REVIEW ARTICLE

DIURETICS AND DIURESIS

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THIS article presents a review of the subject which is frankly and intentionally selective and mainly interpretative; no attempt has been made to cover completely the literature belonging to the subject. A very good review has been published recently by Pitts and Sartorius[1] and the subject has been fairly well covered in a new book by Wolf[2].

DEFINITIONS

There are two ways of defining a diuretic. It can be defined as a drug (or agent) which produces an increased flow of urine: in that case water is the diuretic *par excellence*; or it can be defined as a drug (or agent) capable of removing excess of water from the body (e.g., œdema): in this case, it would be better to restrict the term "diuretic" to those agents which induce a loss of body fluid by increasing the urinary excretion. The term "diuresis" is usually qualified "water diuresis," "salt diuresis," "mercurial diuresis," etc., in which cases reference is made to the specific diuretic agent or drug used irrespective of whether there is a decrease of the volume of body fluid or not.

MEASUREMENT OF A DIURETIC EFFECT

Smith[3] has given certain rules which should be fulfilled every time that a diuretic effect is claimed: the increase of urine flow should be consistent and reproducible, and should be compared with moderate rather than with very low levels of urine excretion; it should be comparable at least with the urine flow observed after the administration of a moderate dose of water and persist for at least 30 minutes. Urine collections of either a few minutes or 24 hours duration are considered to have little meaning.

While these criteria serve well in general, they have been criticised by Wolf[2] on the ground that "it may not be wise to reject the possibility of establishing significant (statistically or otherwise) duration of diuresis which does not conform to arbitrary minimal and maximal periods of urine collection."

Schlosser[4] tested the effect of a combination of some diuretics. Using rabbits, he determined the smallest dose of a given substance which was appreciably diuretic and called it the "minimal diuretic quantity" or D; he then found the minimal diuretic activity of another diuretic D′. On the assumption that 0·5 D + 0·5 D′ would have the same effect as either D or D′ alone, he determined the degree of synergism or antagonism by estimating how the sum D + D′ differed from 1. Potentiation is

evident when the sum of D and D′ is less than 1; there is antagonism when the sum of the coefficient D and D′ is greater than 1.

Lipschitz, Hadidian and Kerpcsar[5] have introduced a method of bioassay of diuretics: they determine the diuretic activity as the diuretic potency of a substance as referred to that of urea. The activity of urea is considered as a standard diuretic and its diuretic activity is taken as equal to 1. Lipschitz *et al.*[5] found that for many substances assayed over a fairly large range of doses the diuretic effects measured in a test group of rats, when compared with those in a control group given saline solution, yield a linear relationship between log dose (mM./kg of body weight) and log effect or response. Plotting the dose effect curve of the substance under investigation and that of urea, it is possible to determine the logarithm of the diuretic activity of that substance[5].

Classification of Diuretics

The classification of diuretics is an arbitrary and empirical device. Some authors divide them into "osmotic," "acid-forming salts," "xanthine," "mercurial," etc. The real defect of such classification is that there are too many exceptions which defeat the object of clarity[6]. For example, there are alkalinising salts, such as potassium salts[7,8,9] which are often quite as effective as acid-forming salts. As for the xanthine derivatives, drugs like melamine, adenine or formoguanamine, which are only remotely related to purines are still very diuretic. (Lipschitz and Stokey[10].) And clearly, heavy metals such as platinum or silver[11], bismuth[12], or cobalt[13], which all have diuretic effects cannot be classified with mercurial derivatives. Finally, under which heading should sodium cyanate (Schütz[14], Dicker[15]) or urethane or colchicine (Dicker[16]) be found?

Water Diuresis

Urine flow begins to increase within 20 to 30 minutes after the ingestion of water; it reaches a peak at about 90 minutes and returns to normal in about 2 to 3 hours (Priestley[17], Baldes and Smirk[18]). This is a commonplace observation. It raises, however, a series of questions: Does the kidney excrete the water that has just been ingested? Why is there a time lag between the ingestion of water and the onset of the diuresis? What stimuli are responsible for the increase of urine flow and its return to normal?

The kidneys do not excrete all the water that has been drunk; they deal with it very slowly: Hevesy and Hofer[19] have shown from observations on the disappearance of ingested heavy water that a water molecule spends an average time of 13 days in the body. In other words, when a water diuresis follows the ingestion of water, it is not *that* water which is excreted; the ingested water replaces tissue water which is excreted. Why this time lag? In the dog, water is absorbed from the gut at the rate of 0·028 ml./cm. length /min. Since the length of the gut of a dog averages 25 cm./kg., a 10 kg. animal absorbs 250 ml. of water in about 25 minutes[20]. In a normal rat or guinea-pig water administered

by a stomach tube is completely absorbed in less than 75 minutes (Heller and Smirk[21]). Water absorption is however significantly slower in the rabbit (Heller and Smirk[21]). In man 1 litre of water is absorbed in 40 to 50 minutes[22]. It would seem that water does not suffer any appreciable delay in passing the pyloric sphincter and is readily absorbed from the gut: the rate of water absorption cannot explain the time lag for the onset of the diuresis. Even when water is administered by mouth, by rectum, by vein (in this case, in the form of an isotonic solution) or otherwise parenterally, the water diuresis will always be characterised by this peculiar time relation. However this latent period can be shortened by increasing the water load: for instance, by administering several doses of water to a rat (5 ml./100 g. of body weight) at hourly intervals, the time lag is reduced to a minimum (Adolph[23], Priestley[17], Liling and Gaunt[24]). An amusing application of this is the famous Sioux alarm clock, described by Jaeger[25]. According to this author a Sioux warrior wanting to be awakened early to go on the war trail drinks a lot of water before going to bed : the earlier he wants to wake, the more water he drinks. However, once absorbed, water is distributed rapidly throughout the body: deuterium oxide administered orally is equilibrated with total body water in about 50 to 60 minutes[26]; if injected intravenously the equilibration is achieved in less than 10 minutes[27].

