MECHANISM OF ACTION AND THERAPEUTIC USE OF DIURETICS

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If one defines diuretics broadly as agents which induce an increased volume flow of urine, then water is the diuretic *par excellence* under most circumstances. From the viewpoint of the clinician whose major interest in diuretics is apt to lie in their use for the relief of edema, it would appear logical to restrict the term to those agents which induce a net loss of fluid from the body by the urinary route. In this limited sense water can be considered as a diuretic only when administered in large quantities, and many agents surpass it in effectiveness. However to appreciate the mode of action of the clinically effective diuretics it is necessary to consider in some detail the mechanisms by which the water and electrolyte contents of the body are regulated. We have therefore adopted the first and broader definition and shall consider five classes of diuretics, including water, acidifying agents, osmotic diuretics, xanthines, and mercurials. To avoid too great a diffusion of effort as well as duplication of material suitable for more extensive review we have chosen to omit consideration of the cardiac glycosides, colloids, and a miscellaneous group of drugs which exhibit some diuretic activity. Furthermore, since this review is both selective and interpretative, it will deal more with mechanisms of action of diuretics than with their clinical use, and will emphasize those deficiencies in knowledge which presently render so many of the interpretations speculative. It is hoped that it will stimulate thought and investigative effort as well as provide a reasonably comprehensive summary of present knowledge of the actions of diuretics.

It is generally accepted that the process of urine formation begins with the expression of an ultrafiltrate from the plasma in the glomerular capillary tufts. The responsible force is the hydrostatic pressure of the blood imparted by the beat of the heart. The filtrate, which is normally formed in large volume (150 to 200 liters per day), contains all crystalloidal constituents in the same concentrations in which they exist in the plasma. During passage along the renal tubules more than 99 per cent of the filtered water and salts and essentially all of the glucose, amino acids and other valuable constituents are absorbed. The excretory products initially present in the filtrate and added by processes of tubular secretion are concentrated in a relatively small volume of urine (1.5 liters per day under normal conditions).

Theoretically, diuretics might act peripherally on the tissues to mobilize salt and water stored in cellular and extracellular depots, on the cardiovascular system to improve circulatory dynamics, or locally on the kidneys to promote

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the excretion of fluid. There is some evidence, largely in the foreign literature that xanthines and especially mercurial diuretics exert a part of their actions peripherally by mobilizing fluid. The cardiac glycosides, which will not be treated at all in this review, exert most if not all of their diuretic action by improving the circulatory status of the patient, including that of his kidneys. Intravenous colloids induce a vascular plethora which results in increased renal blood flow, glomerular filtration rate and urine flow. However, the action of a majority of diuretics is exerted directly on the kidneys. Although some may increase the rate of glomerular filtration and owe a part of their efficacy to a relative flooding of the tubules, hindrance or partial blockage of the reabsorption of electrolyte and water is a far more significant element in diuretic action. In one way or another water, osmotic diuretics, acidifying agents, mercurials and xanthines reduce the tubular absorption of salt and water and thus cause diuresis.

THE DIURETIC ACTION OF WATER

Absorption of water in the gut. In the dog water is absorbed from the gut at a rate of 0.028 cc. per cm. length per min.; it suffers little or no delay in passing the pyloric sphincter. Since the length of the gut averages 24.7 cm. per kgm., a 10 kgm. animal absorbs 250 cc. of water in about 35 min. (252a). In man absorption is equally rapid; a fair proportion of an ingested load of one liter is absorbed in 25 min., and absorption is essentially complete in 40 to 50 min. (433). Absorption is also rapid in the guinea pig and rat but significantly slower in the rabbit (206).

Tissue water load and blood dilution. Since absorption of water proceeds at a faster rate than urinary excretion, dilution of the body fluids occurs with respect to both colloids and crystalloids (18, 296, 382, 432, 433). Measurements of hemoglobin, protein, chloride, vapor pressure and conductivity are consistent in indicating a 2 to 5 per cent dilution of the blood, depending upon the variable measured and the dose of water. Blood electrolytes suffer dilution not only by entry of water from the gut but likewise by diffusion into the unabsorbed residue in the intestine (342). Once absorbed, water is distributed rapidly throughout the body; *e.g.*, intravenously administered deuterium oxide equilibrates with total body water (66 per cent of body weight) in less than 10 min. (141). The comparative slowness of intestinal absorption relative to distribution is indicated by the fact that orally administered deuterium oxide equilibrates with total body water only after 50 to 60 minutes (7).

Red cells and presumably tissue cells as well imbibe water and swell in proportion to the reduction in osmotic pressure of the blood plasma and interstitial fluid (432).

Time course of diuresis. Following the ingestion of a liter of water, urine flow begins to increase within 15 to 20 mins., reaches a peak within 60 to 90 minutes and returns to normal within 2 to 3 hours (6, 436). In general it has been found that the curve of urine flow lags some 15 to 20 mins. behind that of blood dilution or tissue water load (absorbed but unexcreted water) (6, 252a, 382), a fact which indicates that dilution *per se*, although closely correlated with the diuretic

process, is not the immediate cause of diuresis. That plasma colloid dilution is not a causative factor in water diuresis is even more forcibly demonstrated by the complete dissociation of concentration of plasma proteins and urine flow following the ingestion of normal saline. The ingestion of saline causes a greater dilution of colloids than does the ingestion of water for it is retained largely within the extracellular compartment, yet is attended by a relatively insignificant increase in urine flow (6, 18, 432, 436).

Anterior and posterior pituitary hormonal mechanisms in water balance. That the excretion of water is normally regulated by a posterior pituitary hormone was first indicated in 1912 by the observation by Frank (150) of the association of diabetes insipidus with lesions of the neuro-hypophysis. Unfortunately he was influenced by the view, current at that time, that posterior pituitary extract is diuretic, and accordingly thought that diabetes insipidus represents the effects of hypersecretion induced by irritative lesions. The following year von den Velden (473) demonstrated the efficacy of pituitary extract in checking water diuresis in normal man. Somewhat later Motzfeld (326) emphasized the antidiuretic action of posterior pituitary extract and concluded that the pituitary body exerts "a constant, physiological influence on the functional activities of the kidneys." Klisiecki *et al.* (252b) stated the posterior pituitary hypothesis in the following form. "The secretion of water over and above that required for the solutes of the urine, is conditioned by and dependent upon a fall in the concentration in blood and kidney of the antidiuretic principle of the pituitary body. The secretion of the antidiuretic principle is itself controlled, through the intermediation of the nervous system, by the concentration of water in blood and tissues." Evidence in favor of this hypothesis has been marshalled in detail in a number of excellent reviews (139, 195, 347, 474, 475).

The anterior lobe of the pituitary exerts a type of control over water balance scarcely less significant than that of the posterior lobe. Indeed it would appear that normal water balance depends upon an antagonism between a diuretic influence mediated through the anterior lobe and an antidiuretic influence mediated through the posterior lobe (341, 381, 496). In diabetes insipidus this latter antidiuretic influence is lost and the unopposed diuretic action of the anterior lobe results in marked polyuria.

Diabetes insipidus may be induced experimentally by destruction of the supraoptic nuclei, section of the supraoptico-hypophyseal tracts or ablation of the neurohypophysis (138, 139). More than 90 per cent of the posterior lobe must be removed or inactivated (288) and a fair but undetermined proportion of the anterior lobe tissue must remain functional (341, 381) for the development of permanent polyuria. If the anterior as well as the posterior lobe is destroyed, only a transient polyuria develops; thereafter urine flow returns to the preoperative level (139).

It is possible that the anterior lobe of the pituitary promotes diuresis directly either by secreting a specific diuretic hormone (496) or by elaborating a renotrophic hormone essential for the maintenance of renal blood flow and glomerular filtration rate (202, 497). On the other hand, it may act indirectly through

its well known growth, adrenocorticotrophic and thyrotrophic hormones (9). Gaunt *et al.* (163) consider that the diuretic action of the anterior lobe is for the most part an indirect one, and that it is mediated largely, although not entirely, through its influence on adrenal cortical function.

Normal control of liberation of posterior pituitary antidiuretic hormone. According to Verney (474, 475), osmoreceptors located intracranially within the zone of distribution of the internal carotid artery are sensitive to changes in osmotic pressure of the arterial blood of the order of magnitude of 1 to 2 per cent. These receptors are presumed to be the roughly spherical vesicles, some 50 micra in diameter, found in the supraoptic nuclei of the hypothalamus. Upon the surface of these vesicles are applied dendritic terminations of the supraoptic neurons. Were they in reality tiny osmometers, shrinkage might reasonably be expected to translate an increase in osmotic pressure of their immediate fluid environment into nerve impulses. Such impulses, transmitted to the pituicytes of the posterior lobe of the pituitary via the supraoptico-hypophyseal tracts, would stimulate the liberation of antidiuretic principle (347).

Acting directly on the kidney (362, 446), the hormone enhances the conservation of water; the urine formed is highly concentrated; its volume is small. In addition the hormone promotes the excretion of sodium and chloride (2, 293, 434, 446, 459). Both actions, *i.e.*, the restriction of water loss and the promotion of electrolyte excretion, oppose the increase in osmotic pressure which initially stimulated the formation of hormone. Further dehydration is prevented and that presently existent is partially corrected by the elimination of osmotically active salts. It is significant that the osmoreceptors are completely impermeable to sodium and chloride and hence are most sensitive to changes in concentration of these ions. They are relatively permeable to glucose and freely permeable to urea, and hence are but little affected by changes in these plasma components (474). The susceptibility of the infant to dehydration is in part related to the fact that the pitressin content of the neurohypophysis is only one tenth that of the adult (204), and in part to the fact that the renal tubules can be stimulated to conserve water to only a small degree by pitressin (203).

A decrease in osmotic pressure of the body fluids such as that induced by the ingestion of water causes the osmoreceptors to swell and inhibits the outflow of impulses from the supraoptic nuclei, thereby reducing the liberation of antidiuretic hormone. Following a latent period of 15 to 20 min. during which time the circulating hormone suffers progressive destruction, urine flow increases to reach a maximum at 60 to 90 min., at which time the concentration of circulating hormone is minimal. The urine formed is dilute, its volume large and its electrolyte content negligible. Both the promotion of water excretion and the conservation of salt oppose the decrease in osmotic pressure which initially led to the inhibition of hormone secretion.

Rate of liberation of antidiuretic hormone. Motzfeld (326) first observed that graded antidiuresis in hydrated animals is produced only by very small doses (0.001 cc. or less) of pituitary extract. Somewhat larger doses produce a more or less standard oliguria comparable to that observed in moderate dehydration;

increase in dosage merely prolongs the antidiuresis. Shannon (418), infusing graded doses of pitressin into hydrated dogs with diabetes insipidus, found that 1 to 5 milliunits per hour in 10 to 15 kgm. animals established normal rates of urine flow. Since these animals produced little or no endogenous pitressin, it follows that the normal rate of hormone liberation is of this order of magnitude. Such doses of pitressin not only bring about a normal degree of water conservation but likewise promote the elimination of sodium and chloride (2, 396, 418). According to Verney (474), the average normal rate of pitressin liberation in the dog is 3.6 milliunits per hour, a figure agreeing well with that of Shannon.

Magoun *et al.* (288) have demonstrated a safety factor of 10 to 1 in the supraoptico-hypophyseal mechanism. Thus as little as 10 per cent of the normal complement of posterior lobe tissue is sufficient to maintain a normal rate of water turnover in the monkey. Although the liberation of a relatively small quantity of hormone suffices to maintain antidiuresis even in the presence of a high water load, there is evidence that several hundred times this quantity are liberated when the osmoreceptor mechanism is maximally stimulated by the infusion of hypertonic saline (194).

Destruction of antidiuretic hormone. A large dose of pitressin (1 to 10 units) administered subcutaneously maintains antidiuresis in a well hydrated individual for 8 hours or more. Somewhat smaller doses maintain maximal antidiuresis for periods more or less proportional to the logarithm of the dose (234). Heller *et al.* (208) and Jones *et al.* (239) have shown that blood and suspensions of a number of tissues adsorb and reversibly inactivate pituitary antidiuretic hormone. Liver and blood and probably kidney and spleen as well contain enzymes which irreversibly destroy the hormone. The greatest destruction occurs in the liver (208). After intravenous injection of the hormone into decapitate cats, 85 per cent of the antidiuretic activity of the blood is lost in 20 min.; none remains after 2 hours (239). The antidiuresis following an intravenous dose in man is characteristically short lived, indicating that the prolonged action of subcutaneous pitressin is due to slow local absorption. In adrenalectomized animals the capacity of the liver to destroy the hormone is reduced (29), a fact which may explain in part their failure to exhibit water diuresis when water loaded, and their susceptibility to water intoxication (161, 163).

Changes in renal function in water diuresis. In the hydrated normal man (73, 78), dog (420, 486) and rat (118), urine flow may be varied over a wide range by the ingestion of water with minimal changes in renal plasma flow and glomerular filtration rate. It is obvious in these forms that changes in urine flow during water diuresis are mediated through changes in the tubular reabsorption of water, not through variations in the glomerular filtration of water or in the quantity of water delivered to the kidneys by the renal blood stream. Until recently the rabbit appeared to constitute an exception to the above rule for mammalian forms. According to Kaplan *et al.* (242) and Dicker *et al.* (118), urine flow in the rabbit varies as a function of glomerular filtration rate and renal blood flow. However Brod *et al.* (54) have shown that this correlation is largely artificial in the sense that pain and emotional excitement caused by

the initiation of clearance procedures cause intense renal vasoconstriction. As this vasoconstriction wears off, glomerular filtration and renal blood flow increase *pari passu* with urine flow. If emotional disturbances are avoided, urine flow may be varied over a wide range in consequence of changes in tubular absorption of water. It is probable that the correlation between urine flow and filtration rate observed by Friedman (152) in the rat had its origin in the trauma of blood collection during clearance periods, rather than in any fundamental biological relation between the two variables.

It should be emphasized that independence of filtration rate and urine flow is relative, for there is ample evidence that in severe dehydration filtration rate is reduced moderately, that it increases *pari passu* with urine flow on subsequent rehydration and that it may be elevated when rehydration is effected by saline infusion. While variations in filtration rate are of little importance in determining rate of urine flow in well hydrated normal individuals, they may play significant roles in determining urine flow in severe dehydration and in those diseases characterized by imbalance of glomerular and tubular function (47, 348, 353) (*vide infra*).

The effect of pitressin on renal blood flow and filtration rate. The infusion of quantities of pituitary antidiuretic hormone within a physiologically reasonable range (*i.e.*, 1 to 20 milliunits per hr.) or the subcutaneous administration of somewhat larger doses is without effect on glomerular filtration rate or renal blood flow in the dog (418, 486). The intravenous administration of 20 milliunits in a single dose increases filtration rate moderately in the dog (396) and the intraperitoneal administration of 5 milliunits in the rat produces a similar response (162). Such quantities of pitressin have no effect on blood pressure. Indeed, it is unlikely that the pressor action of the hormone is physiologically very significant because of the large quantities necessary to produce the response, *i.e.*, several hundred times or more that necessary to effect antidiuresis.

The intravenous infusion of pitressin in amounts greater than those defined above as lying within a physiological range produces variable responses in renal blood flow and filtration rate (88, 481, 486). Renal blood flow may increase slightly with moderate doses or fall precipitously if doses as high as 0.6 units per kgm. are administered. Glomerular filtration rate is usually significantly elevated with moderate dosage; presumably it would fall with doses sufficiently high to restrict renal blood flow severely. The extremely large doses employed by Trueta *et al.* (466) to demonstrate a shift in the balance of circulation from cortical to juxtamedullary nephrons renders their arguments as to the normal mode of action of the hormone completely unacceptable. If it could be shown that shunting of blood occurs with physiologically reasonable doses, a radical revision of current views of the action of the hormone would be necessary.

Site of action of antidiuretic hormone. Concepts as to the site of action of antidiuretic hormone within the kidney are largely inferential. All begin with the known facts that (a) in diabetes insipidus or in water diuresis, in which conditions circulating antidiuretic hormone is reduced to very low levels, a large volume of hypotonic urine is formed; (b) in the oliguria of dehydration or fol-

lowing pitressin, a small volume of hypertonic urine is formed; and (c) the glomerular filtrate during its transit through the proximal convoluted tubule is in osmotic equilibrium with the plasma (484). It therefore follows that pitressin must regulate the absorption of water at some point distal to the proximal convoluted tubule, stimulating water absorption when hormonal concentration is high, depressing water absorption when hormonal concentration is low. Burgess *et al.* (64), noting that pitressin exerts its typical antidiuretic action only on the mammalian kidney which alone possesses a well developed thin segment of the loop of Henle, concluded this to be the site of action of the hormone. Smith, after initially accepting this view (436), has more recently (435) expressed the opinion that the function of the thin segment is to ensure the establishment of osmotic equilibrium between tubular urine and plasma at the end of the proximal tubular system, a type of activity for which a thin walled tube seems eminently suited. More or less by default, the distal tubule has been assigned the function of water absorption against an osmotic gradient, *i.e.*, that function stimulated by antidiuretic hormone. Shannon (417), in consequence of his postulate that the proximal convoluted tubule can abstract sodium and chloride from the filtrate more or less completely under certain conditions, was forced to conclude that the natriuretic and chloruretic actions of pitressin are consequences of reduction in the proximal absorption of these ions, and that the antidiuretic action is exerted distal to this site, most probably on the distal tubule itself. It is obvious that some variety of concrete experimental evidence as to the sites of antidiuretic, natriuretic and chloruretic actions is much to be desired. The collecting tubule which has been largely ignored by the renal physiologist appears to be cytologically somewhat more differentiated than necessary were its function solely that of a conduit. Perhaps its name has unjustifiably damned it to obscurity.

