lewis, R. A.: Effect of 17-hydroxycorticosterone and related adrenal cortical steroids on sodium and chloride excretion. Science, 94: 348–349, 1941.
531. Tillson, E. K., Schuchardt, G. S., Pitt, A. A., and Beyer, K. H.: The isolation and characterization of the metabolite of 4'-carboxyphenylmethanesulfonanilide (carinamide). Am. Chem. Soc., Abstr. Fall Meeting, p. 21L, 1949.
532. Tillson, E. K., Schuchardt, G. S., Pitt, A. A., Gass, R. W., and Beyer, K. H.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid)—an anticatabolite: its estimation in body fluids. Federation Proc., 9: 320, 1950.
533. Trusta, J.: Kidney. Ann. Rev. Physiol., 12: 309–336, 1950.
534. Tucker, H. A., and Eagle, H.: Serum concentrations of penicillin G in man following intramuscular injection in aqueous solution and in peanut oil-beeswax suspension. Am. J. Med., 4: 342–354, 1948.
535. Umbreit, W. W., Burris, R. H., and Stauffer, J. F.: Manometric Techniques and Related Methods for the Study of Tissue Metabolism. Burgess Publishing Co., Minneapolis, 1945.
536. Utter, M. F., Reiner, J. M., and Wood, H. G.: Measurement of anaerobic glycolysis in brain as related to poliomyelitis. J. Exper. Med., 82: 217–226, 1945.
537. Vail, V. N., and Kochakian, C. D.: Effect of adrenalectomy, adrenal cortical hormones, and testosterone propionate plus adrenal cortical extract on the "alkaline" and "acid" phosphatases of the liver and kidney of the rat. Am. J. Physiol., 150: 580–587, 1947.
538. Van Slyke, D. D.: The effect of urine volume on urea excretion. J. Clin. Investigation, 26: 1159–1167, 1947.

539. Van Slyke, D. D.: Studies of Normal and Pathological Physiology of the Kidney. Thirtieth Mellon Lecture, Edwards Bros., Inc., Ann Arbor, 1949.
540. Van Slyke, D. D., Hiller, A., and Miller, B. F.: The clearance extraction percentage and the estimated filtration of sodium ferrocyanide in the mammalian kidney; comparison with inulin, creatinine and urea. Am. J. Physiol., 113: 611–638, 1935.
541. Van Slyke, D. D., Hiller, A., and Miller, B. F.: The distribution of ferrocyanide, inulin, creatinine and urea in the blood and its effect on the significance of their extraction percentages. Am. J. Physiol., 113: 639–641, 1935.
542. Van Slyke, D. D., Phillips, R. A., Hamilton, P. B., Archibald, R. M., Futcher, P. H., and Hiller, A.: Glutamine as source material of urinary ammonia. J. Biol. Chem., 150: 481–483, 1943.
543. Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S.: Relationships between urea excretion, renal blood flow, renal oxygen consumption and diuresis; the mechanism of urea excretion. Am. J. Physiol., 109: 336–374, 1934.
544. Verney, E. B.: Absorption and excretion of water; antidiuretic hormone. Lancet, 2: 730–744, 781–783, 1946.
545. Verney, E. B.: Antidiuretic hormone and factors which determine its release. Proc. Roy. Soc., London, s. B., 135: 25–106, 1947.
546. Von Mering, J.: Phlorrhizin und Zuckerausscheidung. Verhandl. d. Kong. f. inn. Med., p. 349, 1887.
547. Wachstein, M.: Renal phosphatase in choline deficiency. Arch. Path., 38: 297–304, 1944.
548. Walker, A. M., Bott, P. A., Oliver, J., and MacDowell, M. C.: Collection and analysis of fluid from single nephrons of mammalian kidney. Am. J. Physiol., 134: 580–595, 1941.
549. Walker, A. M., and Hudson, C. L.: Reabsorption of glucose from renal tubule in Amphibia and action of phlorizin upon it. Am. J. Physiol., 118: 130–143, 1937.
550. Walker, A. M., Hudson, C. L., Fiedler, T., Jr., and Richards, A. N.: The total molecular concentration and the chloride concentration of fluid from different segments of the renal tubule of Amphibia; site of chloride reabsorption. Am. J. Physiol., 118: 121–129, 1937.
551. Walker, A. M., and Oliver, J.: Methods for collection of fluid from single glomeruli and tubules of mammalian kidney. Am. J. Physiol., 134: 562–579, 1941.
552. Walker, A. M., Schmidt, C. F., Elson, K. A., and Johnston, C. G.: Renal blood flow of unanesthetised rabbits and dogs in diuresis and antidiuresis. Am. J. Physiol., 118: 95–110, 1937.
553. Warren, C. O.: Role of bicarbonate in action of serum in supporting tissue respiration. J. Biol. Chem., 156: 589–599, 1944.
554. Warren, J. V., Brannon, E. S., and Merrill, A. J.: Method of obtaining renal venous blood in unanesthetised persons with observations on extraction of oxygen and sodium para-aminohippurate. Science, 100: 108–110, 1944.
555. Warren, J. V., and Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure, interpretation of mechanism producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. Arch. Int. Med., 73: 138–147, 1944.
556. Waterhouse, C., and Keutmann, E. H.: Kidney function studies in adrenal insufficiency. J. Clin. Investigation, 26: 1190–1200, 1947.
557. Waters, L. L., and Stock, C.: BAL (British anti-lewisite). Science, 102: 601–606, 1945.
558. Weir, J. F.: Influence of pituitary extract on metabolism in diabetes insipidus. Arch. Int. Med., 32: 617–634, 1923.