As water absorption proceeds at a faster rate than urine excretion, dilution of both colloids and crystalloids of the body fluid will occur[28,29,30,31,32,33]. Could the dilution of body fluids be the stimulus to the diuresis? The curve of urine flow lags some 15 to 20 minutes behind that of tissue water load (= absorbed but non-excreted water[18,20,30]). This indicates clearly that dilution *per se* is not the immediate cause of diuresis. That plasma dilution is not a causative factor in water diuresis can be shown by administering saline solution instead of water; the ingestion of saline solution causes a greater dilution of protein than does the ingestion of water for it is retained largely within the extra-cellular fluid phase; yet it is accompanied by a diuresis which is significantly lower than that obtained with water[18,28,31]. Govaerts[34] has tried in vain to correlate plasma dilution and water diuresis; all his and other investigators' attempts have failed to demonstrate a relation of causality between plasma dilution and diuresis. If such a relation exists, how is it that the diuresis of animals suffering from protein deficiency is so low? (Dicker[35]). Why do these animals develop œdema at all?

Though it is beyond the scope of this review to give all the relevant evidence for it, it would seem that the excretion of water is regulated, directly or indirectly, by an antidiuretic principle of the posterior pituitary gland. To quote from the classical paper of Klisiecki, Pickford, Rothschild and Verney[20] "The excretion 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 favour

of this hypothesis has been accumulating at a steady rate and has been reviewed in detail elsewhere[35,36,37,38,39].

According to Verney[38,39], there are osmoreceptors located intracranially within the zone of distribution of the internal carotid artery which are sensitive to changes in osmotic pressure of the arterial blood of the order of magnitude of 1 to 2 per cent. Impulses from these osmoreceptors are transmitted to the posterior lobe of the pituitary gland *via* the supraoptico-hypophyseal tracts and stimulate the liberation of antidiuretic principle[37]. A decrease of the osmotic pressure of the body fluids such as would result from ingestion of water would cause the osmoreceptors to inhibit the impulses to the posterior lobe and thus reduce the liberation of antidiuretic hormone. Following a latent period of 15 to 20 minutes during which the circulating antidiuretic factor is progressively destroyed (Heller and Urban[40]; Jones[41]), urine flow increases, and reaches a maximum flow at 60 to 90 minutes, at which time the concentration of the antidiuretic hormone should theoretically be minimal. This post-pituitary hypothesis is unquestionably elegant when applied to the phenomenon of water diuresis, and explains all its peculiarities. There are however three irritating criticisms: (1) It has not yet been shown that corresponding gradations in circulating antidiuretic hormone actually occur in the normal animal, despite the fact that graded antidiuresis may be produced in dogs with diabetes insipidus by regulating the administration of vasopressin[42]. (2) It has not yet been explained why a water diuresis falls off at all so long as there is an appreciable water load in the body (Wolf[2]). (3) While the initial, small diuretic effects of loads of isotonic saline fit in nicely with the lack of osmotic stimulation expected from such solutions, the ultimate polyuria which follows prolonged, steady intakes of such solutions cannot easily be accounted for by the theory (Wolf[2]).

However, in spite of these criticisms there is little doubt that the so-called pituitary hypothesis is the best so far known and explains most of the phenomena logically. It remains now to examine how the kidney functions are affected by these changes in the concentration of antidiuretic substances, how the kidneys react and how they adapt their work to the prevailing condition of the body fluids.

A normal man excretes about 1,440 ml. of urine a day; i.e., 1 ml. per minute. Its average glomerular filtration rate amounts, however, to 130 ml. per minute, i.e., 187 l. a day. The highest rate of urine flow encountered in man, either during maximal water diuresis or in cases of complete diabetes insipidus amounts to 13 and 20 ml. per minute (i.e. 1·8 to 2·8 l. a day) representing between 10 and 15 per cent. of the glomerular filtration. Within this narrow range of 10 to 15 per cent. residual water available for urine formation, variations of urine flow appear to be controlled entirely by variations in the rate of water reabsorption by the tubules. This led Smith to distinguish between the "obligatory" and the "facultative" reabsorption of water. In 1937 Smith[3] assumed that the "obligatory" reabsorption of water, accounting for some 80 per cent. of the glomerular filtrate, occurred in the proximal

tubule and was accompanied by the reabsorption of electrolytes, glucose, etc.; the facultative reabsorption by which the actual variations in urine flow are effected occurs in the distal tubule. This simplified mechanism based on an almost unchanged filtration rate has been questioned lately. Glomerular filtration has been shown to vary after heavy hydration or after a meal only: the administration of hypotonic saline solution increases the glomerular filtration rate of rats (Dicker[43]); the excessive water load increases the filtration rate of dogs (Shannon[42]) and of rats (Dicker[44]) and rabbits (Dicker and Heller[45,46]). Ayer, Schiess and Pitts[47] have shown that in dogs fed on a meat diet the rate of glomerular filtration increased by nearly 100 per cent. when compared with dogs fed on a carbohydrate diet. A similar finding was made in rats (Dicker[48]). So far little variation of filtration rate has been observed in human beings, though Smith[49] now says that " it can and does vary under conditions not yet defined." The fact of this variability immediately raises questions concerning glomerular-tubular balances, which may involve the concept of limitation of the reabsorptive capacity of the tubules. This conception needs some explanation, as a lot of theories pertaining to water and electrolyte excretion—and hence to the mechanism of diuretics—may have to be revised.

It has been shown that systems involving tubular transport seem in general to be limited by marginal rates (Wesson, Anslow and Smith[50]). Whether these liminal phenomena result from limitations in available energy or limitations in the enzymatic transfer system has not been investigated yet. Distal tubular water reabsorption, unlike proximal reabsorption (Walker, Bott, Oliver and McDowell[51]), appears to be an active process comparable with other active tubular transport systems (Wesson, Anslow and Smith[50]). If this assumption is accepted it might be anticipated that the absolute quantity of water reabsorbed per unit time would also have some upper limiting value. Wesson, Anslow and Smith[50] suggest that this supposed maximal rate of reabsorption be called $T^d mH_2O$, using Tm in the general sense of a limiting value in any tubular transport system and T^d to indicate specific reference to the distal tubule. T^dmH_2O will, of course, be reached only if the distal load of water is equal to or exceeds the maximal reabsorptive capacity for water, and only if the reabsorptive process is maximally activated by the antidiuretic factor. At partial states of activation of antidiuretic hormone distal water reabsorption (T^dH_2O) would be less than T^dmH_2O and in the absence of it, it might decrease to zero[50].