Presence of antidiuretic hormone in body fluids. Gilman and Goodman (168) were the first to demonstrate the presence of an antidiuretic substance in the urine and to show that its rate of excretion is related to the need for water conservation, a fact which was soon confirmed by Boylston *et al.* (46) and by Ingram *et al.* (229). Because this antidiuretic substance was found following water deprivation and following administration of hypertonic salt solutions in normal animals but was absent from the urine of animals with diabetes insipidus, it was thought to be of pituitary origin. These findings constitute an important link in the evidence that an hypothalamico-hypopyseal hormonal mechanism controls water balance, although they have not been universally accepted (336, 483).

The antidiuretic substance in the urine has been found to be increased in those conditions characterized either by the accumulation of edema or by the delayed excretion of water. Thus Ralli *et al.* (262, 364) have shown in experimental cirrhosis in the rat and in clinical cirrhosis in man an increased quantity of antidiuretic substance in the urine. Teel and Reid (458) and Ham and Landis (191) have made similar observations in eclampsia and pre-eclampsia, and Robinson and Farr (383) have demonstrated increased quantities of the substance in the

urine in Bright's disease and premenstrual edema. In adrenalectomized animals (163), experimental hypertensive animals (128) and patients with clinical hypertension (128, 182) delayed excretion of water is associated with increased rates of excretion of antidiuretic substance.

It is interesting and significant that the substance extractable from the urine is antidiuretic but not chloruretic, in contrast to pitressin which exerts both actions. This has led some to the view that the antidiuretic material of the urine has an extra-pituitary origin (191). Grollman (183) has recently demonstrated that the chloruretic action of pitressin is destroyed by mild oxidation, whereas the antidiuretic action is unaltered, and presumes that some prosthetic group of the natural hormone responsible for chloruresis is removed by oxidation in the body prior to excretion in the urine.

The presence of an antidiuretic substance in urine implies its existence in the circulating blood plasma and its passage through the glomerular filter. Brun *et al.* (59), studying renal function in the period of oliguria following syncope, demonstrated that the transfusion of 200 to 400 cc. of blood from the subject in collapse to a normal hydrated test subject induces oliguria in the recipient. However, until recently it has been impossible to demonstrate antidiuretic substances in the blood plasma except by large transfusions. Birnie *et al.* (30) have now developed methods for assay of the antidiuretic potency of 1 cc. of serum and have demonstrated the presence of a labile substance in the serum of normal rats having the antidiuretic and chloruretic activities of pitressin. The concentration of this substance is increased by dehyration and is reduced by hydration. It is undetectable after hypophysectomy. It is destroyed when incubated with blood or thioglycolic acid, and in these and other respects resembles pitressin. Lloyd (266), in a clinical study, has found low levels of serum antidiuretic substance in diabetes insipidus and high levels in dehydrated normal subjects and in patients with diseases characterized by water retention and delayed diuresis.

Nervous factors affecting release of antidiuretic hormone from the pituitary. Because of the extensive nervous connections of the supraoptic and paraventricular nuclei which together funnel nerve impulses into the neurohypophysis, it is not surprising that psychic as well as somatic stimuli alter urine flow. Emotional stress, such as that induced by exhibition of a cat to a dog, or pain produced by faradic shocks inhibits water diuresis. The inhibition is relatively prompt, well outlasts the stimulus and is unaffected by denervation of the kidneys. The fact that it is unobtainable following destruction of the posterior lobe of the pituitary indicates that it is due to release of pitressin (475). Furthermore it has been possible to develop both conditioned reflex diuresis (68, 299) and conditioned inhibition of water diuresis in animals with kidneys denervated (120).

Release of hormone from the pituitary gland by emotional stimuli is prevented by the administration of epinephrine and tyramine (474, 475), but whether this is due to altered cerebral circulation or to specific chemical inhibition is uncertain. Pickford (346) has found that the injection of acetylcholine into the supraoptic nuclei stimulates the release of pitressin and inhibits urine flow. Since the injection of eserine has a simlar effect she concludes that her

results are consistent with the hypothesis that acetylcholine plays some role in the normal mechanism of excitation of supraoptic neurons.

According to Verney (475), exertion induces antidiuresis by an hormonal mechanism, but whether this is the entire cause is debatable in view of the considerable decrease in renal blood flow and glomerular filtration rate observed in both normal and cardiac subjects (74, 316) when they indulge in moderate exercise (*vide infra*).

Anesthetics in general, although they slow gastro-intestinal absorption, inhibit water diuresis disproportionately (literature reviewed by Heller *et al.* (207) and deBodo *et al.* (38)). In view of the fact that light anesthesia with ether or cyclopropane (Stage III, plane 1) (92) or with pentobarbital sodium (30 mg. per kg.) (89) does not affect renal blood flow or glomerular filtration rate, an hormonal mechanism for the antidiuresis is suggested. deBodo *et al.* (37, 38) have demonstrated that morphine and the barbiturates stimulate the release of pitressin for, although they are antidiuretic in the normal animal, they are without effect on urine flow in the animal with diabetes insipidus. Ferrer *et al.* (135) have reached a similar conclusion with respect to morphine and meperidine antidiuresis in man.

Cold diuresis (5) appears to be due to inhibition of pitressin release, for filtration rate and renal blood flow undergo no change on lowering environmental temperature. The antidiuresis produced by BAL is due to direct or indirect stimulation of pitressin release since it is absent in the dog with diabetes insipidus (121).

Significance of adrenal cortical hormones in promotion of diuresis. As pointed out above the diuretic influence of the anterior pituitary is largely mediated through the adrenal cortex. Gaunt *et al.* in a recent review (163) have treated extensively the relationship of the adrenal cortex to water metabolism and only a brief summary of salient points need be given here. In diabetes insipidus, urine volume is sharply reduced by adrenalectomy and is restored to its previous high level by the administration of cortical extract (230). The adrenalectomized animal and the patient with Addison's disease are unable to excrete rapidly a large load of water, a fact which renders them susceptible to water intoxication (161, 384). This excretory deficiency in the rat and dog and probably in man as well is the result of increased tubular absorption of water (277, 386). It is corrected to some degree although not completely by the administration of cortical hormone (161). The completely hypophysectomized animal exhibits a similar deficiency in diuretic response to water loading, and it too is largely corrected by cortical hormone (240).

According to Gaunt *et al.* (163), adrenal cortical hormones have two independent actions on tubular functions,—they depress the absorption of water and enhance the absorption of electrolyte. Since retention of electrolyte is usually attended by the retention of equivalent amounts of water, adrenal hormones may exert either a diuretic or an antidiuretic action depending upon the conditions under which the hormones are administered and to some extent upon the nature of the specific component given.

The opposite actions of adrenal cortical hormone and pitressin on electrolyte

and water excretion suggest that in the normal animal there exists an antagonism between the salt conserving diuretic action of the former and the chloruretic and antidiuretic action of the latter (90, 309, 386, 427). Reduced formation of adrenocorticotrophic hormone by the anterior pituitary or adrenal insufficiency *per se* disturbs the balance in favor of salt loss and antidiuresis. On the other hand, reduced posterior pituitary function (diabetes insipidus or hydration) favors salt conservation and diuresis. This view is supported by recent clinical findings of Lloyd (266). He has observed that, in the presence of low urine output, whether in patients with cirrhosis or Addison's disease or in dehydrated normal subjects, urinary corticoid excretion is low and serum antidiuretic factor is high. The reverse is true in patients with diabetes insipidus and in hydrated normal subjects. A concept of simple antagonism between adrenal cortex and posterior lobe of the pituitary in the regulation of salt and water balance is somewhat fatuous for it not only neglects the diuretic actions of other hormones, especially the thyroid, but it likewise fails to take into account the diversity of action of the several adrenal cortical factors

According to Gaunt *et al.* (163), whole adrenal cortical extract, Compound E, the amorphous fraction and desoxycorticosterone all promote the elimination of high water loads in the rat. When based on dosages which are equivalent in life-maintaining action in adrenalectomized animals, desoxycorticosterone is the least effective in promoting diuresis. On the other hand, desoxycorticosterone is most effective in causing the retention of sodium, corticosterone is somewhat less effective, and both 17-hydroxy-corticosterone and 11-dehydro-17-hydroxycorticosterone (compound E) enhance salt excretion, at least in the normal animal (84, 462, 463). In general those compounds which enhance salt conservation reduce the quantity of fluid excreted over a 24-hour period, for water is retained in proportion to salt. It is evident, therefore, that desoxycorticosterone may promote diuresis in short-term, water-loading experiments and nduce relative antidiuresis in balance studies. However, when large amounts of desoxycorticosterone are given repeatedly, polyuria develops to an extent comparable to that observed in diabetes insipidus (255, 330). Such toxic doses of hormone cause nearly complete retention of dietary sodium, expand the volume and increase the salt content of the extracellular fluid, and cause thirst. Increased ingestion of water is attended by increased output of urine. The mechanism is obviously different from that of true diabetes insipidus, in which renal water loss is primary and increased water intake is secondary (139).

The complexity of adrenal action is even greater than is indicated above. Thus normal individuals given desoxycorticosterone rarely develop edema. However, unless dosage is carefully regulated, patients with Addison's disease frequently do. These facts indicate that the functioning adrenal gland may secrete some factor opposing the salt retaining action of desoxycorticosterone (437). A further complicating factor is that compound E causes a mild sodium retention in patients with Addison's disease, an effect which is antagonized to some extent by desoxycorticosterone (143). Both effects are contradictory to those observed when the compounds are administered to the normal individual.

As pointed out above, in the rat desoxycorticosterone and adrenal cortical hormone promote the elimination of a test dose of water; in the dog both hormones either exhibit no effect (396) or delay the excretion of water (386).

Significance of other hormones in promotion of diuresis. Thyroidectomy reduces the polyuria of animals with diabetes insipidus by $\frac{1}{4}$ to $\frac{1}{2}$, and subsequent feeding of thyroid substances restores fluid exchange to preoperative levels (9, 137, 139, 289). In addition, the administration of thyroid to normal animals induces polyuria of a mild degree. Both observations indicate that the thyroid promotes diuresis, yet its significance relative to the adrenal is minimized by the fact that removal of the thyroid has little if any effect on the fluid exchange of an otherwise normal animal. Furthermore the polyuria of hyperthyroidism is abolished by adrenalectomy (164).

Epinephrine enhances the excretion of a large water load (165); yet demedullation of the adrenals has no effect on normal fluid balance and does not increase susceptibility to water intoxication. The sex hormones including estradiol, progesterone and testosterone enhance the conservation of salt, and thus, like desoxycorticosterone, induce antidiuresis and fluid retention to the extent of manifest edema in balance experiments (461, 464). Rebound diuresis occurs as the effect of the hormone wears off.

The renal tubular absorption of water and salt. The glomerular filtration rate of the normal adult male averages 130 cc. per min. (436). Urine flow of course varies with fluid intake and exhibits post-prandial peaks, but over a 24-hr. period averages 1 cc. per min. It is therefore evident that less than 1 per cent of the filtered water is discarded in the urine. Under conditions of usual dietary intake less than $\frac{1}{2}$ per cent of the filtered salt is excreted, and even this quantity is salvaged under conditions of salt starvation. Peak diuresis and high salt excretion are effected by the elimination of relatively small proportions of the filtered water and ions. Regulation of salt and water balance therefore depends on relatively minor variations in the completeness with which these components are absorbed from the filtrate. A satisfactory analysis of the mechanisms of salt and water absorption has been rendered difficult by the facts that the proximal and distal tubular processes are apparently dissimilar and that they operate serially on the tubular urine.

The mechanism of proximal tubular absorption of water. There are two observations upon which any hypothesis of the mechanism of proximal tubular absorption of water in the mammal must be based, both derived from the microtubular puncture studies of Walker, Bott, Oliver and MacDowell (484). (a) The volume of glomerular filtrate progressively diminishes during its course through the proximal tubule; at the end of the proximal segment volume has been reduced at least by two thirds and possibly by four fifths or more. (b) The fluid, although progressively altered in composition during its course through the proximal segment, nevertheless is maintained in osmotic equilibrium with the plasma. It is unfortunate that these facts were established only under conditions of moderate urine flow. It is generally assumed, perhaps unjustifiably, that they apply as well to the extremes of maximum water diuresis and oliguria.

In addition, any explanation of proximal tubular absorption of water must account for the nearly linear relationship which has been observed between glomerular filtration rate and the rate of tubular absorption of water and of sodium, chloride and bicarbonate ions (280, 325, 349, 350, 355, 357). Although a linear relationship applies strictly to total tubular absorption, it is true that it describes in roughly quantitative fashion the nature of the contribution of the proximal tubule.

No less than three mechanisms in partial harmony with these facts might be invoked to explain the proximal tubular absorption of water. (a) The force which returns water from the tubular lumen to the blood stream is the colloid osmotic pressure of the peritubular blood plasma. For such a mechanism to be effective, the tubular epithelium must be freely permeable to water and electrolytes. (b) The transport of water is active; electrolytes diffuse passively across the tubular epithelium in consequence of a gradient set up by the active absorption of water. (c) The transport of electrolytes, glucose and other similar substances is active; water diffuses passively across the tubular epithelium in consequence of a gradient set up by the absorption of osmotically active materials. All hypotheses demand the relative impermeability of the tubular epithelium to the common excretory products.

The first two hypotheses fail to account for the facts outlined above in at least one significant respect. Both colloid osmotic transport of fluid and active absorption of water followed by passive diffusion of electrolyte imply that the processes of ion transport should be relatively non-selective, *i.e.*, the diffusion of ions across the tubular epithelium should be conditioned largely by ion mobility. Were this true the filtrate, reabsorbate and residual proximal tubular urine would exhibit nearly the same ionic patterns and concentrations. The micropuncture studies of Walker *et al.* (484) and the studies of Wesson *et al.* (491, 492) and of Mudge *et al.* (329) on the composition of the urine in osmotic diuresis (*vide infra*) suggest that both pattern and total concentration are very considerably altered in the proximal segment. It is necessary therefore to discard both these hypotheses as explanations of water absorption by the normal kidney. However, Richards (377) has observed active filtration in the glomeruli associated with complete absorption of tubular fluid in amphibia poisoned with mercuric chloride. He considers that this absorption is entirely passive and is dependent on the colloid osmotic pressure of the plasma proteins drawing filtrate *in toto* back into the blood stream through the damaged tubular cells.

The third hypothesis that the active absorption of electrolytes, glucose and other valuable substances from the filtrate creates a diffusion gradient which causes the return of water to the blood stream derives its strongest support from recent studies on osmotic diuresis (329, 491, 492). It is possible by the infusion of concentrated solutions of mannitol (491, 492) and urea (329) to increase urine flow to a value roughly half that of the simultaneously determined filtration rate. Although the rates of excretion of sodium, chloride and bicarbonate ions are considerably increased under such circumstances, a larger fraction of the filtered water than of the filtered ions is excreted. Furthermore a greater

proportion of the filtered chloride than of the filtered sodium is excreted, and only a very small proportion of the filtered bicarbonate is eliminated. These facts strongly suggest that ions are actively and semi-independently absorbed. The urine formed is isosmotic with the plasma and filtrate, but a greater proportion of the osmotic pressure is exerted by mannitol or urea in the urine than in the plasma. Thus active absorption of ions causes passive absorption of water, and insofar as water is absorbed mannitol and urea are concentrated in the tubular urine. The entire process is carried out isosmotically, *i.e.*, no osmotic work is performed directly on water.

These findings in reality describe the overall tubular process of urine formation and thus include the combined activities of the proximal segment, thin segment of the loop of Henle, and distal segment. With respect to the proximal segment, one might reasonably argue that they indicate the probability of the active absorption of ions accompanied by the passive absorption of that quantity of water necessary to maintain isotonicity of the tubular urine. The inference of Wesson *et al.* (491, 492) and Mudge *et al.* (329) that they have described in semi-quantitative terms the process of urine formation in the proximal segment is scarcely justified, for it is based on their assumption that the contribution of the distal tubule to urine formation with respect to the absorption of both water and electrolyte is insignificant under conditions of osmotic diuresis. An equally reasonable assumption would be that percentage-wise the contribution of the distal tubule to total absorption of water and ions would increase as proximal absorption diminishes in osmotic diuresis.

Wesson *et al.* (491, 492) claim that a limiting gradient exists against which the proximal tubule can transport sodium from tubular urine to blood; *i.e.*, when the concentration of the tubular urine falls some 60 to 90 milliequivalents per liter below that of the plasma, further transport stops. Were this true, a fact which Mudge *et al.* (329) disclaim, it might form the basis for an explanation of the observed correlation between filtration rate and absorption of electrolyte and water. Thus the greater the volume of filtrate, the greater could be the quantity of electrolyte and fluid absorbed before the limiting gradient is attained in the proximal segment.

It is perhaps well to point out that with methods presently available it is impossible to quantify with any semblance of accuracy the proximal or the distal absorption of water or of any single ion species. Although total (proximal plus distal) absorption is subject to measurement within reasonable limits of experimental error, the assignment of function to any specific site must be based on a number of unproven and often highly debatable assumptions. A contribution which would be of greatest significance would be the provision of methods for such measurements in the intact animal. Lacking this, an extension of the micropuncture studies of Walker *et al.* (484) on the mammal under a variety of conditions is greatly to be desired.

If, as seems probable from the above discussion, the absorption of water in the proximal segment is secondary to the absorption of osmotically active materials and more specifically ions, the intimate cellular nature of those mech-

anisms becomes highly significant to an understanding of water absorption. According to Binkley (28), the enzyme glutaminase constitutes as much as 30 per cent of the protein of the kidney. Because of its insolubility and acid properties it could act as a self regenerating ion exchange resin of the carboxylic acid type. Cations could be absorbed from the filtrate by the enzyme and then removed into the peritubular blood by an enzymatic step involving the hyrolysis of glutamine. Presumably the base absorbing properties of the enzyme could be regenerated by the resynthesis of glutamine from the bound ammonia or by the displacement of ammonia by hydrogen ions. Although these views are highly speculative it is probable that future clarification of the nature of these cellular mechanisms will be effected by joint efforts of the enzymologist and renal physiologist.