559. Weir, J. F., Larson, E. E., and Rowntree, L. G.: Studies in diabetes insipidus; water balance and water intoxication. Arch. Int. Med., 29: 306–330, 1922.
560. Wellen, I., Welsh, C. A., Taylor, H. C., and Rosenthal, A.: The filtration rate, effective renal blood flow, tubular excretory mass and phenol red clearance in specific toxemia of pregnancy. J. Clin. Investigation, 21: 63–70, 1942.
561. Weller, J. M.: Histochemical changes in the kidney during diuresis and dehydration. Am. J. Physiol., 142: 443–451, 1944.
562. Welsh, C. A., Rosenthal, A., Duncan, M. T., and Taylor, H. C., Jr.: The effects of testosterone propionate on renal function in the dog, as measured by the creatinine and diodrast clearance and diodrast Tm. Am. J. Physiol., 137: 338–347, 1942.
563. Welsh, C. A., Wellen, I., Taylor, H. C., and Rosenthal, A.: The filtration rate, effective renal blood flow, tubular excretory mass and phenol red clearance in normal pregnancy. J. Clin. Investigation, 21: 57–61, 1942.
564. Welsh, C. A., Wellen, I., and Taylor, H. C., Jr.: Changes in renal function accompanying the hypertrophy of the remaining kidney after unilateral nephrectomy. J. Clin. Investigation, 23: 750–754, 1944.
565. Wesson, L. G., Jr ., and Amblow, W. P., Jr.: Excretion of sodium and water during osmotic diuresis in the dog. Am. J. Physiol., 153: 455–474, 1948.
566. Wesson, L. G., Jr., Amblow, W. P., Jr., and Smyth, H. W.: The excretion of strong electrolytes. Bull. New York Acad. Med., 24: 586–606, 1948.
567. West, J. R., Smyth, H. W., and Chasis, H.: Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J. Pediat., 32: 10–18, 1948.
568. Wexler, J., and Ellis, L. B.: Toxic reactions to the intravenous injection of mercurial diuretics. Am. Heart J., 27: 86–95, 1944.
569. White, H. L.: The effect of phlorhizin on renal plasma flow, on glomerular filtration and on the tubular excretion of diodrast in the dog. Am. J. Physiol., 130: 582–587, 1940.
570. White, H. L., and Heinbecker, P.: Pituitary regulation of water exchange in dog and monkey. Am. J. Physiol., 118: 276–284, 1937.

571. WEITH, H. L., HEINBECKER, P., AND ROLF, D.: Effect of hypophysectomy on some renal functions. Proc. Soc Exper. Biol. & Med., 46: 44–47, 1941.
572. WEITH, H. L., HEINBECKER, P., AND ROLF, D.: Hypophysis and renal function. Am. J. Physiol., 133: 689, 1941.
573. WEITH, H. L., HEINBECKER, P., AND ROLF, D.: Effects of removal of anterior lobe of hypophysis on some renal functions. Am. J. Physiol., 136: 584–591, 1942.
574. WEITH, H. L., HEINBECKER, P., AND ROLF, D.: Some endocrine influences on renal function and cardiac output. Am. J. Physiol., 149: 404–417, 1947.
575. WEITH, H. L., HEINBECKER, P., AND ROLF, D.: Further observations on the depression of renal function following hypophysectomy. Am. J. Physiol., 154: 67–78, 1948.
576. WEITH, H. L., HEINBECKER, P., AND ROLF, D.: Enhancing effects of growth hormone on renal function. Am. J. Physiol., 157: 47–51, 1949.
577. WIESELMANN, V. D., AND LARDY, H. A.: Phosphorylation of hexoses by brain hexokinase. Arch. Biochem., 21: 231–239, 1949.
578. WIESELMANN, V. D.: Benemid (p-(di-n-propylsulfamyl)-benzoic acid): its effect on certain glycine-conjugation reactions. To be published.
579. WILLIAMS, R. T.: Detoxication Mechanisms: The Metabolism of Drugs and Allied Organic Compounds. John Wiley & Sons, Inc., New York, 1947.
580. WILS, J. H., AND MAIN, E.: Renal function in normal rabbits and dogs and the effect of uranyl salts. Am. J. Physiol., 154: 230–238, 1948.
581. WILMER, H. A.: The disappearance of phosphatase from the hydronephrotic kidney. J. Exper. Med., 78: 225–230, 1943.
582. WILMER, H. A.: Renal phosphatase; the correlation between the functional activity of the renal tubule and its phosphatase content. Arch. Path., 37: 227–237, 1944.
583. WINKLER, A. W., AND SMITH, P. K.: Renal excretion of potassium salts. Am. J. Physiol., 138: 94–103, 1943.
584. WINTERNITZ, M. C., AND WATERS, L. L.: Effect of hypophysectomy on compensatory renal hypertrophy in dogs. Yale J. Biol. & Med., 12: 703–709, 1940.
585. WINTON, F. R.: Physical factors involved in the activities of the mammalian kidney. Physiol. Rev., 17: 408–435, 1937.
586. WOLF, A. V., AND BALL, S. M.: Effect of intravenous calcium salts on renal excretion in the dog. Am. J. Physiol., 130: 205–217, 1940.
587. WRIGHT, L. D., RUSSO, H. F., SKEGGS, H. R., PATCH, E. A., AND BEYER, K. H.: The renal clearance of essential amino acids: arginine, histidine, lysine and methionine. Am. J. Physiol., 149: 130–134, 1947.
588. ZEKWER, I. T.: Compensatory growth of the kidney after unilateral nephrectomy in thyroidectomized rats. Am. J. Physiol., 145: 681–684, 1945.