Since T^dH_2O can vary from zero to T^dmH_2O it is clear that if the filtration is constant, water equilibrium will be maintained by variations in the secretion of antidiuretic factor. The question whether changes in glomerular filtration could be of such a magnitude as to drown the tubular reabsorptive capacity for water still needs to be investigated. However, even small changes in the filtration rate will be of importance, especially if it is borne in mind that urine is not water alone, but contains besides urea, appreciable amounts of sodium and chloride. It can therefore be assumed that there is a maximal rate of sodium reabsorption by the distal tubules (T^dmNa): T^dmNa would only be reached if the

load of sodium in the distal tubules were equal to or exceeded its maximal reabsorptive capacity for Na.

So long as the fraction of filtered sodium reabsorbed by the proximal portion of the tubule remains approximately constant, the load of sodium delivered to the distal tubule will increase or decrease with the filtration rate. At some critical filtration rate this load will be exactly equal to T^dmNa and the subject will be exactly in sodium equilibrium. If the filtration rate is increased the distal load will be increased and come to exceed T^dm Na; this will lead to the excretion of the excess of sodium. Should sodium be excreted more rapidly than water, the sodium content of plasma would decrease and the resultant fall in the osmotic pressure would, through the supraoptico-hypophyseal system, produce an increased excretion of water until the critical osmotic pressure of the plasma was restored. The opposite would occur if the filtration rate was reduced. Thus, and this is the important conclusion to remember, at a given plasma concentration of sodium there will be one, and only one, filtration rate at which the subject will remain exactly in sodium, and hence in water, equilibrium. (Wesson, Anslow, Smith[50].)

The real interest of this conception which, it is admitted, has not been entirely demonstrated experimentally, is that only very small changes in filtration rate need be involved to produce marked effects. For instance, in a man with a plasma sodium concentration of 138 mM per litre and a filtration rate of 130 ml. per minute, a decrease or increase of filtration rate of only 6 ml. per minute would lead to the retention or the excretion of 15 g. of sodium per day. Variations of this order are scarcely beyond the experimental error of our present methods of investigation. It follows that in a normal animal or human being the composition and the volume of the extracellular fluid is regulated by a system in which the renal mechanism for controlling the excretion of sodium, the supraoptico-hypophyseal mechanism for controlling water excretion and the glomerular apparatus controlling the filtration rate are coupled and integrated. It is with this modern system of integrated controls in mind that the action of diuretics must be investigated.

Mercurial Diuretics

Mercurial diuretics were known already in the 16th century. Mercurous chloride was used as a diuretic by Paracelsus. It was also an ingredient of the famous " Guy's Hospital pill " (calomel, squill and digitalis).

All soluble mercury compounds are diuretic[52,53], a property which is in no way related to their individual toxicity. Chemical structure appears to play a role in the diuretic activity, and most important, the presence of ionisable mercury in the compound; Sollman and Schreiber[54,55] found that the concentration of mercury in the urine is very much greater for the organic than for the ionisable derivatives, and showed that it may require 1500 times more organic mercury than ionisable mercury to produce the same diuretic effect.

Mercurial diuretics are, according to Wolf[2], drugs leading " to an

absolute dehydration of the body." They have also a marked chloruretic effect. As a rule they are active in normal[56] and sometimes even in dehydrated dogs[57], in normal human subjects[58] and in those with œdema[59]. Mercurial derivatives have also a diuretic effect when injected in hydrated rats[43]. The chloruresis is usually roughly proportional to the quantity of mercurial given, within range of small doses. In dehydrated dogs there is frequently a marked chloruresis without any diuretic effect. Mercurial diuresis in man usually begins in the first half hour after intravenous injection and becomes maximal in the second hour (see Wolf[2]). In normal human beings the diuretic effect lasts as long as that of the mercury excretion. In people suffering from œdema the diuresis is prolonged and lasts often for more than 24 hours[60] : this lasting effect has been attributed to the sol-called " mobilisation " of œdema fluid.

In spite of scores of papers published on the subject, little is actually known about how mercurial diuretics act. A critical analysis will, however, reveal two fundamentally different viewpoints. There are those who believe that the diuretic effect is primarily extrarenal : they believe that Hg produces a dilution of the blood (Jendrassik[61,62], Saxl and Heilig[63,64]) : hydræmia following administration of diuretics has been found repeatedly in normal and nephrectomised dogs[65], in rabbits[66] and in human subjects[67,68]. An indirect argument supporting this view is the prolonged diuresis observed after administration of mercurials to œdematous patients. The whole hypothesis of the extrarenal action of mercurials is based on the assumption that blood dilution is *the* stimulus for diuresis, which in itself cannot be accepted without damaging reservations (Wolf[2]).

A second type of evidence for extrarenal diuretic action is that of Tezner[69], who found that in children subcutaneous injections of potassium iodide are more rapidly absorbed after administration of merbaphen. Edlund and Linderholm[70] found an increased absorption of hæmoglobin and water from the knee joints of rabbits treated with mersalyl. The main criticism of these experiments is that it is not clear what significance these effects have for diuresis.