The mechanism of distal tubular absorption of water. The problem of distal tubular absorption of water is perhaps more clear cut though no better understood than that just discussed in connection with the proximal segment. The formation of urine hypertonic to the plasma must involve either the active absorption of water in the distal segment or the secretion by the distal segment of osmotically active substances into the urine in high concentration. Rapoport *et al.* (369) have shown in dehydrated subjects that the intravenous infusion of equivalent quantities of a variety of substances in concentrated form is attended by the formation of urine of equivalent hypertonicity. Under these circumstances the osmotic pressure of the urine is largely determined by the infused substances. Since the distal secretion of all these substances is highly unlikely, it follows that they must be concentrated by the active absorption of water. All evidence points to the fact that posterior pituitary antidiuretic hormone enhances the capacity of the distal tubule to perform osmotic work; yet it may not be essential to the process, for dogs with diabetes insipidus when severely dehydrated can still elaborate hypertonic urine (417).

Smith (435) and Wesson *et al.* (492) maintain that 80 to 87 per cent of the filtered water is absorbed in the proximal segment, and that the remainder is subject to facultative absorption in the distal segment, depending on the concentration of circulating antidiuretic hormone. If hormone concentration is negligible (water diuresis and diabetes insipidus), up to 15 per cent of the filtered water is excreted; none is absorbed in the distal segment. With respect to proximal function they hypothesize constancy of the fraction absorbed at all filtration rates. Such evidence as exists is opposed to this concept (356, 417) and favors the view that at low filtration rates absorption in the proximal segment proceeds more nearly to completion than at high filtration rates.

However, one may reasonably infer that proximal absorption of water outweighs distal absorption under most if not all circumstances and that distal absorption is stimulated by antidiuretic hormone, yet may proceed at a reduced rate in its absence. With respect to the intimate cellular mechanism by which water is transported across the distal tubular epithelium against an osmotic gradient nothing is known.

The dehydrating effect of large quantities of water. When normal subjects ingest

from 20 to 200 cc. of water every 10 minutes for 3 to 7 hours, the total urinary output of water may exceed intake by as much as 8 per cent (72). If one includes some 50 cc. per hour additional loss as insensible perspiration, the negative water balance becomes appreciable. It is apparent from the work of Marshall (297, Wolf (503) and Stewart and Rourke (450) that the ingestion or intravenous administration of very large water loads increases the excretion of salt. The elimination of increased quantities of water to compensate for salt loss is to be expected as a means of limiting derangement of osmotic pressure of the body fluids, and undoubtedly depends upon inhibition of secretion of posterior pituitary hormone. These principles have been applied by Schemm (400, 401) in his regimen of high fluid intake for the management of edema. One of the very significant features of this regimen, however, is limitation of sodium intake, for without restriction of salt, edema accumulates in proportion to fluid intake (408). Urinary loss of salt is dependent upon high water load since moderate loads have been observed to reduce sodium output (96, 396) rather than to increase it.

Little definite information exists upon which to base an explanation of increased loss of electrolyte in excessive water diuresis. One might reasonably hypothesize that the increased rate of transport of fluid through the distal tubular segment in consequence of reduced absorption of water would interfere with mechanisms of base absorption and lead to increased salt excretion. Or it is thoroughly possible that hyperhydration could increase filtration rate (79, 419–421) and deliver increased quantities of water and electrolyte to the distal tubule, a portion of which escapes in the urine.

Factors involved in delayed diuresis and in the accumulation of edema. A delayed or poor diuretic response to water and a retention of salt characterize a variety of seemingly unrelated clinical conditions, including salt depletion, Addison's disease, shock, congestive heart failure, anemia, acute nephritis, nephrosis and the nephrotic stage of glomerulo-nephritis, cirrhosis, eclampsia, hypoproteinemia and acute infections (42). In certain of these conditions, edema tends to accumulate spontaneously; in others, one can induce edema by increasing the salt load moderately. No matter how diverse these conditions may be they have one element in common,—the kidneys in all are incapable of eliminating water and salt at normal rates. At least four factors may be causatively involved in the observed retention of salt and water: (a) reduced glomerular filtration rate, (b) increased renal venous pressure, (c) increased antidiuretic hormone activity, and (d) increased adrenal cortical activity. It is probable, in many instances, that more than one of these factors play a role in fluid retention; yet at the present time it is impossible to assess the magnitudes of their respective contributions.

a. *Factor of reduced glomerular filtration rate in salt and water retention.* Glomerular filtration rate and renal blood flow are reduced in chronic congestive heart failure (312, 325, 487), in which condition there is a considerable incapacity to eliminate water and especially sodium (63, 156, 408, 465). In patients with low cardiac reserve, exercise reduces renal blood flow and glomerular filtration rate and leads to the accumulation of edema; rest increases renal blood flow and

filtration rate and restores compensation. According to Merrill and Cargill (316) the critical level of filtration rate below which salt and water excretion becomes deficient is 70 cc. per min. It is inferred that the delivery of a reduced volume of filtrate into tubules having essentially normal absortive capacities favors relative over-absorption of water and salt. The significant factor may well be slowing of the rate of transport of fluid along the renal tubule and prolonged contact of the fluid with the epithelium (356, 417). Others, however, observing recovery of compensation and loss of edema without increase in renal blood flow and glomerular filtration rate (52, 156, 416, 430), minimize the significance of these factors or even deny their existence.

The difficulties in the clinical analysis of the problem are evident. Chronic renal disease is often associated with congestive failure, and reduced filtration rate may in any given instance be more related to the former than to the latter. Furthermore, except in the studies of Merrill and Cargill (316), changes in renal plasma flow and filtration rate occurred slowly over a period of days, and recovery of capacity to excrete salt and water might well have resulted from readjustment of tubular absorptive capacity rather than from the delivery of an increased volume of filtrate into the tubules.

Recent studies of Selkurt *et al.* (411) and Pitts *et al.* (356) have shown that a decrease in filtration rate very greatly reduces the capacity of the kidney to eliminate salt and water. Thus a 25 per cent reduction in filtration rate may lead to a 90 per cent reduction in sodium and water excretion (356). In these experiments, changes in filtration rate were produced by partially clamping the aorta or renal artery to lower filtration pressure, and effects on renal function were induced instantaneously. Since recovery of function was equally rapid, the responses could not have been mediated through hormonal mechanisms which typically exhibit delayed and prolonged actions. One may infer from these experiments that, insofar as filtration rate is reversibly reduced in disease, renal capacity to eliminate salt and water will be adversely affected, and that restoration of filtration rate will tend to restore excretory capacity. However, these experiments do not in any sense gauge the role played by this factor in any specific instance; they merely indicate that the factor must be taken into account in any general consideration of the pathogenesis of edema.

Reduction in filtration rate may play some role in salt and water retention in acute nephritis (31, 122), in nephrosis (124, 263), in severe anemia (48, 147, 451), in shock (258), following hemorrhage (43), in salt deficiency (304) and in exercise (74, 316). In addition, low filtration rate relative to tubular absorptive capacity may account in part for the deficient diuretic response of the new-born infant (105, 203, 205, 305, 306).

(b) *Factor of increased venous pressure in salt and water retention.* It has been known for many years that obstruction to the venus outflow of the isolated kidney results in diminished output of salt and water (502). Furthermore, chronic passive congestion has been cited as a major cause of deficient excretion of fluid in congestive heart failure (196). Bradley *et al.* (49) have shown that pressure on the abdomen exerted by a pneumatic girdle elevates visceral venous pressure

and reduces excretion of salt and water. Recently Blake *et al.* (32) have shown in dogs that elevation of renal venous pressure from 100 mm. to 400 mm. saline by partial occlusion of the renal vein depresses the excretion of salt and water without significantly altering renal blood flow or filtration rate. Only when pressures exceeded 400 mm. saline were these latter variables altered. Since values within this range are commonly observed in congestive failure, it is obvious that elevated venous pressure must play some role in the pathogenesis of edema in this condition. Its significance relative to other factors or the mechanism by which it exerts its effects cannot be assessed at present.

(c) *Factor of increased pituitary antidiuretic hormone activity in salt and water retention.* As pointed out in an earlier section of this review increased quantities of an antidiuretic substance, presumably of pituitary origin, have been identified in the urine in cirrhosis (364), in eclampsia (191, 458), in Bright's disease and in pre-menstrual edema (383), and in hypertensive disease (182). In addition, a similar material has been identified in the serum in cirrhosis (266). In those studies which were designed to test the point, the antidiuretic material has been found in greatest quantities in the urine during the phase of water retention. The reviewers have been unable to find relevant data on patients in congestive failure, but one would anticipate an increase of antidiuretic factor in this condition also. The antidiuretic substance is found in high concentration in the urine and serum of adrenalectomized animals and patients with Addison's disease (30, 266). Although one does not usually associate these latter conditions with the development of edema, it is well recognized that adrenal insufficiency is characterized by poor excretion of large loads of either water (163) or salt (386), and that over-enthusiastic treatment of Addisonian patients with salt can lead to the development of anasarca (180, 373).

Gaunt *et al.* (163) have pointed out that increased antidiuretic activity may result from (a) increased liberation of pitressin; (b) decreased destruction of pitressin; or (c) hypersensitivity to pitressin by virtue of an altered hormonal balance. To date, it has been impossible to assess the role of these several mechanisms.

(d) *Factor of increased adrenal cortical hormone activity in salt and water retention.* Following the demonstration by Loeb *et al.* (267, 268) and Harrop *et al.* (197, 198) of the significance of the adrenal cortex in the renal tubular absorption of sodium and the recognition of the effects of overdosage of desoxycorticosterone in replacement therapy (134, 180, 373), there have appeared numerous references to the possible role of increased adrenal cortical activity in the retention of salt and water in edema (42, 52, 156, 430). It is unfortunate that so much of the evidence has been of a negative sort, namely, that if reduced filtration cannot explain retention, increased tubular absorption must be invoked; and that the most reasonable explanation of increased tubular activity is stimulation by adrenal hormones. The recent recognition that the concentration of salt in sweat varies as an inverse function of adrenal cortical activity has provided more direct evidence for increased cortical function in congestive heart failure (313) and nephrosis (124). With the development of relatively specific

methods for the assay of urinary corticoids (67, 101), a more direct approach to the problem would appear feasible.

According to Borst (42), a reduction in blood flow through some receptor area in congestive failure, shock, hypoproteinemia, etc. triggers a hormonal mechanism which stimulates the renal tubular absorption of electrolyte. Water and salt are retained, circulating blood volume is expanded, venous pressure rises and fluid filters into the interstitial spaces. The receptor-humoral-tubular mechanism functions in a compensatory manner, for the expanded blood volume and venous pressure tend to bolster cardiac output. He suggests that the hormone may be of adrenal cortical origin. Others would view the retention of salt and water less as evidence of a compensatory adjustment than as an indication of malfunction of the kidneys.

One might speculate that overactivity of both the pituitary antidiuretic and adrenal cortical salt-conserving mechanisms might occur simultaneously in those conditions characterized by the formation of edema. In patients in which the plasma concentration of base is low, one might infer a relatively greater overactivity of the antidiuretic mechanism. In others in which plasma base is high, the adrenal mechanism might be the more dominant one. It is perhaps best to acknowledge that several factors probably play a role in fluid retention in any given patient, rather than to attempt a unitary explanation as has so frequently been done.

OSMOTIC DIURETICS

The limiting concentration of the urine. If the fluid intake of a normal individual is severely restricted, urine output decreases to a minimum of 0.1 to 0.3 cc. per min. and urinary specific gravity and osmotic pressure increase to maxima of 1.029 to 1.040 and 1,200 to 1,400 milliosmols per liter, respectively (81, 257, 333, 334, 367, 369). Since specific gravity and osmotic pressure of the urine are largely contributed by urea and electrolytes, the minimum urine volume is ultimately determined by the load of these substances demanding excretion and any increase in load must be reflected by an increase in volume. When any excretory solute, whether a normal urinary constituent or a foreign substance, is administered in a concentration higher than that in which it can be eliminated, water is abstracted from the body, *i.e.*, osmotic diuresis results.

According to Davies (103) and others (159, 169, 300, 307) who have administered hypertonic saline to dehydrated subjects, the maximum concentration of chloride which the kidneys can effect is 330 millimols per liter. The salt excreted would therefore contribute 660 milliosmols per liter to the osmotic pressure of the urine. A similar maximum is attained after hypertonic sodium bicarbonate, and when the two salts are ingested simultaneously the sum of their urinary concentrations never exceeds 660 milliosmols per liter. It would appear at first glance that the kidney is limited in its capacity to concentrate chloride, bicarbonate and base to a value somewhat less than half of its capacity to concentrate the usual mixture of urinary constituents eliminated in simple dehyration (*i.e.*, 1400 milliosmols per liter). Indeed, evidence has been presented that the

maximum attainable concentration of chloride is unaffected by the simultaneous presence of relatively large quantities of urea in the urine (103, 169), an observation which led Gamble (159) to claim a special biological fitness for urea, namely, that it could be excreted along with other substances without much increase in water requirement.

It must, however, be remembered that the evidence quoted above was obtained under conditions of high solute load brought about by the administration of hypertonic saline, bicarbonate or urea. In all instances urine volume exceeded the minimal levels characteristic of dehydration (*i.e.*, 0.1 to 0.3 cc. per min.). Recently it has been demonstrated that even in severely dehydrated subjects an increase in the urinary load of any solute is accompanied not only by an increase in urine volume but also by a fall in total osmolar concentration of the urine (219, 307, 369, 370). Under conditions of salt loading, total ion concentration may peak at 660 milliosmols per liter; but owing to the increase in urine flow, total osmolar concentration is considerably below the maximum observed in uncomplicated dehydration. Indeed in dehyration, minimal urine flows and maximal concentrations are exhibited only if salt load is low. Therefore, conditions following solute loading, even in hydropenic subjects, are in no wise comparable to those of simple oliguria. In addition, recent work has failed to confirm the independence of water requirements for the solution of urinary salt and urea (219, 370).

Present evidence would indicate that in simple dehydration with normal solute loads a limiting osmotic pressure determines the minimal rate of urine flow, and that this limiting osmolar concentration is independent of urine composition (80, 219, 369). As urinary solute load is increased, volume rises and osmotic pressure falls. Under such conditions of osmotic diuresis, factors other than limiting osmotic pressure must determine urine flow.

The limiting osmotic work capacity of the kidney. The production of urine more concentrated than plasma involves *per se* the performance of osmotic work on water by the renal tubules. The alterations in composition which proceed simultaneously likewise involve work which can be designated as chemical osmotic work. Von Rohrer (387), Borsook and Winegarden (41) and more recently the Newburghs (333, 334) and Rapoport *et al.* (369) have calculated the total work involved in the production of urine on the assumption that the transformations are carried out independently and in a thermodynamically reversible fashion. The last named investigators, by making the additional assumptions that the changes in composition are effected isosmotically in the proximal segment and that the urine is rendered hypertonic by the absorption of water in the distal segment, have separated these two moieties of renal work (370).

It is evident that osmotic work must be some function of the products of the several concentration differences established between plasma and urine and the volume of urine elaborated. It is possible that minimum volume and maximum concentration in dehydration as well as the inverse relation between volume and concentration on progressive solute loading might be related to a limited capacity of the renal tubules to perform osmotic work.

Hervey *et al.* (219) and Rapoport *et al.* (368, 369) have recently described in detail the relationship between urinary solute load and urine volume, and have demonstrated that neither constitution nor mode of excretion of the solute affects the relationship. Thus eleven solutes administered to hydropenic normal subjects, including glucose, urea, sodium sulfate, mannitol, sucrose, sodium para-aminohippurate, sorbitol, sorbose, xylose and creatinine, all increase urine flow in identical fashion and in exact proportion to the increase in urine solute load (368, 369). The work of elaborating urine by dehydrated subjects with normal solute loads is rather small, amounting only to 0.6 gm. cal. per min. per 1.73 m^2S.A. Although the U/P concentration ratios are high, low volume minimizes the work performed. When solute load is increased by administering hypertonic solutions, renal work increases some 7-fold to reach a true limiting maximum of about 4.0 gm. cal. per min. Under such conditions less work is performed per cc. of urine formed, but more work is performed per min. in consequence of the increased volume. Obviously the maximum urine concentration of 1,400 milliosmols per liter observed in simple dehydration cannot be assigned to a limitation of osmotic work capacity of the kidney *per se*; rather it must find its explanation in some absolute inability of the renal tubule to absorb water against a gradient of limiting steepness.

Glomerular filtration rate as a limiting factor in determining solute load and urine flow. Chesley (80, 81) has noted in dehydrated subjects that, as the rate of urine flow decreases from 0.35 cc. per min. down to 0.1 cc. per min., the clearances of urea, phosphate, creatinine, total nitrogen and total solids decline in exact proportion to urine flow, *i.e.*, the U/P ratios for all substances become fixed as does the total osmolar concentration of the urine. If one accepts the endogenous creatinine clearance as a rough approximation of glomerular filtration rate, it follows that solute load and hence urine flow within this range of minimal volumes are determined by filtration rate.

Summary of factors determining urine volume in hydropenia. In summary, the urine flow of the hydropenic subject is dependent on three factors. First and most significant in simple dehydration is the limited capacity of the tubules to establish high U/P ratios, and since this capacity is non-specific (*i.e.*, with respect to endogenous creatinine, urea, phosphate, total nitrogen and total solids) it must be related to the steepness of the osmotic gradient against which the tubule can absorb water. Second and of special significance in extreme oliguria (volumes of 0.1 to 0.35 cc. per min.) are fluctuations in filtration rate which alter the load of excretory solutes delivered into the urine. Since concentration is maximal, volume will vary directly with solute load within this limited range. Third, and of significance at very high solute loads, is the limited capacity of the renal tubules to perform osmotic work, which again is non-specific with respect to the nature of the solute. Maximum work is performed by the elaboration of fairly large volumes of urine only moderately hypertonic to plasma. Extreme hypertonicity, represented by urines having a concentration of 1400 milliosmols per liter, can be effected only when solute load is low and urine flow is minimal. The thermodynamically reversible work involved is small in comparison with

the maximum observed with high solute loads. Perhaps the efficiency of absorption of the final salvageable moiety of water drops sharply in comparison with the efficiency of absorption of that initial moiety which first renders the urine hypertonic to the plasma.

Characteristics of the ideal osmotic diuretic. Rapoport (369) has pointed out that the most effective osmotic diuretic is one which (a) is distributed in the smallest volume in the body; (b) is not metabolized by the body; and (c) is not reabsorbed (and, better, is secreted by) the renal tubules. For clinical use one would necessarily add the requisites of oral administration and absence of gastrointestinal or systemic disturbances. There is, however, a still more significant factor than any of these, namely, the promotion of sodium and chloride loss from the body, for were water alone to be abstracted by an osmotic diuretic it would be clinically ineffective in the treatment of edema. The individual would suffer a pure primary water loss, and fluid volume would be completely restored upon the ingestion of water. Although there is disagreement in the literature, it would appear fair to state that any osmotic diuretic, excreted in sufficient quantity in the urine, abstracts sodium and chloride from the body more or less in proportion to the increase in urine flow (370). On the other hand there may well be real differences among various compounds in the efficacy with which they promote loss of these ions. It is rather difficult to evaluate different solutes in this respect because of conflicting claims. For example, intravenous sodium sulfate is variously stated to produce either insignificant (278, 370, 409) or moderate (1, 175) chloride loss. Potassium salts may effectively promote the excretion of sodium (166, 317, 501) or produce only a transient or insignificant loss of this ion (62, 284, 318). Some of the discrepancies may well be related to dose employed, route of administration, and available volume of extracellular fluid. In the most carefully controlled study to date, Rapoport (366) has shown in hydropenic subjects a difference in the efficacy of a variety of anions in promoting chloride loss, when administered in equimolar quantities as sodium salts. The order from most to least effective is $CNS > NO_3 > HCO_3 > PAH > FeCN_6 > SO_4 > S_2O_3 > PO_4$.

Mechanism of sodium, chloride and water loss in osmotic diuresis. As was pointed out in an earlier section of this review, most of the electrolytes and other valuable constituents of the glomerular filtrate are actively absorbed in the proximal segment of the renal tubule (484). Water diffuses freely across the proximal epithelium to maintain osmotic equilibrium between blood and tubular contents. The fluid delivered into the distal segment contains waste products concentrated to a moderate degree by virtue of the reduction in filtrate volume, and a somewhat reduced concentration of sodium and chloride, *i.e.*, reduced in proportion to the increased concentration of excretory products (329, 491). Although composition has been altered, osmotic pressure is the same as that of the plasma and original filtrate. Continued but usually incomplete absorption of electrolyte and further concentration of waste products by the absorption of water completes the elaboration of urine in the distal segment.

When the filtrate contains an excess of some absorbable solute (*e.g.*, glucose)

over that which the tubules can salvage, or some relatively unabsorbable material such as mannitol, sucrose or sulfate, the proximal absorption of sodium and chloride are reduced, and in consequence the absorption of water declines (329, 491). The distal tubules are flooded and an increased volume of urine is excreted containing not only the osmotic diuretic but also an excess of sodium and chloride. Two views as to the cause of reduced absorption of these latter ions have been expressed. According to Wesson *et al.* (491), the proximal tubules cease to absorb sodium when the concentration of this ion in tubular urine is reduced some 60 to 90 milliequivalents below that of the plasma, *i.e.*, the proximal tubules can establish a U/P ratio for sodium of roughly 0.5. When an osmotic diuretic is present in the filtrate in large quantities, the abstraction of a given proportion of the sodium and chloride can be attended by the absorption of less than an equivalent proportion of the water because of the osmotic pressure exerted by the residual unabsorbed solute. A limiting U/P ratio for sodium and chloride would therefore be attained when less than normal quantities of ions and hence of water have been absorbed. On the other hand, Mudge *et al.* (329) claim that no such limiting U/P ratio exists; but, that as water absorption is diminished and as rate of flow increases in the lower part of the proximal tubule, the time of contact of the fluid with the tubular epithelium is insufficient to permit adequate absorption of ions.

The use of potassium salts as osmotic diuretics. Of the several osmotic diuretics currently used, potassium salts are the most venerable. Thomas Willis in 1679 first recommended the administration of potassium nitrate in the treatment of dropsy, and even today the nitrate is accepted as the most effective salt. The order of efficacy is claimed to be nitrate, chloride, and bicarbonate, acetate and citrate, the last three having essentially equal diuretic potency (246). All salts produce a loss of body sodium and water and of body weight when administered in adequate dosage to edematous patients (13, 246, 269, 317). In normal animals and man they cause only a minor and short-lived negative balance of sodium and water (62, 166, 317, 318, 498). Even in edematous patients the response has not been found to be uniformly significant (284), although negligible diuresis may in part be assigned to inadequate dosage. Potassium nitrate and sulfate increase the excretion of chloride, whereas potassium chloride initially increases the excretion of bicarbonate and renders the urine intensely alkaline (269, 501). Alkalinity of the urine is rather evanescent, for with continued administration, chloride replaces bicarbonate as the predominant anion in the urine (269).

Potassium salts have been administered orally in daily doses from 5–10 gm. of the chloride (284), to 8–12 gm. of the nitrate (246) to 20 gm. of the citrate (13). They may be given in divided doses three to four times daily in 10 to 12 per cent solution or in enteric-coated capsules. In general, the larger the dose the greater is the diuretic response. Within the range noted above, potassium salts are well tolerated and cause only minimal increases in serum potassium. In anuria or in chronic renal disease with markedly reduced renal function and basally elevated serum potassium, this ion should not be used because of the danger of potassium intoxication with its manifestations of cardiac conduction

disturbances and even cardiac arrest (221, 222, 247, 295). Renal disease *per se* is not a contraindication to the use of potassium salts as diuretics, for the capacity to excrete potassium is well maintained until late in the disease process (248).

There is at present no evidence that potassium salts act as diuretics except by virtue of the osmotic pressure which they exert in the urine. However, they are much more rapidly eliminated than are sodium salts, and the difference is especially marked in edematous patients. In the post-absorptive state, the potassium clearance of the normal individual is less than one quarter of the glomerular clearance, a fact which indicates extensive tubular reabsorption. Following the ingestion of one of its salts, the clearance of potassium rises sharply with relatively little increase in serum level to approach and even exceed the glomerular clearance (20, 328). Potassium therefore is secreted by the renal tubules. Secretion plus temporary intracellular storage of potassium accounts for the insignificant increases in serum level which attend the ingestion of relatively large doses of potassium salts.

The use of urea as an osmotic diuretic. Friedrich (153) in 1892 first employed urea as a diuretic in patients with cirrhosis and congestive heart failure and obtained favorable results with doses as small as 2 to 14 gm. per day. Others have found it necessary to administer from 30 to 100 gm. per day to obtain significant diuresis (93, 133, 319). In general 50 to 60 gm. of urea per day, divided in 3 doses, produce nearly maximal diuresis (93, 319). The increase in daily urine output may be 2- to 4-fold in patients in which prediuretic output varies from 300 to 700 cc. (93, 151). Since the diuretic response to adequate doses of urea is claimed to be somewhat superior to that to theophylline, although less than that to organic mercurials (151, 155), this drug has a definite place in the therapeutic armamentarium (83, 86, 201).

Two difficulties may be experienced in the use of an adequate dose of urea as an osmotic diuretic: (a) in some patients gastrointestinal disturbances, including nausea and vomiting, may be sufficiently intense to preclude its use (172), although if administered immediately after meals little disturbance usually results. All complain of its disagreeable taste, which may at least be partially masked by various flavoring agents (83, 319). (b) In patients with severely reduced renal function, nitrogen retention occurs with the development of weakness, lassitude and loss of appetite (93), necessitating discontinuance of the drug. Counterbalancing these difficulties are virtues of non-toxicity on prolonged use, undiminished diuretic potency over a period of years, and additive response when combined with other diuretics (151, 319). It is properly claimed to be the safest, although certainly not the most effective, of all diuretics.

The excretion of chloride and sodium is increased by the administration of urea more or less in proportion to the diuresis provoked (93, 155, 328). The diuresis in turn is proportional in any individual to the increase in serum concentration of urea attained (93, 328). However, if the blood chloride is abnormally low, diuresis may occur in the absence of increased excretion of chloride (285). The increased excretion of ions in urea diuresis as in other types of os-

motic diuresis depends on diminished proximal tubular absorption of sodium and chloride in consequence of the rapid flow of urine (329) or of the development of some limiting U/P ratio for sodium (491).

Urea is fairly extensively reabsorbed by the renal tubules, *i.e.*, some 40 to 70 per cent or more of that filtered is returned to the blood stream by passive diffusion (420, 421, 425). At least 40 per cent is absorbed in the proximal segment under normal conditions independent of urine flow (420), a value which is reduced during severe osmotic diuresis to about 10 per cent. An additional 10 to 40 per cent is absorbed in the distal segment, the proportion varying as an inverse function of urine flow or directly with the degree of concentration of the urine (420, 421). To whatever extent absorption occurs, the efficacy of urea as an osmotic diuretic is reduced. Because of relative non-toxicity and tolerance of high blood levels, neither tubular absorption nor reduced filtration seriously limits the capacity of the kidneys to excrete osmotically significant quantities of urea in the urine. If no diuresis occurs by virtue of severely reduced renal function, the blood urea may rise to toxic levels, and use of the drug as a diuretic is precluded.

The use of other substances as osmotic diuretics. A variety of substances including glucose, sucrose, mannitol, sorbitol, sorbitan, xylose, sodium sulfate, sodium phosphate, sodium nitrate, sodium succinate, sodium fumarate, sodium para-aminohippurate and creatinine act as osmotic diuretics when given intravenously in hypertonic solution (211, 329, 337, 369, 491). With the exception of the last two, all are more or less absorbed by the renal tubules; these two are secreted, at least by man and the anthropoid apes. To obtain adequate blood levels and rates of excretion, it is necessary to administer these substances intravenously because of rapid metabolism (glucose), digestion (sucrose), or relatively poor intestinal absorption with resulting purgation (most of the remainder). For this reason they are clinically less useful as osmotic diuretics than are potassium salts and urea.

The carbohydrates glucose, sucrose and xylose and the polyhydric alcohols mannitol, sorbitol and sorbitan are effective diuretics when administered intravenously in large doses, causing the loss of body sodium, chloride and water (3, 194, 224, 369, 423, 491). Glucose is the only one of these substances which is significantly absorbed by the renal tubules (423, 424) or significantly metabolized in the body. Thus, per gram administered it is the least effective, but its lack of toxicity and low cost largely neutralize this objection. Sucrose, although not metabolized when administered parenterally and only slightly absorbed by the renal tubules, may cause some renal pathology and may reduce renal function (265). Mannitol is apparently inert, only little absorbed by the renal tubules, and an effective osmotic diuretic (491).

Sodium sulfate and sodium phosphate, when given intravenously, are rapidly eliminated in the urine and may be employed to abstract water from the body. Although both substances are reabsorbed in large part by the renal tubules at normal blood levels, absorptive capacity is readily exceeded after intravenous injection, and clearance rises to approach the rate of glomerular filtration (4,

175, 278, 351, 354, 402). The use of phosphate is limited by the danger of tetany, that of sulfate by its relative ineffectiveness in promoting loss of chloride and sodium (366, 409). Sulfate has found favor in some quarters in the treatment of anuria following burns (338) and crush injuries (290, 291), in which circumstances it is given as an isotonic solution of the sodium salt by slow continuous intravenous drip. Evidence of its efficacy clinically in anuria is lacking, and it is probable that more damage than good would result from its indiscriminate use.

Sodium chloride and sodium bicarbonate are relatively ineffective osmotic diuretics. Although both abstract water from the body when given in hypertonic solution, the resulting dehydration is more cellular than extracellular (500). The ionic concentration of the extracellular fluid is increased and the water deficit is restored when fluid is ingested. All osmotic diuretics are relatively ineffective in newborn infants, largely because of low rate of glomerular filtration (106, 305) and consequent low load of osmotically active substances delivered into the urine.

ACIDIFYING DIURETICS

Action of acidifying agents. The acidifying diuretics that have been commonly employed clinically and experimentally include ammonium chloride and nitrate, calcium chloride and nitrate, and to a lesser extent dilute hydrochloric acid (447). The action of these acidifying agents is dependent upon the destructibility or non-absorbability of the accompanying cation. Thus, the ammonium salts are readily absorbed; but, on passage through the liver, the ammonium fraction is converted into urea, freeing the anion (39, 70, 140, 171, 250, 294). Calcium, on the other hand, is poorly absorbed, being precipitated within the intestinal tract as the insoluble phosphate and carbonate (160, 189), while the anion is readily absorbed. In both instances the excess anion displaces bicarbonate in the body fluids (160, 189). Recently the insoluble cation exchanging resins have been employed as acidifying agents. The action of these resins depends on their capacity to abstract fixed base unaccompanied by anions from the body reservoirs, thus creating an endogenous acidosis without the addition of electrolyte.

With the daily administration of 10–15 grams of ammonium chloride to a normal subject, immediate neutralization of the excess anion occurs at the expense of bicarbonate, in consequence of which the plasma hydrogen ion concentration increases (190). Because of this increase in plasma acidity, respiratory ventilation increases and arterial pCO_2 decreases (188, 190, 398). With a decrease in plasma pH from a normal of 7.40 to a level of 7.25, the subject experiences some increased ventilation at rest, with obvious dyspnea on exertion (398). Plasma bicarbonate falls in proportion to the increase in plasma chloride so that the sum of the anions remains essentially constant. In consequence of the elevated plasma chloride, a greater amount of chloride is delivered to the kidney and excreted in the urine (250, 398).

Effects of alteration of ionic pattern on electrolyte excretion. As noted above, an increase in the plasma level of chloride promotes the excretion of this anion.

On the first day of acidosis, the excess urinary chloride is neutralized for the most part by sodium derived from body buffers (189, 250, 397, 398). Since the major body buffers can yield sufficient base within a pH range compatible with life to neutralize at most one mol of strong acid (343), it is apparent that a subject receiving 10–15 grams (0.19–0.28 mole) of ammonium chloride daily could not long survive without adequate renal compensatory mechanisms for base conservation. That these mechanisms are promptly brought into action is evidenced by the fact that sodium excretion decreases progressively after the first day of ammonium chloride administration and indeed attains a positive balance around the 5th day (398).

No less than three distinct mechanisms aid in the restriction of sodium loss from the body. Initially, as bicarbonate is converted to chloride, an increase in the tubular reabsorption of this latter ion species serves to restrict its loss and thus the loss of sodium which accompanies it into the urine. The increased tubular reabsorption of chloride is more or less proportional to the extent of the conversion of bicarbonate to chloride and is of sufficient magnitude to restrict the initial loss of sodium by two-thirds or more (398). An additional consequence of this renal response is the maintenance of constancy of total ionic concentration despite considerable shifts in ionic pattern.

Sodium loss is further restricted on the second and third days of acidosis by increased excretion of potassium and calcium derived from intracellular and osseous reserves (27, 250, 398). Since under controlled dietary conditions no appreciable change occurs in the plasma potassium or calcium levels during acidosis, these ions must be delivered from the tissues into the blood at the same rate as they are excreted in the urine. However, even though sodium loss is curtailed by increased potassium and calcium excretion, fixed base loss remains unchanged or actually increases slightly. Thus, this mechanism may be considered corrective only in the sense that ionic losses are more equitably distributed between the extra- and intra-cellular compartments.

The third mechanism, namely, the renal production of titratable acid and ammonia, represents the only completely corrective compensation in that it permits the restoration of fixed base reserves in the presence of continued acid excretion. Under the stimulus of either fixed base depletion (157) or lowered plasma bicarbonate (352), urinary buffers are converted to titratable acid (489) to the limit of the capacity of the kidney to establish a high hydrogen ion gradient *i.e.*, a urinary minimum pH of 4.4 to 4.7 (210, 358). Because of the limited renal capacity to form highly acid urine, titratable acid production can result in the neutralization of at most the equivalent of one-fourth the acid load imposed by the daily administration of 10–15 grams of ammonium chloride (398).

Thus, the major burden for the restoration of altered ionic pattern and the repletion of fixed base reserves rests with the renal production of ammonia. That urinary ammonia is of renal origin (19, 331, 332) and is derived from the deamination of amino acids, especially glutamine (279, 352, 472), in the cells of the distal tubule (482) is well established. The stimulus conditioning the rate of excretion of ammonia is less well defined, but it would appear that some

factor other than or in addition to plasma bicarbonate concentration and plasma and urine pH must be responsible (398). Whatever the underlying stimulus, it is certain that the rate of ammonia production increases in stepwise fashion under a continuing acid load until a positive fixed base balance is attained (398, 469).

It is apparent that the action of ammonium chloride in promoting base loss and hence diuresis depends primarily upon the renal lag in adequate ammonia output, for were it not for this lag, no loss of base would occur. Furthermore, the magnitude and duration of base loss are directly related to the acid load administered. Thus with the daily administration of 15 gm. of ammonium chloride, positive fixed base balance may be attained on the 8th or 9th day, while with 10 gm. daily, balance may be reached on the 5th or 6th day. Following the attainment of fixed base balance or following the discontinuance of the acid load, ammonia production remains high and base derived from ingested salt is retained in the body to rebuild depleted buffer stores. Only after these stores are replenished does the excretion of ammonia decrease in stepwise fashion to normal values. Overcompensation with elevated plasma sodium and bicarbonate is frequently observed during recovery (398). Plasma phosphate and potassium, however, may remain low during recovery for a considerable period of time. These low plasma levels undoubtedly result from the continued replenishment of depleted cellular reserves of potassium and phosphorus from limited circulating stores (3, 187, 398).