Evidence for a direct renal action of mercurials is given by Govaerts[71], Bryan, Evans, Fulton and Stead[72], Gremels[73] and many others (Bartram[74], Walker *et al.*[75]; Blumgart *et al.*[76]). Govaerts[70] took a kidney from a dog at the height of merbaphen diuresis and transplanted it in the neck of a normal dog. The transplanted kidney continued to exhibit a diuresis, whereas the control kidneys of the host excreted urine at a lower rate. When a normal kidney was transplanted into the neck of a mercurialised dog, it failed to show any diuresis while the host's kidneys were secreting at an enhanced rate. Another proof of direct renal action was given by Bartram[74], who showed that when a small dose of mercurial diuretic is injected slowly straight into the renal artery of one kidney, that kidney responds with a diuresis while the opposite kidney continues to form urine at its normal rate. These experiments are, however, difficult to understand as it has been shown repeatedly that there is a significant delay after the injection of mercurial derivatives before the

diuresis starts. In rats, the diuretic effect was obtained about 10 hours after the intramuscular injection of the mercurial compound (Dicker[43], Lipschitz *et al.*[5]).

Finally a middle course is held by Möller[77] and Engel and Epstein[78], who believe that the evidence supports both renal and extrarenal action. Engel and Epstein[78] believe that mercury affects the osmotic pressure in tissues, and consequently that the changes effected by mercury with respect to tissues in general include changes in the renal tissue itself.

How do mercurial derivatives act and produce a diuresis? Again, in spite of an enormous amount of literature on the subject, little is known with certainty. It is admitted that mercurial compounds hinder the tubular reabsorption of water, sodium and chloride[3]. An indirect confirmation of this is given by the fact that certain thiols[79,80,81], like 2:3-dimercaptopropanol (dimercaprol, BAL) thioglycollic acid or glutathione, prevent their diuretic effect. The T^dm of man[82,83] and of rats[43] is depressed by mersalyl. Dimercaprol reverses this effect in man. It has also been alleged that mercurial diuretics may increase the excretion of potassium to such an extent that its clearance exceeds that of creatinine[84]; this would suggest that potassium can actually be secreted by the tubules. This, however, does not seem to be a specific reaction to a mercurial compound: potassium can be secreted during the peak of a water diuresis[85]. Walker *et al.*[51] have shown that the diuretic effect is obtained without any change in blood flow or in the glomerular filtration rate. There is, however, evidence that mercury compounds increase the glomerular filtration rate in rats, so that their action seems to be a double one, increasing glomerular filtration and diminishing reabsorption[43].

Duggan and Pitts[86] were able to show that the site of action of mercurial diuretics was limited to the distal tubules. They used trained unanæsthetised dogs, and showed first that the unprepared dog was not suitable: the loss of excessive quantities of sodium and water in the urine so compromises circulatory function that the animal could not maintain a stable renal hæmodynamic state; this led to such a fall in the glomerular filtration rate that the diuretic effect was foreshortened and often absent. Further, the sole intravenous injection of mercurials in the range of dosage necessary to produce diuretic effects produced an immediate depression of the glomerular filtration rate well before there could be any suggestion that the sodium excretion was approaching a ceiling. In a prepared unanæsthetised dog (which had been infused for more than 2 hours with 0·85 per cent. saline solution, to avoid a fall in glomerular filtration rate) they found that the depression of renal tubular reabsorption of sodium which could be produced by a mercurial compound was limited: once the ceiling was reached any further increase of mercury did not result in a further increase of sodium excretion. It is interesting to note that the magnitude of the reabsorptive system corresponded quantitatively to the magnitude of distal tubular reabsorp-

tion as estimated by other methods, i.e., 13 per cent. of the filtered sodium. This supports the assumption put forward by Wesson, Anslow and Smith[50] that in the dog 87 per cent. of the filtered sodium is reabsorbed actively by the proximal tubule. The same authors[87] showed also that, as stated above (see discussion about T^dmNa), a moderate reduction in the glomerular filtration rate restricted the capacity of the kidneys to eliminate water and electrolytes; in other words, a reduction in the glomerular filtration resulted in relative over reabsorption of salt and water by the proximal portion of the tubule. If the filtration rate was significantly below normal, reabsorption in the proximal segment was so complete that practically no sodium reached the distal tubule: thence even after complete blockage of absorption at that end by a mercurial diuretic there was no significant increase of the amount of sodium excreted (Pitts and Duggan[87]). This finding provides a rational explanation for the observation of Weston and Escher[88] that those patients who are clinically resistant to mercurial diuretics have exceptionally low filtration rates; a satisfactory diuresis will, however, occur if the filtration rate can be increased.

A curious feature about mercurials is that their action can be potentiated by other drugs. The most common synergism is that between ammonium chloride and mercurial diuretics (Keith, Barrier and Whelan[59]). A similar synergism exists between mercurials and acidifying salts, ammonium nitrate and ammonium chloride[89,90,91,92,93].

The nature of these synergisms is not well understood. It has been said that when the plasma chloride concentration is low, mercurials do not have a marked diuretic effect[94]. This is indirectly borne out by Pitts's experiments[86,87]. It may be that when ammonium chloride is given, the ammonia is converted into urea, leaving the chloride ion to form hydrochloric acid. Since the kidneys cannot eliminate the acid without some sodium with which it is combined, they respond as they do to primary sodium deficiency by sacrificing some water in the interest of the electrolyte osmotic pressure of the body fluids (Peters[95]).

It is not possible to enumerate all the synergetic actions which have been reported in the medical and scientific literature. The reader will find a remarkable list of them in Wolf's book[2]. More work on the lines of Pitts and Duggan's[86,87] investigations may clarify the problem and would show very likely that most of the synergism can, after all, be explained by simple changes in the glomerular filtration accompanied by corresponding changes in the tubular functions. For instance, it has been reported that sodium chloride potentiates mercurial diuresis; this is not surprising now that it has been shown that the administration of saline solution increases the rate of glomerular filtration (Ladd and Raisz[96]; Duggan and Pitts[86]), and avoids the fall of filtration rate which follows the intravenous administration of mercurials. Ascorbic acid has been shown to have a protective action and so has magnesium sulphate[97,98]. Little is known as to their protective mechanism.