Effect on water balance. The loss of base from both intra- and extra-cellular compartments during acidosis is accompanied by a compensatory loss of water leading to cellular and interstitial dehydration (189, 232, 469). However, if fluid intake is unrestricted, loss of fluid does not completely compensate for loss of base, for the total base concentration of the plasma usually decreases significantly (398). Since the excretion of total fixed base resulting from the ingestion of 10 to 15 grams of ammonium chloride reaches a maximum on the third day of acidosis, net water loss is also greatest at that time. Net daily fluid loss then progressively decreases until the attainment of positive alkali balance.

As stated previously, the major body buffers can yield sufficient base within a pH range compatible with life to neutralize at most one mol of strong acid (343). On this basis the normal subject could yield at most 6.5 liters (1 mole/0.155 mole per liter) and experience a weight loss of 6.5 kilograms. When ammonium chloride is given in the dosage indicated above, some 450 milliequivalents of base are excreted with a weight loss of 3.0 kilograms. However, in edematous subjects with expanded extracellular fluid reservoirs, larger volumes of water and salt are available for excretion (245).

With attainment of positive base balance, fluid and salt are retained until body buffer stores are replenished, and both ionic pattern and balance are reestablished. With continuance of the acid load and provision of an adequate fluid intake, urine flow remains elevated while body weight is slowly regained. With discontinuance of the acid load, on the other hand, urine flow falls sharply and body weight increases rapidly (398).

From calculations of the relative amounts of sodium and potassium lost during acidosis, it is possible to estimate that one half to three fourths of the subject's weight loss can be ascribed to a reduction in volume of extra-cellular fluid (282, 398). In the normal subject, the loss of extra-cellular fluid may lead to a significant reduction in circulating blood volume (282) with a resultant compensatory fall in renal plasma flow and glomerular filtration rate (142, 158). The reduction in blood volume is a manifestation of dehydration, not of the acidosis itself. Consequently, there may be no change (102) or an actual increase in the renal plasma flow of subjects with initially expanded extra-cellular space. Presumably, it is also the dehydration that is responsible for the reduction in urea clearance and for the nitrogen retention often observed in severe acidosis (302).

Effect on non-electrolytes. With conversion of ingested ammonium compounds into urea, plasma urea rises slightly and urinary excretion of urea increases (177). Total urinary nitrogen, however, increases to a proportionately greater extent than does urea during acidosis, thus indicating some tissue catabolism (468). The excretion of ascorbic acid is increased by ammonium chloride (200).

Route of administration and absorption. Absorption of ammonium salts is rapid and complete when they are administered orally in dilute solution. The first definite changes in plasma chloride, bicarbonate and pH are evident within $7\frac{1}{2}$ minutes after the ingestion of a single dose of ammonium chloride (398). However, when this compound is administered in the form of enteric-coated tablets, in order to avoid nausea or gastric irritation, absorption becomes less definitive and the degree of acidosis is less predictable (335, 412, 478). Indeed, many clinicians have seen these tablets excreted in the feces unchanged or have visualized them in the large bowel of patients during x-ray examination. When given in a gelatin-coated tablet, there is usually complete absorption (412). If given intravenously, ammonium salts rapidly raise the ammonia content of the blood to toxic levels (231).

Calcium salts are effective only when given by the enteric route. Injected calcium or magnesium salts may be recovered quantitatively in the urine with no additional excretion into the bowel (303, 363, 490) and consequently no acidifying or diuretic effect other than can be obtained as a result of their osmotic action (98).

Dosage. The dosage schedule commonly employed clinically is 1–3 grams of ammonium chloride or nitrate 4 times a day for 4 days, with a week's rest between courses (245, 264). Larger amounts have been given for longer periods of time, 162 grams having been given in 18 days (245). Calcium salts may be administered in capsules in dosage of 10 grams daily (244).

Toxicity. Toxic manifestations from ammonium chloride administration may arise from primary or secondary effects of the salt. Toxicity due to ammonia arises most frequently after intravenous administration, and may include tetany, intermittent rigidity, salivation, irregular respirations and hyperexcitability (50, 177, 231, 438). Since similar body changes occur with ammonium hydroxide and ammonium bicarbonate, it is probable that ammonia rather than the

acidosis is responsible. It has been suggested that ammonia increases intracellular acidity independently of the accompanying anion and resultant arterial pH change by exerting an anticholinesterase effect (50, 51). The normal plasma ammonia level is in the range of 1.4 to 1.6 mg % and the above toxic manifestations have been produced in dogs by raising the level to 2.8 mg % (231). Individual susceptibility to plasma ammonia elevation apparently exists, for cases with plasma ammonia levels of 3 to 23 mg % have been reported (308). Patients having plasma levels above 3 mg % were found to have liver disease, thus indicating a probable interference with the normal conversion of ammonia into urea by the liver (308) or in the amide forming capacity of blood proteins (33). Since it has also been shown that the xanthines inhibit the formation of urea from ammonia in the liver of experimental animals, these substances should be used with caution when administering ammonium chloride until further evidence is obtained. Apparently, ornithine and glutamine overcome this inhibition (24).

Ammonium chloride has been reported as increasing the production of acetoacetic acid from pyruvic acid in the rat's liver, and accelerating the formation of beta ketonic acids from most fatty acids in well-nourished livers (125). However, the significance of this finding in clinical usage has not been established.

The finding of fat emboli in the lungs and of renal tubular epithelial necrosis (primarily distal) after administration of large doses of ammonium chloride to rabbits has been reported (177). More recently pulmonary edema has been reported as occurring in guinea pigs, rats and cats approximately 15–60 minutes after the subcutaneous, intramuscular, intravenous, intraperitoneal and enteric administration of therapeutic doses of ammonium chloride. Bilateral cervical vagotomy, atropinization and barbiturate anesthesia did not prevent the development of pulmonary edema (253). A tendency for red cells to hemolyze with the development of mild subsequent anemia may occur after ammonium chloride acidosis (190).

Ammonium chloride is not tolerated in concentration greater than 2.5% when administered orally (188), and even in lesser concentration may induce anorexia, nausea, vomiting and occasionally diarrhea.

Calcium salts, when taken in therapeutic dosage, may produce severe intestinal reactions. Thus, intense diarrhea followed by constipation with general discomfort, pains in the head, limbs and back have been reported (189). Such symptoms are not found with other acidifying agents and may be attributed to the calcium itself (189, 398).

Secondary manifestations may develop due to the administration of acidifying salts. When administered over long periods of time to subjects with impaired renal capacity to produce ammonia, these agents may reduce body buffer reserves to dangerous levels. Undoubtedly many unreported deaths have occurred from the injudicious use of these agents in the elderly patient. Acidifying agents may occasionally cause the increased mobilization of heavy metals, such as bismuth and mercury (57, 91), from bones and other storage depots with possible resultant heavy metal toxicity (504). Also, osteoporosis and osteitis fibrosa have been shown to occur in young animals after ammonium chloride (36, 233). Due to the

large amounts of calcium which may be lost during therapeutic courses of acidifying diuretics, it is readily understandable that such a state might occur in young subjects.

On the other hand, the administration of ammonium chloride may prevent the development of such symptoms as muscle cramps during courses of salt restriction and mercurial diuresis (114). Ammonium chloride has likewise been shown to protect rats completely from the nephrosclerotic changes and the cardiac lesions produced by the prolonged administration of desoxycorticosterone (414).

XANTHINE DIURETICS

The xanthine diuretics are methylated dioxypurines; the number and position of the methyl groups determine the physiological and pharmacological activity of the particular compound. Thus, caffeine is 1:3:7 trimethyl xanthine; theobromine; 3:7 dimethyl xanthine; and theophylline, 1:3 dimethyl xanthine. These substances, and in particular theobromine and theophylline, are conjugated with other compounds in order to improve their solubility and effectiveness (45). The most commonly employed conjugated xanthines are caffeine sodium benzoate, theobromine sodium salicylate (diuretin) and theophylline ethylenediamine (aminophylline). Although the several xanthines have qualitatively similar pharmacological properties, they differ quantitatively. Thus caffeine excells as a central nervous and respiratory stimulant, theobromine as a stimulant of skeletal muscle, and theophylline as a cardiac stimulant and diuretic (34, 173, 292, 298, 440). Conflicting evidence in the literature as to the diuretic effect of the group as a whole no doubt has its origin in failure to recognize these quantitative differences.

Absorption and excretion. Although the xanthines as a group are readily absorbed from the gastro-intestinal tract, parenteral administration is restricted to the more soluble conjugated compounds (45). These substances are rapidly metabolized in the body and their nitrogen for the most part is excreted as urea (173). Herbivorous animals excrete approximately 6–8% and on occasion as high as 14% of parenterally administered caffeine in an unaltered state. Elimination begins 15 to 45 minutes after subcutaneous administration and continues for 48 to 72 hours. Carnivorous animals, on the other hand, excrete approximately 1% of the xanthine unchanged; the remainder is metabolized (394).

Mechanisms of action. The mechanisms by which the xanthines exert their diuretic action are: (a) peripheral mobilization of salt and water, (b) alteration of circulatory dynamics, and (c) depression of renal tubular absorption.

A peripheral action of the xanthines is suggested by the fact that 0.48 gram of aminophylline administered intravenously to the normal subject produces an increase in plasma volume amounting to 400–1200 cc. The first rise in plasma volume coincides with the time of maximum diuresis.[2] Plasma volume then drops slightly during the period of accelerated urine flow but increases again as the

[2] This finding is of such significance in interpreting the mode of action of xanthine diuretics that it demands confirmation if it is to receive unreserved acceptance.

diuresis abates, dropping sharply approximately 6 hours later (69). The finding of increased plasma chloride immediately after the administration of aminophylline has likewise suggested an action of the xanthines on the tissues (97). To what extent these factors are causally related to the diuresis is uncertain.

Xanthines in general and theophylline and its related compounds in particular exert a direct action on the myocardium to increase cardiac output, stroke volume, and heart rate and work, and effect lowering of the filling pressure of the right heart (148, 178, 225, 430). Aminophylline, for instance, has been found to increase cardiac output approximately 12% in the normal subject (178). A further direct action on venomotor tone has been postulated recently (225). It has been considered probable that an increase in renal blood flow and a lowering of renal venous pressure in consequence of a general improvement in the circulatory state of the individual play a significant role in diuresis. Thus it was noted some years ago that kidney volume increases following the administration of xanthines and this finding was interpreted as signifying increased renal blood flow (174, 225, 345). Subsequently doubt was cast on this interpretation when Cushny pointed out that an increase in kidney volume does not necessarily mean an increase in renal blood flow (98). However, more recent studies with improved technics have shown conclusively that the xanthines accelerate renal blood flow in the experimental animal, in the normal subject and in the decompensated individual (53, 99, 104, 339, 404, 476, 486). However, it has been observed that if renal blood flow is maintained constant in the perfused kidney caffeine still increases urine flow (379). Furthermore, even though blood flow increases in the intact animal following caffeine, diuresis commences before and persists after the circulatory change (99, 403). Hence the relation of hyperemia to diuresis is not clear.

In the early part of this century, it was postulated that the diuretic action of caffeine depends on increased glomerular filtration as a result of altered vascular tone (99, 270). Richards (380) observed that only a fraction of the glomeruli of the frog are active at any one time and that the number of patent capillaries in any one glomerulus is also variable. He noted that the number of active glomeruli is increased by caffeine and postulated that the action of caffeine and its derivatives is to dilate the afferent arterioles to a greater degree than the efferent, thereby increasing effective filtration pressure (378, 380). It is evident that the xanthines are capable of increasing glomerular filtration rate in the intact animal and man by as much as 15% (104, 179). The claim has been made frequently that the diuretic action of the xanthines is dependent on this elevation of filtration rate (26, 45, 107, 115, 215 216, 218, 405, 493,). However, others employing primarily theophylline derivatives have either failed to observe any change or have noted only inconstant changes in glomerular filtration rate in experimental animals and man despite marked diuresis (34, 144, 486).

Conclusive evidence for a direct tubular action of a xanthine diuretic was first presented by Bartram (12) and by Christian and Bartram (82). These investigators injected various diuretics in small, moderate and large doses directly into one renal artery of the dog and observed the diuretic responses of the two kidneys.

Small doses of those diuretics which depress tubular absorption, *e.g.*, mercurial diuretics, increased urine flow of the injected kidney above that of the uninjected control. Moderate doses produced equal responses in the two kidneys, while large doses depressed the injected side. Theophylline sodium acetate (theocin) exerted an action similar in type to that of the mercurial diuretics but of lesser magnitude. The results with theobromine were suggestive of a similar action but were inconclusive, whereas caffeine was found to produce a diuresis of equal magnitude on both sides in all dosage. Other evidence as well suggests that the xanthines may exert a diuretic action through depression of renal tubular activity which is independent of, or in addition to, their effect on renal hemodynamics (8, 18, 104, 404, 486). Furthermore, in clearance studies on both experimental animals and human subjects, sodium chloride and water excretion has been found to increase, particularly after theophyllin in its conjugated forms, to a greater extent than can be accounted for by the increase in glomerular filtration rate (104, 179, 430, 486).

It is difficult from a review of the evidence to determine to what extent caffeine and theobromine directly depress renal tubular activity, since the resultant diuresis, being small in magnitude, is difficult of interpretation if an increase in glomerular filtration rate occurs. However, it seems well established that the theophylline compounds produce diuresis by depression of the reabsorptive capacity of the renal tubular cells in addition to the effects induced by the increase in renal blood flow and glomerular filtration rate.

Water excretion. As with other agents, the diuretic efficacy of the xanthines varies with both dosage and availability of extracellular fluid (34, 35, 456). Caffeine is the poorest diuretic of the group and is not used as such clinically (393, 456). Theobromine, theobromine sodium salicylate (diuretin) and 1-substituted theobromines have been reported as being slightly less, or only slightly more, effective than caffeine (155, 391, 410, 456). Theophylline and its conjugated forms including theophylline-ethylenediamine, theophylline methylglucamine (glucophyllin) and theophylline sodium acetate (theocin), are decidedly superior to the other xanthines (34, 173, 179, 292, 335, 361, 393, 410, 440).

In the normal subject, therapeutic doses of theophylline compounds produce a net loss of 500–1000 cc. of water over a 24-hour period (34, 155, 292). The diuresis usually begins within 30 minutes of intravenous administration and reaches a maximum in 2–3 hours (12, 82, 471). While satisfactory diuresis may often be obtained, it is generally agreed that the xanthines are much inferior to the mercurials in diuretic potency (34, 35, 155, 335, 393). Their value in augmenting the action of mercurial diuretics will be discussed elsewhere.

Electrolyte and non-electrolyte excretion. The xanthines increase the excretion of sodium, potassium, chloride and calcium but are without effect on the excretion of phosphate, sulfate and ammonia (34, 98, 155, 179). The fraction of chloride excreted exceeds that of water so that urinary concentration increases (34, 155). Furthermore, the excretion of chloride is greater in magnitude than that of sodium (34), although a twofold increase in sodium excretion after the administration of aminophylline has been reported (179). If glycosuria is present,

the excretion of sugar increases during xanthine diuresis (98). Urea excretion is increased by all xanthine diuretics, the increase being greatest with theophylline, somewhat less with caffeine and least with theobromine (361). No other change in nitrogen occurs (23, 395). Water loss in xanthine diuresis can be blocked by pitressin, but not the loss of sodium chloride (335). BAL has no effect on xanthine diuresis (131).

Dosage. The dosage for theophylline derivatives is from 0.2–0.3 gm. t.i.d. orally, or 0.24–0.48 gm. intramuscularly or intravenously (148, 264, 298, 430). The dosage for theobromine is 0.6 gm. 3–5 times a day (298, 314). However, Taylor (456) claims that theobromine in dosage of 2 gm. daily causes but little response, 3 gm. daily produce a moderate diuresis, while 5 gm. daily evoke a prompt and vigorous diuresis.

Tolerance to xanthines. It was first noted in 1910 that increased resistance to caffeine was commonly seen after repeated administration of gradually increasing doses in cats, dogs and rabbits (392). Tolerance increased 60–70% for cats, 30–33% for dogs and 15–20% for rabbits. Somewhat later Eddy and Downs (123) tested 3 normal individuals over a 2-year period for the minimum dose of caffeine, theobromine and theophylline necessary to produce diuresis in the normal subject, and after the subject had been drinking coffee for an appreciable length of time. The tolerance to caffeine, theobromine and theophylline increased significantly. Approximately 2 months of abstinence from caffeine beverages was necessary in order for the individual to lose the acquired tolerance. In view of these findings, the diuretic response of a given individual should be expected to be less in the chronic coffee or tea-consumer than in the non-habituated person.

Toxicity. Toxic manifestations resulting from the ingestion of xanthines in therapeutic dosage are limited to gastro-intestinal symptoms such as anorexia, nausea and vomiting, with occasional cramps and diarrhea (170, 298). In somewhat larger dosage, headache, palpitation or even gastric pain and hemorrhage may become evident (440). Although claims have been made that some salts are less irritating than others to the gastro-intestinal tract (148), this difference is not sufficiently significant to make any one preparation outstanding (173). The fatal oral dose of xanthine for man is unknown since no deaths have been reported. However the LD_{50} for mice with theophylline compounds is in the range of 540–600 mg./kilogram or the equivalent of 38 to 42 grams for a 70 kilogram subject (400).

A species difference in susceptibility to the ingestion of xanthine is suggested by the finding that rabbits and guinea pigs tolerate a somewhat higher dose of caffeine than do cats and dogs (393).

With parenteral administration of theophylline compounds or caffeine to mice, rabbits and dogs, the LD_{50} is in the range of 150 mg./kilogram or the equivalent of 10 grams for an adult of average weight (391, 400). Death is usually preceded by convulsions and occurs within 90 minutes of the injection, although occasionally death may be delayed for a few days (400). Although many clinicians warn of the danger of theophylline compounds administered intravenously,

only three deaths have been reported, all occurring in elderly individuals with serious cardiac disease (315). As with any medication, intravenous administration of theophylline compounds to cardiac patients carries an increased risk (470). It has been recommended and it is now common practice to inject theophylline compounds intravenously at a slow rate (315).

Therapeutic usefulness. The efficacy of the xanthines and particularly the theophylline compounds as diuretics in congestive heart failure is well established (45, 148, 179, 298). However, patients with chronic passive congestion resulting from arteriosclerotic and hypertensive heart disease respond to the xanthine diuretics more consistently and to a greater extent than do those with rheumatic heart disease (148, 298). When edema is of extracardiac origin, the diuretic response may be poor or entirely absent (45, 148).

Although the theophylline compounds are inferior as diuretics to the mercurials (173, 298, 440), they may serve as valuable adjuncts in the therapy of so-called mercury resistant subjects by raising effective filtration pressure (493) In other cases in whom the mercurials are contraindicated because of advanced renal disease, the xanthines may be of value in prolonging life.

MERCURIAL DIURETICS

Although the efficacy of mercury as a diuretic was first recorded in the 18th century, it remained for Saxl and Helig in 1920 to renew interest and to stimulate investigative work through their report on the diuresis produced by an organic mercurial compound, novasurol. Since that time the literature on the application of mercury in the treatment of edema has become voluminous. Accordingly the reviewers have confined themselves primarily to the more significant contributions and, for the most part, to those in the English literature. For an historical review of the subject, the reader is referred to the recent report by Ray and Burch (371).

Organic versus inorganic mercurial compounds. It is often assumed, without adequate evidence, that organic compounds of mercury are superior in diuretic potency to the inorganic salts (441). Actually, however, the diuretic potency of the organic compounds is much inferior to that of both the inorganic and colloidal forms when compared in terms of mercury dosage (146, 310, 441, 442). When administered in doses producing equal diuresis, the concentration of mercury in the urine is greater following the organic compounds than following the more highly ionizable inorganic salts, suggesting that the organic mercurials are not only less potent, but also that their action is dependent upon the liberation of ionic mercury (441). However, when administered in therapeutic dosage by both the intravenous and intramuscular routes, the organic compounds surpass the inorganic by producing a diuresis of somewhat greater magnitude and longer duration (441).

The virtue of organic mercurial diuretics lies in the fact that they ionize poorly (235). Weakly ionizing mercury compounds fail to precipitate tissue proteins, presumably because at the repository site a large excess of protein relative to mercury ions prevents precipitation. The absence of protein precipitation di-

minishes local irritation, favors the penetration of mercury and increases absorption. Upon entry into the general circulation, the organic mercurials are probably occluded to a lesser extent by the circulating protein, with the result that a greater amount is filtered and the urine concentration is higher.

That the organic mercurials are less toxic than the inorganic salts is generally accepted (60, 145, 238, 254, 260, 324). This is true of both acute and chronic manifestations of toxicity (238, 260, 324). However, all organic mercurial diuretics are not equally benign. Thus salyrgan and novasurol (merbaphen) conjugated with a benzene ring are organic diuretics of high toxicity. The minimum lethal dose of these compounds in cats approaches that for mercuric chloride, namely, 15 mg. mercury per kilogram. Mercurin (novurit), on the other hand, is conjugated with a cyclopentane ring and has been found to have a minimum lethal dose of 30 mg. of mercury per kilogram (324).

The toxicity of many organic mercurials has been reduced by the discovery that the acid aminophylline combines with the basic organic mercury compound to form a stable, less toxic complex (108, 216, 324). Thus salyrgan with theophylline is one-half as toxic for cats as salyrgan alone (324). On the other hand, theophylline does not alter the toxicity of mercuric chloride nor does it affect either the minimum lethal dose or the nephrotoxic action of mercurin (with theophylline-mercurpurin) (324, 385). Mercuhydrin (meralluride) is less toxic locally than other theophylline containing organic compounds (75, 243, 323) yet is of similar toxicity with reference to lethal dose.

Recently Lehman (261), proceeding on the findings of Farah and Maresh (131) that monothiols such as glutathione and cysteine hydrochloride reduce the cardiac toxicity of organic mercurials without affecting the diuretic response, replaced the aminophylline component of mercuzanthine with a sodium mercapto-acetate compound to obtain MT-6, known as thiomerin. Mercuric chloride, salyrgan-theophylline, mercuzanthine, mercuhydrin and thiomerin were compared with respect to cardiac toxicity in the cat, with the EKG as the indicator. The toxicity decreased in the order given, and thiomerin in doses up to 160 times the maximum tolerated dose of mercuhydrin produced no immediate change in EKG. Lehman attributed the improvement to a relatively greater stability of the mercaptide as compared with the theophylline complex. When observed for lethal dose over a 4-day period, however, thiomerin intravenously had the same order of toxicity as the other organic materials tested (214, 261). This would be expected if only cardiac toxicity was altered. The diuretic response to thiomerin is similar to that of mercuzanthine and mercuhydrin (170, 185).

Absorption and route of administration. The efficacy of any mercurial compound depends ultimately on its solubility and rate of absorption (457). Clinically, mercurials have been given orally, subcutaneously, intramuscularly, intravenously, intraperitoneally and in suppository form.

a. Oral. Organic mercurial compounds may be administered by the oral route with attainment of a satisfactory diuresis in a high percentage of cases (14–16, 40, 71, 117, 228). Although the therapeutic response by this route is usually inferior to that obtained after intravenous injection (14, 16, 71), ease of ad-

ministration in addition to freedom from serious toxic manifestations make it ideal for (a) patients not requiring emergency measures, (b) when edema should be removed gradually, and (c) when parenteral injection is contraindicated (5). The young individual with severe edema of recent onset would appear to be the ideal subject for oral mercury since the therapeutic response in this type of patient approaches that found after intravenous administration (71).

The efficacy of this form of treatment may be enhanced by administering the tablets several times a day rather than giving a single dose. Not only is the total diuretic response superior by the multiple dose method but the response is spread over 2–3 days, thus alleviating to some measure the dangers attendant upon the rapid removal of salt and water (14, 16). Therapeutic dosage by the oral route is significantly higher than by the parenteral routes because of poor gastro-intestinal absorption. There would appear to be little difference in absorption between enteric-coated and the more rapidly dissolving sugar-coated tablets for in each case a very significant fraction of the ingested mercury may be recovered in the feces with less than 3% being recovered from the urine (226).

When administered in total daily dosage of 150 to 640 mg. Hg in the form of salyrgan-theophylline, mercupurin or mercuhydrin, toxic manifestations are rare and not of a serious nature, being seen more commonly in the ambulant than in the hospitalized subject (16). Nausea, vomiting, diarrhea, epigastric discomfort and general weakness have been ocasionally encountered (16, 40, 66, 71, 117).

b. Intraperitoneal. Little is known about absorption or the effect of mercurial diuretics by intraperitoneal injection. That absorption occurs by this route is indicated by the report of Edwards (126) who administered mercuric chloride intraperitoneally to frogs, rats, guinea pigs and rabbits. Renal damage occurred in all. Friedenson (151), however, observed no diuresis following two intraperitoneal injections of an organic mercurial in a young edematous girl who showed a good response by other routes of administration.

c. Intrarectal. Organic mercurials may frequently be administered effectively in suppository form, although the resultant diuresis is usually of lesser magnitude than that attainable with parenteral injection (151, 216, 251). Absorption is extremely poor so that the diuresis is even more delayed and prolonged than with orally administered compounds (15). However, the therapeutic response is still adequate to relieve failure or to maintain comfort in a high percentage of patients with congestive heart disease (251). One to 7 suppositories per week, containing 195 mg. Hg per suppository in the form of mercuhydrin, may be used on retiring without evidence of local or systemic toxicity (251). Other mercurials may produce mild rectal irritation or, as with salyrgan, result in actual ulceration (112, 376). Therapeutic efficacy may be augmented moderately if an enema is given prior to insertion of the suppository (216).

d. Intramuscular. Intramuscular injection of organic mercurials is the mode of administration most commonly employed by the general practitioner. DeGraff *et al.* (109) studied the rate of absorption of intramuscular mercurials with and without theophylline by direct determination of the amount of mercury remaining

in the anterior tibialis muscle of rabbits at various intervals following injection. The rates of absorption of mercupurin without theophylline and of salyrgan were practically identical, with roughly 15% of the mercury being absorbed after 20 minutes, 62% after 8 hours and from 73–84% at the end of 24 hours. When theophylline was combined with these compounds, the rate of absorption increased markedly, such that 51% of the mercury was absorbed in 10 minutes, 67% in 20 minutes and from 91–95% at the end of the 45 minutes. That theophylline promotes a greater absorption of the organic mercurials has been confirmed by others (111, 335). It has recently been reported that the absorption of thiomerin as estimated by direct muscle analysis is the same as that for mercuzanthine and salyrgan-theophylline (261).

The mercurial diuretics with and without theophylline have also been compared as to local toxic action. Thus, mercury without theophylline caused necrotic obliteration of all vessels in the vicinity and a striking absence of defense reaction (108, 259). A definite slough occurred at the end of 24 hours. With theophylline a diffuse wheal and vasodilatation occurred without evidence of slough (108). One mole equivalent of theophylline was the limiting amount necessary to prevent the local toxic action of mercurin and salyrgan (110). This observation provided additional evidence for compound formation between theophylline and organic mercurials.

More recently, thiomerin has been compared with mercuzanthine and mercuhydrin as to their local effects after intramuscular injection in the tibilias anterior muscle of the rat. All of these mercurials produced inflammatory reaction with polymorphonuclear infiltration. However, 96 hours later no residual tissue reaction was seen with thiomerin, but with both mercuzanthine and mercuhydrin marked fibroblastic proliferation remained (455). In spite of advances made in the reduction of local irritation, local tenderness or burning sensation remained as subjective evidence of tissue irritation. Indeed, Hermann (213) notes that mersalyl with theophylline and mercurophylline are too irritating to be injected in any way except intravenously or intramuscularly with local anesthesia.

Despite the fact that intramuscular injection may cause moderate local tenderness, it eliminates serious immediate reactions (320). That absorption of theophylline containing mercurials is rapid and efficacious is evident in the finding that no substantial difference in diuretic efficacy existed between the intramuscular and intravenous routes of administration in extensive clinical trials on 92 patients with congestive failure (323). Furthermore, 0.2 cc. mercupurin given both intravenously and intramuscularly to each of 12 rabbits produced a larger response by the intramuscular route (154). Sollman in 1936 (441), in a review of the available data comparing the diuretic potencies of mercurial compounds administered by the intravenous or intramuscular routes, found it notable that the intravenous is inferior to the intramuscular route more often than superior. Systemic toxicity resulting from this route of administration will be discussed in fuller detail under the section on toxicity.

e. Intravenous. No other route of administration provides a more reliable way of administering known amounts of mercury. However, as with other agents,

this route of administration is not without danger and must be used with caution. The systemic toxic effects resulting from the mercurials given by this route are discussed in detail in the toxicity section of this review. The addition of theophylline to mercury and dilution with 5 cc. of saline lessens considerably the incidence of pain, venous thrombosis and slough formation (115, 444). It is interesting that mercupurin, salyrgan and mercuhydrin have been found to exert a definite thromboplastic effect on the blood of rabbits and cats 1–2 hours after either intramuscular or intravenous administration (283). This effect might possibly be responsible for the thrombotic action of mercurials.

f. Subcutaneous. In the past, the subcutaneous route of administration has been avoided because of pain and slough formation. Recently, however, thiomerin has been given subcutaneously to both experimental animals and to patients with congestive failure without local irritation (17, 185, 213, 214, 455). When injected subcutaneously in the abdomen of mice, thiomerin produced no gross pathological change, while mercuzanthine and mercuhydrin caused varying degrees of necrosis (455). Complete absorption from the subcutaneous site has been reported with no toxicity except for an occasional burning sensation. A satisfactory diuresis was obtained in 86.6% of 45 patients with congestive failure by this route, whereas mercuzanthine intravenously produced a satisfactory diuresis in 83.3% of the cases (17). Over 200 subcutaneous injections have been given to 40 patients with no systemic reaction. Two local reactions were seen: (a) ecchymosis in a patient with a bleeding diathesis, and (b) necrosis and sloughing of the skin when thiomerin was administered into an area of dependent edema (185). No significant difference was observed in the time or extent of diuretic response when thiomerin was given subcutaneously or intravenously to the same patient. Herrmann (213, 214) has obtained satisfactory diuresis in 135 patients treated with thiomerin subcutaneously. He has found this route of administration especially useful in patients whose heart muscle is known to be hypersensitive to mercury.

Distribution in the body. Organic mercury, when administered via the enteric or parenteral routes, ultimately enters the bloodstream, wherein it combines to some extent with albumin (85). Repeatedly crystallized serum albumin has been found to combine with $\frac{1}{2}$ mol of mercury per mol of protein (227), *i.e.*, 2 albumin molecules linked to one atom of mercury. With entry into the systemic circulation, the heavy metal is distributed throughout the body in a manner similar to that of lead (457, 504). In the presence of high blood content of mercury and during the period of active excretion of the ion, mercury is found in rather high concentration in muscles, bone, liver and kidney, but following this period the muscles and kidney show only traces of the heavy metal. The concentration in the liver decreases about one half, while the concentration in the bones remains unchanged. The degree of deposition appears to be altered by the pH of the body fluids for with increasing alkalinity there is increased deposition in bone, while with increased acidity the mercury is mobilized from the bones with a resultant increase in plasma concentration. This finding is of clinical significance in instances of prolonged administration of mercury, for if the

subject is on an alkaline diet a large amount of mercury may be deposited in the body and suddenly be released by any circumstance which lowers the pH of blood or tissues (504). Further studies have been made on the effects of acids, alkalies, potassium iodide, calcium chloride and ammonium chloride on the diffusion of inorganic and organic mercurials *in vitro*. Ammonium chloride in a 10% solution greatly increased the diffusibility of organic mercurials while potassium iodide increased the diffusion of all mercurial compounds, except mercuritetraiodide (457). What relation these observations may have to the potentiation of the diuretic action of mercury clinically is uncertain to the reviewers.

Excretion of mercury. Parenterally administered mercury is eliminated from the body primarily by the kidneys, to a lesser extent by the bowel, and in negligible quantities by the salivary and sweat glands (173, 272, 440). The fecal excretion of mercury ordinarily amounts to but $\frac{1}{6}$ to $\frac{1}{3}$ of the urinary excretion (272). While small amounts of the heavy metal probably enter the alimentary tract from swallowed saliva and from the excretion of mercury through the intestinal mucosa, the major fraction is excreted into the gut through the biliary tract (440). The fecal excretion of mercury, at least by rabbits, may be increased some ten-fold by the administration of ammonium chloride (504). Poor intestinal absorption accounts for the larger amounts of mercury excreted per rectum after oral administration (226).

The renal excretion of mercury is dependent upon the plasma concentration of the metal (440). In consequence, the rate of elimination and the completeness of excretion are in turn dependent on the route of administration, *i.e.*, with intravenous injections a relatively high concentration of mercury is rapidly attained in the plasma and urine, with lesser amounts being occluded by the tissue proteins. Inasmuch as mercury and its compounds become bound to plasma proteins which are non-filtrable substances, the excretion of the metal is also related to the dissociation constants of the protein complexes. Inorganic mercurial complexes, having higher dissociation constants, are more rapidly excreted than are the organic compounds (441). The addition of theophylline to organic mercurial compounds probably increases the rate of excretion in two ways: (a) it increases the rate of absorption and therefore increases the plasma concentration of mercury; (b) it increases the ionization of the resultant compound and therefore increases its filtrability. The rate of renal excretion of all mercurials is further increased by ingestion of acidifying salts and is decreased by alkalizing agents and particularly by calcium salts (504).

In view of the many factors upon which the excretion of mercury is dependent, it is not surprising that conflicting reports are to be found in the literature as to the completeness of excretion of therapeutic doses of mercurials. Thus, estimates range from 60 to 100% excretion of a single therapeutic dose in 24 hours (87, 171, 250, 256, 440). In all probability, some mercury is retained for long periods of time within the body regardless of dose or route of administration (504). Little valid basis for choice, as to rate of excretion, is to be found between the several preparations, thiomerin, salyrgan-theophylline, mercuzanthine and mercuhydrin (261).

Site and mode of action. A precise definition of the site or sites of action of mercurial diuretics is impossible at the present time. While the weight of presently acceptable evidence strongly favors a direct action of these agents on the kidney, a pre-diuretic effect on the tissues has not been conclusively ruled out. Thus, many investigators in the middle twenties reported that plasma volume increases following the administration of mercurial diuretics prior to the onset of diuresis or even in its absence (25, 69, 94, 415). However, more recent studies have failed to confirm this finding (61, 406). To what extent divergence of view may be related to methodological inadequacies in the early studies is uncertain; but if serious consideration is to be accorded to the concept of peripheral action of mercury in mobilizing tissue fluid, additional evidence must be forthcoming. The fact that mercurial diuretics are ineffective in the presence of low plasma chloride (129, 130), does not constitute evidence in favor of peripheral action, despite claims to this effect.