There is an interesting antagonism between posterior pituitary extracts and mercurials: the antidiuretic vasopressor fraction, vasopressin, inhibits the increased urinary output produced by mercury, but does not affect the increased chloride excretion (Earle and Berliner[79], Fulton *et al.*[99]). This finding supports those of Chalmers, Lewis and Pawan[100] on man and of Dicker and Heller[101] and of Heller and Stephenson[102] on rats: these authors have shown that in these two species vasopressin has no action on the urinary output of chloride; it affected the water reabsorption only. The antagonism between vasopressin and mercurials does not suggest that the diuretic effect of the mercurials is the result of an osmotic effect. In contrast with vasopressin, the administration of the oxytocic factor enhances the chloruretic effect of mercurials: this may be the result of an increased glomerular filtration rate (Dicker and Heller[101]) or a cumulative effect of oxytocin and mercury on the rate of chloride reabsorption by the tubules.

Recent studies on the antagonism between mercury and dimercaprol provided some indication as to the mode of action of mercury. Hatta[103] had shown a long time ago that mercuric chloride inhibited many proteolytic enzymes but that inhibition could be reversed by substances, such as potassium sulphide, which precipitate the mercury radicals. Fildes[104] in 1940 showed that sulphydryl compounds such as glutathione and cystine also antagonised the bactericidal effects of mercuric chloride. It is beyond the scope of this review to trace back all the work on this subject: the general conclusion is that mercury, as organometallic compounds in general, deprives cells of their essential sulphydryl-containing metabolites (Fildes[104]). This would explain why dimercaprol counteracts the effects of mercurial diuretics. During their investigation on the antagonism between dimercaprol and mercurial diuretics, Earle and Berliner[79] showed that not only did dimercaprol prevent or interrupt the diuresis and chloruresis resulting from the intravenous injection of mercupurin, but inhibited a normal water diuresis. The authors suggest that the dimercaprol inhibits the chloruretic effect of mercupurin by combining with the mercury; the inhibition of the water diuresis, however, they explain by a stimulation of the secretion of the antidiuretic hormone of the posterior pituitary gland.

Xanthine Diuretics

The diuretic effects of xanthine derivatives were first established by von Schroeder[105], who studied caffeine, theobromine and related substances. The action of caffeine is complicated by its circulatory and central nervous system effects, but like many other diuretics, xanthine derivatives appear to act primarily by hindering the tubular water reabsorption.

The diuretic action of xanthine derivatives is almost proportional to the degree of hydration. When administered in dogs in water-balance they decrease the daily urine output (Wallace and Pellini[106]); the same thing was observed when injecting daily some theophylline sodium acetate

into rats which were in water-balance (Dicker[107]). Rabbits on a dry diet show no caffeine diuresis[108]. The same was observed in rats: the injection of the theophylline sodium acetate exerted a marked diuretic effect in well hydrated rats only (Dicker[43]). As a rule the diuretic action of xanthine derivatives appears where there is excessive water in the body; there are, however, more specific differences: rabbit, rat and man[108] seem to be more responsive to caffeine than dogs or frogs. Human therapeutic doses act, however, on the isolated dogs' kidney (Verney and Winton[109]). Cats, in general, do not respond well to diuretics. Comparing the diuretic activities from the dose-action curves and from human therapeutic doses, Lipschitz, Hadidian and Kerpcsar[5] found that in the rat, theobromine, theophylline sodium acetate and caffeine were 7·2, 11·5 and 30 times more active than urea. In man, however, taking the diuretic activity of urea as 1, they found that the diuretic activity of theobromine, theophilline sodium acetate and caffeine were 150, 480 and 625, respectively.

The main characteristics of the diuresis following administration of xanthine compounds have been summarised by Cushny[108]. The diuresis is accompanied by an augmented excretion of the solids of the urine, though this increase is less than that of water[105]. This results in a fall of the specific gravity of the urine and of its molecular concentration. The chloride excretion is markedly increased. If the rabbit has been fed on a diet rich in salts and has accordingly been passing urine relatively concentrated in chloride, there will be a decrease of the urinary concentration of chloride during the action of caffeine, while if the diet has been deficient in chloride, and hence the urine has been poor in its chloride concentration, there will be an increase in the chloride concentration during diuresis[110]. An extreme example of this is given by Grünwald (see Cushny[108]) who fed rabbits on maize until the chloride disappeared from the urine altogether: chloride, however, reappeared during theobromine diuresis. The change in the proportion of water and chloride during the xanthine diuresis thus depends on the condition of the urine previously; however, in every case under conditions of a xanthine diuresis the urine approaches the serum in respect of its chloride concentration (Cushny[108]). If the chloride of the blood has been replaced by bromide the excretion of bromide after administration of caffeine is exactly analogous to that of chloride[108,110]. Xanthine derivatives have also an action on other urinary solids; there is an increase of sodium and to a lesser extent of potassium urinary concentration. Urea excretion increases, though its concentration falls. When glycosuria is present, the amount of sugar excreted rises during the diuresis. In birds, caffeine induces a diuresis during which the urinary concentration of uric acid decreases significantly; its total excretion is, however, not much altered (see Cushny[108]). It is interesting to note that in a heart-lung-kidney preparation, caffeine diuresis produces just the same change in the urinary concentration of urea and chloride as that of an equal "pressure" diuresis (Winton[111]).