Govaerts in 1928 provided the first evidence in favor of a direct renal action of mercurial diuretics by transplanting the kidney of a mercurialized dog into the neck of a normal recipient. A continuing diuresis was observed in the transplanted mercurialized kidney; but when the process was reversed and a normal kidney was transplanted into a mercurialized dog, no diuresis resulted (176). Somewhat later, Bartram (12) and Christian and Bartram (82) injected a small dose of a mercurial diuretic directly into one renal artery of an anesthetized dog and produced diuresis on the injected side but not on the opposite side. With slightly larger doses, a diuresis occured on both sides, while with still larger doses urine flow of the injected kidney was depressed and that of the opposite side was increased. The latter observation probably accounts for the failure of Melville and Stehle (310) to obtain a diuresis upon injection of mercuric chloride directly into the renal artery of the dog (*i.e.*, overdosage effect).

Further evidence that mercurials act directly upon the kidney is found in investigations on plasma volume changes during diuresis. Plasma volume, as determined either directly (107, 281, 282) or indirectly by plasma protein and specific gravity determinations (61, 69, 406), has been found to decrease after mercurial diuretics, the degree of diminution depending upon the drug dosage and the availability of interstitial fluid (406). As the rate of mercurial diuresis diminishes, the plasma volume is partially restored (69).

Any direct renal action of a diuretic must be mediated through one or another of these discrete mechanisms: (a) increased filtration rate, (b) increased tubular secretion, or (c) decreased tubular reabsorption. There is no evidence for the second of these possibilities at the present time. With respect to the effect of mercurial diuretics on glomerular filtration rate, numerous investigations have failed to show any significant increase in the rate of filtrate formation in the experimental animal (102, 119, 405, 486), in the normal subject (34, 58, 340, 356), or in the edematous subject (132) during mercurial diuresis. In the normal animal or subject, a fall in filtration rate and renal plasma flow is not infrequently seen immediately following intravenous injection (10, 119, 356). This effect is undoubtedly due to a toxic cardiovascular action of the drug and can be abolished

by the addition of mono- or dithiols (131). It is evident that mercurial diuretics must partially and reversibly block the reabsorption of water and electrolytes by the renal tubules (12, 34, 58, 61, 94, 119, 132, 216, 218, 314, 335, 356, 405, 494). The extent of this blockage will be discussed under water and electrolyte excretion.

When an attempt is made to localize the site of tubular reabsorptive depression within the renal tubule, great difficulty is encountered for any approach to this problem at the present time must of necessity be indirect and based on assumptions.

One line of approach has been the study of pathological lesions in the renal tubules following the administration of inorganic or organic mercurial compounds. While many workers have described the lesions only in general terms as involving the convoluted tubules, some have attempted a more precise localization with respect to distribution within proximal or distal segments (126, 127, 212, 238, 286, 429, 499). When minimal renal necrotizing doses of mercury are administered to the experimental animal, the proximal tubule alone shows evidence of pathologic change (126, 127, 212, 429, 499). With subnecrotizing dosage, increased deposition of fat is apparent in these tubules (429). The usual interpretation of these findings by the pathologist is well expressed as follows: "The conclusion would seem to be justified, therefore, that an extremely small dose, incapable of producing visible injury, would induce disturbances of function that would be limited even more closely to that part of the tubule in which the particular poison in larger doses produces its characteristic necrosis" (429).

However, if the dose of mercury is increased beyond a minimal necrotizing range, the distal convoluted tubules and the ascending limb of Henle exhibit changes similar to those observed in the proximal tubule. If the animal survives a large dose for a sufficient period of time, all segments under discussion exhibit complete necrosis (238). This is in accord with general autopsy findings in mercury poisoning (44, 65, 249, 254, 259, 286, 287, 399, 439, 445). It would appear that, while the proximal segment may be involved to a greater extent than the remainder of the nephron, all segments may bind sufficient mercury to interfere with vital cellular functions. Until we obtain a fuller understanding of the enzyme systems involved in reabsorptive transport, the susceptibility of these systems to mercury, and the interrelationship of enzyme transport systems to cell viability systems, we can only speculate that mercury may affect the functional capacity of any cell that it is capable of destroying, namely, the proximal and distal tubule and a portion of the loop of Henle.

Apart from the pathologic anatomical approach, additional evidence for the site of mercury action has accrued from physiological studies of altered renal function. Walker *et al.* (484, 485) have demonstrated by micro-puncture of the renal tubules that glucose is reabsorbed in the first half of the proximal segment in the necturus, frog, guinea pig and rat. It has been found that the maximum tubular reabsorptive capacity for glucose (glucose Tm) is reduced some 40–80% by organic mercurials both in the human subject and in the dog (185, 494). This reduction in glucose Tm coincides with maximal electrolyte and water

diuresis and, as diuresis diminishes, TmG returns towards normal (185). The fact that no pathological change can be found in the initial segments of the proximal tubule with mercurial diuretics (127, 429) might explain the failure of the above workers to block glucose reabsorption completely. With larger doses of mercurials, glucosuria at normal blood glucose levels may be produced in the dog (212, 428). While these observations clearly indicate an interference of mercury with at least one proximal tubular function, namely, glucose absorption, they do not prove that the resulting diuresis of water and salt is necessarily a consequence of depressed proximal function.

The secretion of PAH and diodrast are other functions generally attributed to the proximal tubule (58). However, a species difference with respect either to the anatomical site of secretion or to the nature of the cellular enzyme transport systems vitiates arguments based on the action of mercury on secretion of these substances. Thus it has been recently demonstrated that the mercurial diuretics depress Tm PAH and TmD in man (22, 58) but not in the dog (22). The mercurials are, of course, equally effective as diuretics in the two species.

Functions of the nephron that are attributed to the distal tubule are (a) the secretion of ammonia and titratable acid (375, 482), (b) the active reabsorption of water to produce a hypertonic urine (435), (c) the active reabsorption of sodium and chloride to produce a hypotonic urine (310), and (d) possibly the secretion of potassium (21). Following the administration of therapeutic doses of mercury, no significant change can be detected in the output of ammonia or titratable acid (184, 471). However, with doses sufficiently large to produce distal tubular necrosis, a decrease in ammonia output to the extent of 58–89% of the normal has been observed (449).

Functional evidence as to the site of action of mercurial diuretics in blocking the reabsorption of water, chloride and sodium is entirely indirect and largely inferential. Thus Mudge *et al.* (329) claim that mercurial diuretics block sodium and water reabsorption in the proximal tubule, a view based entirely on their assumption that in osmotic diuresis distal tubular reabsorption is negligible. The opposite view, *i.e.*, that mercurials block distal absorption of water and sodium, has been expressed by Duggan and Pitts (119) on equally presumptive evidence. They assume that a large dose of a diuretic can completely block absorption in that segment on which it acts, and that the proximal segment is responsible for two thirds or more of total renal absorptive capacity for water and sodium. Their finding that large doses of mercurial diuretics block about 20 per cent of absorptive capacity inclined them to the view that they act on the distal segment. It is, however, possible to interpret their evidence in favor of proximal action if it can be shown that two or more discrete absorptive mechanisms reside in this segment, only one of which is mercury sensitive. Farnsworth (132) claims that the mercurials block the reabsorption of water in the proximal tubule and the reabsorption of chloride in the distal tubule, a view completely unsupported by the data presented.

Perhaps it is most reasonable to admit that the site of blockage of ionic absorption is unknown at present. Furthermore it is even undetermined whether

the active transport of sodium or of chloride or of both ions is blocked by mercurial diuretics.

Little work has been done on the effects of mercurial diuretics on water excretion *per se*. Indeed it is not well established that there is any direct effect and the possibility exists that the increased water output is secondary to electrolyte excretion.[3]

The secretion of potassium has been shown to be blocked by mercurials (21, 327). However, the site of potassium secretion, while speculatively placed in the distal tubule (21), is not well established at this time.

In *summary*, it would appear that mercury in large doses is capable of entering and damaging cells of both the proximal and distal segments. In therapeutic doses it diminishes glucose Tm, reduces the secretion of PAH and diodrast in man but not in the dog, partially blocks the secretion and absorption of potassium, is without effect on the excretion of ammonia and titratable acid, and partially blocks the reabsorption of salt and water. Except for the probable proximal locus of action on glucose absorption, the sites at which mercury exerts the above mentioned effects are at present uncertain.

Mode of entry into renal tubule cells. Little is known as to whether mercury is filtered by the glomerulus and subsequently reabsorbed by the tubular cells or whether it enters the cells directly from the blood stream in the course of secretion. The latter concept has been postulated by Brun *et al.* on the basis that (a) mersalyl is excreted rapidly during the 1st hour after intravenous injection, as are substances known to be secreted by the tubules, and (b) that mersalyl is an organic cyclic acid similar in character to substances known to be secreted by the tubules (58). However, it would seem as though gomerular filtration alone could account for all of the mercury excreted without the need for invoking a secretory process. Also, all diuretic mercurial compounds do not depend upon the cyclic structure for their activity.

The interesting observation has been made that a hydronephrosis of five days duration protects the rabbit kidney against the nephrotoxic effect of mercury bichloride; this suggests that glomerular filtration is the excretory mechanism. Reinecke *et al.* (375), however, claim that ureteral ligation does not interfere with glomerular filtration in rats for they observed that the establishment of hydronephrosis did not prevent the inhibition of renal gluconeogenesis which follows the administration of mercury. The accuracy of these observations is somewhat questionable since their data in a subsequent paper (374) would seem to indicate no significant inhibition of gluconeogenesis by the heavy metal. Furthermore, if mercury penetrates the cell from the blood stream directly, their findings would have no bearing on the question of glomerular filtration in hydronephrosis. At best, little is currently known of the effects produced by hydronephrosis on renal blood flow, renal secretory processes, and even on glomerular filtration itself. The means by which the renal tubular cells are protected from

[3] Recent unpublished work of Wesson and Anslow and of Capps, Axelrod and Pitts indicates clearly that mercurial diuretics do not block the "facultative" absorption of water, *i.e.*, that moiety absorbed under the aegis of posterior pituitary antidiuretic hormone.

damage by mercury by hypoproteinemia (223), by hemoglobinuria (199), and by testosterone (413) are equally speculative.

Action within the cell. It has been shown that salts of mercury enter the tissue cells at a rapid rate, yet inhibit susceptible enzyme systems slowly (169). The evidence suggests that the salts are adsorbed by some substance in the vicinity of the enzyme system or by the enzyme itself, and that the enzyme is subsequently inactivated by ionized mercury. The resultant chemical bond is stable. The rate of enzyme inactivation is proportional to the concentration of enzyme still active, and also to the amount of mercury adsorbed (241). Since the organic mercurials are even more poorly ionized than the mercury salts, it is probable that these compounds exhibit a similar sequence of cellular reaction.

Within the cell, mercury combines with sulfhydryl enzyme systems (10, 11, 192, 209, 274, 431, 488) Sulfhydryl enzymes are hydrolytic and oxidative in nature and are intimately linked with carbohydrate, fat and protein metabolism (11). The affinity of the sulfhydryl enzymes for —SH reagents varies from protein to protein, depending among other factors on the position of the reactive group in the molecule and the degree of dissociation of the reactant (11, 228). Approximately 90% inhibition of sulfhydryl enzymes is produced by mercury in a concentration of 10^{-5} molar (10).

Since the degree of enzyme inhibition is determined by the quantity of inhibitor per unit volume of cell substance (192, 241, 274), it is not surprising to find the greatest degree of enzyme inhibition in renal cells within which mercury is specifically concentrated. Thus, the succinic dehydrogenase activity of the rat kidney may be inhibited 20–50% by the intravenous administration of nonlethal doses of mercurial diuretics while no inhibition is found in the liver and heart. However, when mercury in concentration of 5×10^{-6} to 10^{-5} is added to homogenates of heart, liver and kidney, a comparable inhibition is found in all (192). Enzyme systems within the heart may be inhibited by mercury *in vivo* with similar concentrations of the heavy metal (274).

Restoration of enzyme activity *in vitro*, in the intact animal, and in the human may be accomplished with mono- or dithiols (10, 22, 121, 131, 167, 209, 273–276, 327, 407, 431, 452, 488). Physiologically, it appears probable that glutathione is of major importance in maintaining sulfhydryl enzymes at optimum activity (431). The almost universal presence of this tripeptide as an intracellular constituent plus the demonstration of enzyme activity restoration on addition of glutathione makes plausible this concept (274, 431). While glutathione and cysteine hydrochloride are as effective as the dithiols (BAL) in their cardiac protective action in the heart-lung preparation, they are only $\frac{1}{5}$ to $\frac{1}{8}$ as potent in the intact dog (274). This observation may possibly be attributed to differences in distribution or rate of destruction of the monothiols in the intact animal. It has likewise been shown experimentally that glutathione in a concentration 20 times that of BAL, and cysteine hydrochloride in a concentration 50 times that of BAL, do not counteract mercurial diuresis, while BAL is completely inhibitory when administered in the proportion of $\frac{1}{2}$ mole per mole of mersalyl (131, 193), The failure of the monothiol to restore enzymatic activity in the renal tubular cell may be related to the high concentration of mercury

within the cell (10) or possibly to cellular enzyme differences. Whatever the explanation of the above observations, it is significant that effective mercurial diuresis can now be obtained with a marked reduction in cardiac toxicity through the expedient of incorporating a sulfhydryl group into the organic mercurial complex (see section on organic versus inorganic mercurials-thiomerin).

That BAL not only inhibits a mercurial diuresis but also prevents the nephrotoxic action of mercury has been adequately demonstrated (100, 121, 167, 193, 276, 452, 488). BAL, 2,3-dimercaptopropanol, may be administered subcutaneously or intramuscularly. It is adsorbed rapidly into the circulation reaching a maximum concentration in 1 hour and maintaining that level for approximately 2 hours. A single dose is largely excreted in 6 to 24 hours (344). While toxic reactions may be prevented by BAL or BAL glucoside if these compounds are administered sufficiently early, it is evident that BAL cannot restore viability to a necrotic cell. Thus, with the administration of mercury in nephrotoxic dosage to rabbits, BAL protects 90% of the animals when administered 5 minutes later, 20% thirty minutes later and none after one hour has elapsed (167). In the case of dogs, BAL protects but 57% of the animals if administered one hour after the mercury, with practically no protection 3 hours later (167). The importance of early treatment in acute mercurial poisoning in the human has been adequately discussed by Longcope and Leutscher (276). Since BAL itself is an enzyme inhibitor (488), it is not surprising that the drug may produce toxic manifestations such as nausea, vomiting, chills, paresthesias and elevation of blood pressure (452).

Physiological response to therapeutic doses

a. *Plasma composition.* Changes in plasma composition following mercurial diuretics are in large part if not entirely secondary to the diuretic response. Due to the more rapid loss of fluid in the urine than to replacement from the interstitial reservoir, colloid osmotic pressure and specific gravity of the plasma increase (61, 107, 116, 281). This change is of lesser magnitude in edematous than in normal subjects, due to their larger reservoir of interstitial fluid (116). Chloride is usually lost in excess of fluid so that plasma chloride decreases in spite of hemoconcentration. In normal subjects the decrease in plasma chloride may be slight (34), but it has been found to be significant in normal dogs if the urinary excretion is marked (155). In patients with congestive failure, mercurials usually produce a fall in plasma chloride and a corresponding increase in bicarbonate. Following the diuresis, electrolyte concentrations return to normal (35). Blood sodium and calcium usually show little change in either normal subjects or patients with congestive heart failure (34, 216, 250).

Venous pressure usually falls with mercurial diuresis (281, 477), and the greater the diuresis the greater is the fall in pressure. This finding may be of special significance in patients with congestive failure in view of the recent observation that an elevation of venous pressure increases the renal tubular absorption of sodium and water independent of any change in renal plasma flow and glomerular filtration rate (32).

b. *Electrolyte excretion.* It is well established that mercurial diuretics increase

the excretion of chloride both in the normal and edematous subject and experimental animal (34, 35, 94, 132, 145, 155, 170, 171, 216, 250, 360, 388). Sodium excretion is also increased (465) but not to the same extent as chloride (35, 216). Chloride and sodium excretion follow the same general curve as water excretion, but are of slightly greater relative magnitude (94). Reaser (372), using radioactive tracer Na^{22}, found with 1 cc. of mercuhydrin intramuscularly in a patient with congestive heart failure that the increased sodium excretion preceded water excretion. This observation would appear to indicate that mercurial diuretics act primarily on electrolyte reabsorption, and secondarily on water. Potassium excretion is increased by mercurial compounds if the initial excretion is low; but, if the initial excretion is elevated to active secretory values, the action of these drugs is to depress excretion (21, 327). It thus appears that mercurial diuretics depress all renal cellular processes, whether they are secretory or reabsorptive in nature. The excretion of calcium is increased by mercurials to a moderate degree (34, 388), no doubt in consequence of diminished tubular absorption. No significant change occurs in phosphate or sulfate excretion (8, 37), or in the excretion of ammonia, titratable acid and total nitrogen (34, 94, 388).

c. *Excretion of non-electrolytes.* Effects of mercurials on the excretion of urea appear to be variable. Thus no change (94, 155, 340) or a depression (361) of urea excretion has been observed in experimental animals. On the other hand, increased urea excretion has been reported in both cardiac patients and in patients with ascites from hepatic disease (218, 388). Mercurials in toxic dosage may produce glycosuria (212), while in therapeutic dosage the tubular reabsorptive capacity is diminished (reduction in glucose Tm) (185, 494).

d. *Water excretion.* The diuretic response to mercurials is dependent on (a) the route of administration and the completeness of absorption, (b) the dose of mercury administered, (c) the amount of interstitial fluid available for exretion, and (d) the adequacy of renal function. Thus, the amount of excess fluid excreted may vary from zero to the extreme of Ramsden's case in which a 15-year old rheumatic boy with generalized massive edema responded to a 1 cc. intramuscular dose of neptal with a 24-hour diuresis of 14,220 cc. (365). However, as a general rule, for an equivalent amount of mercury administered by the same route, we can expect the diuresis to be greatest in those patients with the most edema (35, 40, 98, 115, 320). The experimental animal reacts in a similar manner (61, 130, 448). Occasionally, the effectiveness of mercurials may diminish after prolonged use, as a result of the depletion of ions necessary to maintain ionic equilibria (115).

Not only does diuresis vary with ionic and fluid availability, but also with the state of acid base balance. Thus, Ethridge (129) has shown the diuretic response of mercurials to be enhanced by the administration of acidifying salts, to be unaltered by neutral salts, and to be reduced by alkalizing salts with an elevation in carbon dioxide-combining power (335). This effect may be due to the greater dissociation of mercury in an acid urine, thus increasing absorption by the renal tubules (335); but further investigative work is needed to clarify the means by which disturbed acid base equilibrium alters the efficacy of mercurials.

In normal subjects an average loss of 2.5% of the body weight, or approximately 1730 cc., results from 2 cc. of mercupurin intravenously (281). Similar figures have been found for both the normal individual and the patient with congestive heart failure (151, 323, 356).

Modell *et al.* (322) determined the diuretic response of 69 ambulatory cardiacs in a state of advanced heart failure to increasing dosage of intravenous mercurials. A dosage response curve was constructed with the data from 773 injections. The curve was sigmoid in character with the steepest portion occurring in the range from 0.5 to 1.5 cc. representing weight losses from 2–4.35 lbs. The authors felt that quantitative comparisons of these diuretics can best be made in this range. Salyrgan diuresis may be inhibited by pitressin (22, 145, 155) or by the intramuscular administration of BAL (121, 452).

e. *Time relationships.* The time of onset and the duration of diuresis vary with the route of administration; the onset is delayed and the duration is longer with the oral and rectal routes, and both are shortest with parenteral injection. With 1 cc. of mercuhydrin intramuscularly, diuresis becomes evident in less than 2 hours, reaches a maximum in 4–6 hours and lasts for almost 24 hour (372). Most workers agree that, with parenteral injection, diuresis usually commences within 3 hours, reaches a maximum in 6–9 hours and is usually complete in 12–24 hours (94, 115, 314). In young individuals the diuresis is usually complete in 12 hours, whereas in elderly and weak individuals the diuretic response may last for 24–48 hours (415). However, after oral dosage, the diuresis may last for 48–72 hours (14, 16). In normal dogs, the intravenous administration of mercury usually initiates a diuresis in ½ hour which reaches a peak in the second hour and is complete in approximately 6 hours (130, 356).

f. *Source of fluid excreted.* Blumgart *et al.* (34, 35) have estimated from careful balance studies on both normal subjects and on patients in congestive heart failure that during mercurial diuresis roughly 90% of the fluid excreted is of extracellular origin and only 10% is of intracellular origin. During rapid salyrgan diuresis, the fluid eliminated is largely at the expense of circulating plasma for the first several hours (69).

Potentiation of action of mercurial diuretics. It is now well established that the administration of an acidifying agent prior to a mercurial diuretic potentiates its action (115, 129, 155, 216, 282, 444). Formerly, this potentiation was believed to be additive rather than synergistic (250). However, in 1936 Ethridge tested normal dogs under controlled conditions of nutrition and electrolyte balance with respect to their diuretic response to ammonium chloride alone, to mercury alone, and to a combination of the two. The response to the two drugs given in combination was found to be greater than the sum of the responses to each separately (129). Similar findings have been reported for the normal subject (282) and the edematous individual (115, 444).

Apparent potentiation of a mercurial diuretic by urea has been reported (106). However, since the study was restricted to but one subject, substantiation appears desirable.

As has been mentioned previously, the combination of theophylline with mercurial diuretics augments the effect of mercury (115, 213, 216–218, 385, 389).

This has been found to be true for all mercurial compounds except mercuric chloride and mercurin (385). The addition of theophylline to mercury probably enhances absorption of the heavy metal, decreases its occlusion by the tissue and circulating proteins, and increases the rate of filtration and excretion of mercury (213, 216–218). Careful studies are needed to determine the extent of the augmentation of activity of mercurial compounds by the xanthine.

Other substances such as ascorbic acid and sodium dehydrocholate augment mercurial diuresis to some degree (76, 77, 321, 335).

Dosage. Although Blumgart (34) in 1930 reported that doubling the dose of salyrgan and merbaphen from 1 cc. to 2 cc. approximately doubled the duration of diuresis and trebled its magnitude, subsequent observers have been more impressed by the efficacy of multiple small doses. Thus, ambulatory edematous cardiac patients were found to lose a greater amount of weight with 1 cc. of an organic mercurial diuretic twice a week than with 2 cc. once a week. Furthermore, multiple small doses maintained the patient's weight curve at a more constant level than did less frequent larger doses (320). In another study, an average weight loss of 4.05 lbs. was found after 1 cc. of either mercupurin or mercuhydrin intravenously, while with 2 cc. the weight loss increased to only 4.3 lbs. With intramuscular injection, the difference between 1 and 2 cc. was similarly small, averaging 3.5 as against 4.15 lbs. (32). When graded doses of mercurial diuretics were administered to 69 cardiac patients in a state of advanced heart failure, the dose response curve was sigmoid in character with the steepest part occurring in a range from 0.5 to 1.5 cc. Maximal responses were obtained with doses of 2.25 cc. (322). The authors felt that the greatest clinical effects per unit weight of drug could be expected from doses lying within the range of 0.5 to 1.5 cc.

Kwit *et al.* (256) have recommended the intramuscular injection of 1 or 2 cc. of mercuhydrin daily in the treatment of congestive heart failure. When this mode of therapy was combined with a low salt diet, 2 quarts of water daily and digitoxin, they found that 90% of their cases of congestive heart failure subsided completely in 6 days with a mortality of 9%. Other authors recommend doses from 0.5 to 2 cc., repeated either every 3 days or twice a week (243, 264, 314, 444). The initial dose and test dose should be 0.5 cc. (264, 444). The use of 2 cc. for the first injection has been condemned especially in elderly patients (390). Not infrequently 0.75 cc. is sufficient to produce the desired effect without symptoms of dehydration or toxicity (390). The dosage of mercurials used, as with digitalis, should be varied to fit the individual case. Dosage of mercurials should perhaps be based on the weight of the patient rather than on accepting 1 or 2 cc. as a standard dose. Deaths have been reported after the administration of 1 or 2 cc. to children (243), a dose which, when calculated on a mg./kilogram basis, is the equivalent of 6–8 cc. for the average adult.

Toxicity. The toxicity of organic mercurials may be conveniently considered under three major headings: (a) the toxic action of mercury itself, (b) hypersensitivity of the subject to the specific mercurial diuretic administered, and (c) secondary manifestations due to excessive loss of salt and water.

ics is the presence of severe kidney damage (16, 114, 314, 467). Merrill (314) feels that benign hypertension and albuminuria *per se* are not contraindications to the use of mercurials unless there are signs of malignant hypertension or if the NPN exceeds 100 mg. %. Patients with cardiac disease secondary to severe anemia or pulmonary disease may be made worse by any procedure of dehydration (443). The mercurials are also contraindicated in patients in which the drugs have previously produced toxic effects (71).

CONCLUSIONS

In the edematous patient the quantities of salt and water absorbed by the renal tubules are excessive relative to those delivered into the tubules in the glomerular filtrate. In consequence, fluid and electrolyte are retained and diverted peripherally to expand the interstitial reservoirs of the body. The major action of the 5 classes of diuretics discussed above is depression of the renal tubular absorption of salt and water. Use of these agents to reverse the abnormal processes which lead to the accumulation of edema therefore constitutes rational therapy.

All diuretics must be employed with care in patients with severely reduced renal function, and especially in those with absolute renal insufficiency, because the capacity of the diseased kidney to compensate for the insult of injudicious therapy is reduced. They must not be used at all in the presence of anuria, since each, if accumulated in the body in excess, is toxic. This applies no less to large quantities of water which may produce fatal dilution than to more obviously toxic substances such as potassium and mercury which may cause cardiac arrest or tissue damage.

Despite the necessity for caution, diuretics should be used early for the relief of edema, not as a last resort when massive accumulation of fluid itself jeopardizes life. Treatment should be individualized, not administered by rule of thumb. In each instance one should employ the most benign drug capable of causing the desired fluid loss, in the minimum effective dose and at such intervals as are necessary to avoid marked fluctuations in weight.

There is reason to believe that more effective and safer diuretic agents may be developed in the future. This optimism is based on two facts. First, the most effective agents available at present, namely, the organic mercurial compounds, when administered in maximal and just sublethal doses block the reabsorption of only 20 per cent of the salt and water normally returned from the glomerular filtrate to the blood stream. If more were known of the chemical and physical processes involved in tubular transport, the remaining 80 per cent might be made vulnerable to therapeutic attack. Not that one would dare block reabsorption completely, but an agent which could accomplish this end would be a highly effective diuretic when administered in small quantities. Second, no less than four factors are now recognized as being causally related to overabsorption of water and salt by the renal tubules, namely, reduced glomerular filtration rate, elevated renal venous pressure, and excessive stimulation by adrenal cortical and posterior pituitary antidiuretic hormones. It is possible that effective means

mal subjects produce evidence of dehydration. In addition to weakness and apathy, many subjects exhibit dizziness and faintness suggestive of a diminution in cardiac output (281). The results of salt depletion have been recently reviewed by McCance (301), Schroeder (407) and Soloff (443).

Reduction in toxicity. The local toxic actions of organic mercurials may be decreased by using theophylline-containing compounds (108, 110, 113, 115). Intramuscularly, mercuhydrin and thiomerin appear to be the least toxic (75, 213, 243, 260, 261), while intravenously, thiomerin appears to be the least cardiotoxic (260, 261). DeGraff (113) has reported a lower intravenous lethal dose in cats with slower injection and with greater time intervals between repeated injections. This has not been confirmed by Modell (324) who found no consistent or significant difference in the lethal dose for unanesthetized cats by varying the rate of injection. There is no evidence that dilution of the drug is helpful (495). Other agents commonly employed in conjunction with the mercurials, such as digitalis and ammonium chloride, have no effect on the toxicity of the heavy metal (495). The toxicity of mercuhydrin intravenously may be halved by the simultaneous administration of ascorbic acid (76). Ascorbic acid has no effect, however, on the toxicity of mercupurin or salyrgan with theophylline (77).

Symptoms referable to dehyration may be alleviated by the oral administration of water and sodium chloride; the latter may be given either in capsular form or as a 1% solution. Parenteral administration is recommended if the oral route is not feasible (360).

Therapeutic usefulness. Mercurial diuretics have been found to be particularly effective in patients with congestive heart failure after full digitalization (171, 201, 264). Age, sex, blood pressure, duration of disease process, the degree of cardiac enlargement and the cardiac rhythm are apparently unimportant in predicting the efficacy of a diuretic (171, 359). Patients with hypertensive heart disease seem particularly suitable for a good diuretic response (444). A good response may usually be obtained in previously unresponsive cardiac patients following the administration of aminophylline (493). The daily weight should guide the therapy, and the patient should be given mercurials regularly rather than waiting for the massive accumulation of edema fluid (170). In subjects on daily or near daily maintenance doses, evening administration of the mercurial has been recommended in order to obtain augmentation of effect by bed rest (186). The enhancement of the action of mercurial diuretics by the administration of ammonium chloride or the xanthines has been previously discussed.

Mercurial diuretics have been employed successfully in ascites due to hepatic disease. Rowntree *et al.* (388) obtained an effective diuresis in 19 of 20 patients. In many cases ascites recurred but was readily controlled. Other investigators have obtained similar results (27, 171, 201). Patients with nephrotic edema have responded more regularly to ammonium chloride and salyrgan or to urea than to other diuretics (201). However, in the presence of serious cardiac, renal or hepatic injury, the usual progressive course of the disease is not altered by the relief of edema (27). DeTakats (453) emphasizes the benefit to be derived from the use of mercurial diuretics for the management of acute thrombophlebitic edema.

Contraindications. The foremost contraindication to the use of mercurial diuret-

While the above reports serve to indicate that renal damage may occur after the chronic use of the mercurial diuretics, other evidence indicates that damage need not necessarily occur after prolonged use of these compounds. Thus, only one case of mercurialism was found at autopsy in patients receiving more than 3000 injections (454). No evidence of renal damage was found in a 24-year old girl who had received 627 injections or the equivalent of 1250 cc. of salyrgan or mercupurin over a 12-year period (151). Another case of a patient receiving 343 injections of salyrgan and mercupurin over a 7½-year period without any deleterious effect has been reported (136). No significant renal change, as indicated by blood NPN values and examination of the urine for specific gravity, albumin, casts and cells, was found in 92 patients with congestive heart failure receiving 1–2 cc. injections of mercuhydrin or mercupurin intramuscularly or intravenously (323). However, of 216 cases of edema of different etiology treated with various diuretics, but primarily mercury, an increased blood urea developed in 41%, and in a great number of patients a decreased PSP excretion was found (27).

(b) *Sensitivity to mercurials.* Non-fatal and fatal toxic reactions due to an apparent anaphylactoid response to mercurial diuretics have been reported (114, 149, 170, 220). These reactions are usually delayed and may occur 1–2 hours following administration. Asthmatic attacks and even the development of pulmonary edema have been described (495). Other manifestations of idiosyncrasy include dyspnea, substernal pain, cyanosis and collapse, which in many respects resemble the acute fatal reactions described above (71). Non-fatal toxicity may take the form of flushed skin, erythema morbilliformis, pruritis, urticaria, chills, fever and exfoliative dermatitis (114, 170, 220). These latter symptoms are not in themselves serious, but serve as warning signals of more serious reactions if mercury is continued (71, 114). Changing the route of administration is usually of no help (114), but on occasion altering the mercurial used may ameliorate minor sensitivities (149, 243).

(c) *Dehydration.* Following either an unusually large diuretic response or repeated losses of salt and water, weakness, lassitude, anorexia, nausea, vomiting, restlessness, thirst unrelieved by water, apathy, mental confusion, fall in blood pressure, increase in pulse rate with diminution in the volume of the pulse, clammy skin, shock and coma may develop (60, 114, 170, 314, 320, 359, 360, 443). Four fatal cases occurring in cardiac patients subjected to a regimen of salt restriction and salt diuresis have been reported recently (443). In digitalized cardiac patients, the picture may be further complicated by symptoms and signs referable to resultant digitalis toxicity (16, 60, 114).

Russek (390) has reported 3 deaths occurring in elderly patients as a result of cerebral thrombosis with hemiplegia apparently precipitated by mercurial injections. In all cases the complication followed a profound diuresis and fall in blood pressure, with symptoms as described above. Signs of dehydration usually become evident in 6–12 hours after injection and are more commonly observed in elderly patients (390).

Dehydration is a possible etiological factor in the producton of temporary renal insufficiency. Increases in blood urea concentration have been reported as occurring in 41% of 216 cases of edema (27). Mercurials administered to nor-

(a) *Toxic action of mercury.* Local reactions due to parenteral injection have been discussed under the heading of absorption and route of administration. That sudden death may result from the intravenous injection of an organic mercurial is well recognized (56, 114, 218, 236, 243, 359). Most of these fatalities have occurred in 1–3 minutes following the injection. Typically, the patient gasps, shows cyanosis and pallor, dyspnea, orthopnea and irregular respirations, and may complain of substernal distress. Irregularity of the heart rhythm may develop which is shortly followed by convulsions and finally by coma and death. Death is usually due to ventricular fibrillation (114, 243, 495).

The majority of deaths have occurred following use of salyrgan or mercupurin (243), probably because of their more widespread clinical use, possibly because of their somewhat greater toxicity. The vast majority of patients succumbing have shown premonitory signs and symptoms of toxicity to mercurials after previous injections (71). Recently a new compound, thiomerin, has been shown to be 1/20 as toxic as other mercurials tested within the first ½ hour after injection (261); indeed, this drug was found to produce no immediate changes in the EKG of cats in doses up to 160 times the maximum tolerated dose of mercuhydrin, a substance of lower cardiac toxicity than salyrgan-theophylline or mercuzanthine (261). As mentioned previously, theophylline has been found to lower cardiac toxicity of many organic mercurials (324).

Other manifestations of mercurialism include gastro-intestinal disturbances, stomatitis, salivation, colitis, occasionally of a hemorrhagic nature, and renal damage (16, 60, 170, 281). Gastro-intestinal manifestations occur most frequently after the oral route of administration (16, 40, 66).

More significant and more common are the renal lesions produced by the repeated administration of mercurial diuretics. Despite the widespread view that these agents produce no renal damage, a number of cases have been reported in which patients receiving therapeutic doses of organic mercurials have developed oliguria, anuria and edema followed by death. These cases have shown at autopsy varying degrees of proximal tubular degeneration with areas of complete necrosis (60, 72, 426, 480). In one of these cases, mercury was recovered from the kidney in a concentration of 3–5 mg. of mercury per 100 gm. of tissue (60). In other autopsies on patients who were known to have received organic mercury therapeutically, similar tubular necrosis has been reported (218, 445).

When mercury is administered to animals in dosage corresponding to the therapeutic level for the human subject, little or no evidence of toxicity may be found or the animal may succumb in several weeks time, depending upon the species of animal used, the dosage employed and the frequency of repetition of the dose (95, 126, 127, 212, 237, 238, 286, 287, 311, 399, 429, 445) Rabbits are probably the most sensitive to mercury of the commonly employed experimental animals. It appears significant that early renal damage may be evidenced by intermittent albuminuria or a rise in the cast count, these changes being reversible if the drug is discontinued (55, 249). Of equal interest is the observation that the previous administration of a sub-lethal dose of mercury increases the lethal dose for that animal (95).

might be found to raise filtration rate, reduce venous pressure, and inhibit either the secretion or the renal target action of the above mentioned hormones. Such therapy would constitute a truly physiological means of combating edema.

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