A critical analysis of these changes suggests that the glomerular filtration is mainly affected. The main factor leading to an increased glome-

rular filtration could be either a constriction of the efferent glomerular vessels, an increase of the renal blood flow, or an increase in the number of functional nephrons. Schroeder[105] in 1888 already suspected that some of the effects following administration of caffeine were due to changes in the blood circulation. An intravenous injection of caffeine is sometimes followed by a rise in the blood pressure; the rise in blood pressure was ascribed to stimulation of the vaso-constrictor centre (Cushny[108]). Phillip and Bradford[112], in oncometer experiments, found that the renal volume fell at first from a direct action on the walls of the renal vessels; this was followed, however, by a marked rise in the renal volume accompanied by a rapid urine flow. These findings were confirmed by other investigations (see Cushny[108]), and have been regarded as evidence that the renal vessels are dilated during caffeine diuresis. However, Cushny[108] pointed out that the oncometer record cannot be taken as an exact indication of the state of the vessels or of the supply of blood to the kidneys during diuresis. He based his criticism on the following points: the volume of the kidney does not depend on the calibre of the blood vessels only, but also on that of the renal tubules and on the amount of lymph; during a diuresis the tubules are much wider than during a less active secretion, and therefore a part of the increased renal volume must be ascribed to the dilated tubules. How large a share of the increased volume should be referred to each of these is, of course, unknown (Cushny[108]). For this and other reasons Cushny summarised the action of xanthines on the diuresis by stating that "all indications point to the direct action of the purines on the renal cells, and not on the vessels, and diuresis might arise either from lessened absorption in the tubules, as was suggested by Sobieransky, or by increased permeability through the capsule in which the resistance to filtration is reduced. This would increase the amount of the filtrate without changing the relative proportions of its constituents, but these, of course, would undergo some elaboration in their passage along the tubules. No such alteration in the capsule has hitherto been shown to occur, but the hypothesis is frequently made to explain phenomena observed in other cells, and a change in the rate of filtration through a membrane is stated to occur in chemical manipulations" (Cushny). It is interesting to record Cushny's views and to compare them with more modern opinions. Using clearance methods Chasis, Ranges, Goldring and Smith[113] arrived at the following conclusion: the xanthine derivatives have a complex effect upon the renal circulation, (1) there is a delayed reduction in renal blood flow which appears to be a result of the action of the drug upon the glomerular arterioles, mediated perhaps through increased sympathetic tone; (2) there is a slow but progressive increase in filtration rate as a result of dilatation of the afferent glomerular arterioles. In well hydrated rats, the administration of theophylline sodium acetate increases both the renal plasma flow (as estimated by the diodone clearance) and the glomerular filtration rate. There is also an increase of the filtration fraction (Dicker[48]). These effects are much the same as those observed by Verney and Winton[109] in the heart-lung-

kidney preparation. In a more recent study on man Smith[113] found that the administration of caffeine resulted in a decrease of the diodrast clearance, thus of the renal plasma flow, while the filtration rate consistently increased. Neither caffeine in man (Smith[114]) nor theophylline sodium acetate in rats (Dicker[43]) had an effect on the tubular transfer (Tm_d), indicating that neither of these xanthine derivatives disturbed the tubular function. According to these later findings, it would thus seem that the diuretic effect of xanthine compounds is the result more of the increased rate of filtration than that of a decrease of the tubular rate of water reabsorption.

An interesting observation was that of Salant and Rieger[115], who found that an increased resistance to caffeine can be seen after repeated administration of gradually increasing doses in cats, dogs and rabbits. The same kind of observation was made on man, by Eddy and Downs[116]. In view of these findings, the diuretic response of a given individual should vary according to whether he is a coffee drinker.

A word must be said about the so-called xanthinoid compounds: they are drugs containing the group N-C-N several times in their molecule. They are melamine, adenine and formoguanamine (Lipschitz and Stokey[10]). Given to the rat, they proved to be both diuretic and chloruretic. Their diuretic effect is not antagonised by vasopressin. Is it not possible that sodium cyanate, NaCNO (Birch and Schütz[117]; Dicker[15]) should be included under the same heading of xanthinoids? It is diuretic and chloruretic when injected into non-hydrated rats; its diuretic effect is not antagonised by vasopressin (Dicker[15]). Cyanate produces all the "caffeine effects" studied by Keilin[118,119], i.e., dispersion and solution of a number of hæmoglobin derivatives, reinforcement and shift of absorption bands, prevention of spontaneous aggregation and precipitation. Further both caffeine and cyanate stabilise proteins against heat and increase the ultrafiltration rate of buffered, diluted protein solutions (Schütz[120]). It would be extremely interesting to see whether the other xanthinoids studied by Lipschitz and Stokey[10] produce the same "caffeine effect" as cyanate. If so it would form a sound basis for a new classification of various diuretics. The fact that urea, biuret and the xanthines contain the same group N-C-N at least once in their molecule and are all diuretics suggests the possibility that urea may exert some specific renal action. The formation of cyanate from urea under physiological conditions has been discussed by Schütz[117]. Lipschitz[12] tested about 50 substances from that point of view and arrived at the following conclusions: (1) acid amides are diuretics, but weaker ones than urea. (2) α-oxy-acid amides are more active diuretics than the corresponding acid amides. (3) Urea and simple urea derivatives are about equally active. (4) Substances of the aliphatic type containing more than one N-C-N group are more active than urea. (5) The puryl and amidine groups are very diuretic. (6) Among the cyclic compounds containing the N-C-N group once or several times, there are substances which surpass by far the xanthine diuretics in activity and harmlessness.

Such findings are certainly very promising and may form a physico-chemical basis for a classification of diuretics much more useful than those proposed so far.

Osmotic Diuretics

Defining osmotic diuresis, Smith[3] wrote: "When substances which are not reabsorbed by the tubules to any considerable degree are injected intravenously, or, if they are absorbed from the gastro-intestinal tract, given by mouth, the rate of water excretion increases, rises to a maximum, and decreases again when the concentration of the diuretic agent in the urine falls to negligible values. Urea, sucrose, sodium sulphate and other salts act in this manner. There is no reason to believe that, in mammals at least, the diuresis is due to anything more than the opposition which these substances offer, by virtue of their osmotic pressure or ionic strength, to the reabsorption of water. It is clear, however, that the resulting diuresis will be determined by the balance of forces between the concentration of the urine and the tendency of the tubules to reabsorb water, and that the latter may be inconstant in consequence of variations in the secretion of the anti-diuretic hormone."

To understand the mechanism of an osmotic diuresis two factors have to be analysed: (1) the limiting concentration of the urine, (2) the limiting osmotic work capacity of the kidney.

If the fluid intake of a normal individual or animal is restricted, the urine output decreases to a minimum and urinary specific gravity and osmotic pressure increase to a maximum. The maximum urinary specific gravity and osmotic pressure vary from species to species. In normal hydropenic man, maximum specific gravity and osmotic pressure of urine amount to 1·030 to 1·040, and 1200 to 1400 milliosmols per litre respectively. The ability of adult guinea-pigs to concentrate urine is much less marked than that of adult rats, the maximum concentration observed under the same conditions being 1·056 $\pm$ 0·0022 in rats and 1·026 $\pm$ 0·0016 in guinea-pigs (Dicker and Heller[121]). It varies also in relation to age: newborn animals concentrate less well than adults, though here again there are variations from species to species. The specific gravity of urine of newborn guinea-pigs dehydrated for 24 hours amounts to 1·026 $\pm$ 0·0013, a figure comparable to that of adult guinea-pigs (Dicker and Heller[121]), while that of dehydrated newborn rats amounts to 1·012 $\pm$ 0·005 only as compared with 1·056 $\pm$ 0·0022 in adult animals (Heller[122]). After 24 hours without water the concentration of urine of newborn babies amounts to about 400 milliosmols per litre only (McCance[123]). However, according to Pratt, Bienvenu and Whyte[124], babies 1 to 2 months old can, during dehydration, excrete urine with osmotic pressures as high as 1200 milliosmols, which is comparable with the adult level. As a corollary of the inability of newborn babies to concentrate the urine to the same extent as adults, it can be calculated that the volume of water required to excrete 1000 mM of urinary solids

amounts to about 0·9 litre in adult man and to about 2·3 litres in a newborn baby (McCance[123]).

The administration of hypertonic saline solution to hydropenic subjects will result in a urine excretion characterised by its maximum concentration of chloride: this limit of chloride concentration amounts to 330 milliosmols per litre; it indicates that the excretion of salt may contribute to a maximum of 660 milliosmols per litre to the total osmotic pressure of the urine. This ceiling of the chloride concentration is unaffected by the simultaneous presence of large quantities of urea in the urine[125,126]. Similar observations can be made after administration of hypertonic sodium bicarbonate. Where hypertonic sodium chloride and sodium bicarbonate are administered simultaneously, the sum of their urinary concentration never exceeds 660 milliosmols per litre[125,127,128,129]. There is thus a limit to the capacity of the kidneys of human beings to concentrate chloride or bicarbonate; under specific conditions this limit is reached when the urinary chloride concentration represents 47 per cent. of the possible total maximum concentration of all urinary constituents, which, it will be remembered, does not exceed 1,400 milliosmols per litre. It is, however, impossible to observe a maximal urine concentration of 1400 milliosmols per litre together with a maximal concentration of ions equal to 660 milliosmols per litre. The kidneys have the choice between two possibilities: either to concentrate the urine to the maximum (i.e., 1400 milliosmols per litre) with a minimum urine flow (0·1 to 0·3 ml. per minute in a human being), as during simple dehydration, in which case the urinary concentration of ions is always less than 660 milliosmols per litre; or to decrease the total osmolar concentration of the urine and increase the urine flow as after conditions of salt loading, in which case the total ion concentration may peak at 660 milliosmols per litre. It is this impossibility for the kidney to excrete a minimum volume of urine in which the total ionic concentration would be maximal (i.e., 660 milliosmols per litre) which differentiates the urine excretion during simple dehydration from that observed after salt loading in hydropenic subjects and which forms the basis of osmotic diuresis. As Pitts and Sartorius[1] said, " 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[130,131,132]. 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."

They are (1) the limiting osmotic work capacity of the kidney, (2) the glomerular filtration changes.

It is a truism to state that the production of urine more concentrated than plasma involves the performance of osmotic work by the renal tubules. On the assumption that the chemical transformations which occur during the process of urine formation are independent and are carried out in a thermodynamically reversible fashion, a series of authors

have calculated the total work involved in the production of urine (Von Rohrer[133], Borsook and Winegarden[134], Newburgh[135], Rapoport, Brodsky, West and Mackler[132]). Assuming that the changes in the composition of urine are effected iso-osmotically in the proximal portion of the tubules, Rapoport *et al.*[132] concluded that, according to their calculations, water alone moves across the distal tubular wall either in the process of reabsorption for the production of hypertonic urine or in that of secretion during water diuresis.

Osmotic work is a function of the product of differences in concentration between plasma and urine and the volume of urine formed; hence minimum volume of urine with maximum concentration, as observed during simple dehydration, and the inverse relationship between urine volume and concentration, as observed under solutes loading in hydropenia are two expressions of the same function, i.e., the limited capacity of the renal tubules to perform osmotic work.

From the independent investigations of Hervey, McCance and Taylor[131] and Rapoport, Brodsky and West[132], it could be shown that in dehydrated subjects with normal solute loads the work required for the elaboration of urine is relatively small; it amounts to 0·6 g. cal. per minute per 1·73 m^2. This small amount of work which is accompanied by the very high U/P concentration ratios is explained by the low volumes of urine involved. When hypertonic solutions of salt, bicarbonate, urea, etc., are administered renal work increases until it reaches a true limiting maximum of about 4·0 g. cal. per minute per 1·73 m^2. Under those circumstances less work is performed per ml. of urine formed, but more work is performed per minute in consequence of the increased urinary volume. In this connection, Eggleton, Pappenheimer and Winton's work will be remembered[136]; they showed on the isolated kidney that during urea diuresis the doubling of the urine flow was accompanied by a marked increase of the osmotic work, without changes in the consumption of oxygen.

The low amount of work involved in the formation of urine during dehydration makes it difficult to believe that the maximum urine concentration of 1400 milliosmols per litre is the result of a limitation of osmotic work capacity of the kidney. The likelihood is that the limitation of the concentration of urine is not the direct result of a limitation in the osmotic capacity of the tubules but rather that of an inability of the renal tubule to absorb water against a gradient of limiting steepness. Whether this issues from limitations in available energy or in an enzymatic transfer is still unknown[50].

So far, no allowance has been made for possible changes in glomerular filtration. During severe dehydration there is an unmistakable decrease of the glomerular filtration rate. This has been shown in human beings[130] by estimating endogenous creatinine clearances; and in dogs by means of both inulin and urea clearances[137,138]. There is also evidence that it occurs in the rat[139]. It is clear that if there is a marked decrease of the glomerular filtration rate during dehydration, the solute load and hence

the urine flow will be influenced by it. It is interesting to speculate how much of the difference in the renal responses to dehydration in newborn and adult animals (or human beings) is actually due to the very low glomerular filtration found in the former more than to undeveloped tubular functions. It may explain the discrepancy of McCance and Wilkinson's[140] and Dicker's[141] results: the former administered highly hypertonic solutions of sodium chloride or urea which may have had a dehydrating effect (McCance and Robinson[142]) which would result in a further decrease of the normally low glomerular filtration rate, hence the absence of diuresis. The latter used subcutaneous injection of 20 per cent. sucrose solution and showed that there was a marked diuresis in newborn rats[141]. However, the diuretic effect was smaller in newborn than in infant rats aged 5 days, and smaller in newborn and infant rats than in adults: likewise, it could be shown that the glomerular filtration rate was smaller in infant than in adult rats, but greater than in newborn animals (Dicker[141]).

Thus the urine flow of an hydropenic mammal depends on three factors. First and foremost in simple dehydration (without administration of any extra solute load) there is the inability of the tubules to concentrate the urine beyond a certain limit: this limit seems to vary from species to species and seems to be indirectly an expression of the steepness of the osmotic gradient against which the tubule can absorb water. Second, and almost of equal importance, are fluctuations in filtration rate: any change of filtration rate will result in changes of the load of excretory solutes delivered to the tubules; since concentration is maximal, urinary volume will vary directly with changes of solute load delivered. Third is the limitation of the tubules to perform osmotic work; this is important only in cases where the solute loads are very high: maximum work is performed by the elaboration of fairly large volumes of urine only moderately hypertonic.

What are the characteristics of the ideal diuretic? Rapoport *et al.*[132] have defined the best osmotic diuretic as that which (1) is distributed in the smallest volume in the body; (2) is not metabolised by the body; (3) is not reabsorbed (or even better, is secreted) by the renal tubules. These authors investigated the action of 11 solutes which were administered to hydropenic normal subjects; they were: glucose, urea, sodium sulphate, mannitol, sucrose, sodium para-aminohippurate, sorbitol, sorbose, xylose and creatinine. They all increase urine flow in identical fashion and in exact proportion to the increase in urine solute load[132,143]. According to Pitts and Sartorius[1], Rapoport has further shown that in hydropenic subjects there is a difference in the efficacity of a variety of anions in promoting chloride loss, when administered in equimolar quantities as sodium salts. The order from most to least effective would be: $CNS > NO_3 > HCO_3 > p$-aminohippurate $> Fe(CN)_6 > SO_4 > S_2O_3 > PO_4$.

The mechanism of an osmotic diuresis has been investigated by Wesson and Anslow[144]. They injected intravenously concentrated solutions of mannitol in trained, unanæsthetised dogs and estimated the glomerular

filtration rate, together with the clearance of sodium, potassium, chloride and bicarbonate. The amounts of mannitol injected were considerable: in one case a total of 670 ml. of a 25 per cent. solution of mannitol was injected during 50 minutes, i.e., at a rate of 13·4 ml./minute; in another, the infusion of a 20 per cent. solution of mannitol was made at a rate of 9 ml./minute for 52 minutes (total injected 468 ml.). Under those conditions they showed that there was a dissociation between the reabsorption of sodium and the reabsorption of water, the rate of excretion of sodium continuing to increase with increasing urine flow. This can be explained by one of the following assumptions: (1) Mannitol exerts a toxic action on the tubular cells; however, as an increased sodium excretion has been observed during glucose diuresis, this appears improbable; (2) an increase in the average velocity of the tubular flow which would impair a normal reabsorption; this is unlikely as phosphate and bicarbonate continue to be reabsorbed normally; (3) under the osmotic action of mannitol the retention of water in the proximal portion of the tubules dilutes the sodium concentration in the urine below that of the plasma and thus establishes an increasing concentration gradient between urine and plasma, which progressively reduces the rate of sodium reabsorption. Wesson and Anslow[144] showed that as osmotic diuresis increases in magnitude and the values for creatinine U/P ratios fall below 3·5 the difference in concentration between plasma and urine sodium tends to approach a constant value of 60 to 90 milliequivalents per litre which is maintained despite marked variations in the absolute values of the plasma and urine sodium concentration. The progressive failure of sodium reabsorption leaves increasing quantities of sodium in the urine which by its own osmotic pressure prevents water reabsorption still further. Thus failure of water reabsorption in osmotic diuresis following injection of mannitol is attributable both to the osmotic action of the diuretic (mannitol) and to the unreabsorbed sodium (Wesson and Anslow[144]).

It is easy to generalise and to conclude that this is what is happening during any kind of osmotic diuresis. It is however difficult to explain in the same way the diuresis following administration of urea. Wesson and Anslow[144] boldly said: " It is possible that our interpretation of the action of mannitol in retarding the reabsorption of sodium is applicable to unreabsorbed solutes normally present in the glomerular filtrate. Urea, the most important of these, may, by the osmotic pressure developed as it becomes progressively concentrated in its passage down the proximal tubule, restrict the proximal reabsorption of water and thus restrict the proximal reabsorption of sodium. It may be that this action of urea contributes to the circumstance that only 85 per cent. of the filtered sodium (and water) are normally reabsorbed in the proximal system." Even assuming that this interpretation could be verified experimentally, it would not explain the osmotic diuresis following injection of sodium sulphate.

Wolf and Ball[145] claim that the diuresis following intravenous injections of sodium sulphate resembles that following administration of water;

according to these authors it does not, as a rule, produce any significant loss of sodium or chloride, as does mannitol or sucrose. This could not, however, be confirmed on chloralosed dogs[146]. Schou[147] calculated that in the rabbit up to 66 per cent. of the glomerular filtrate leaves the kidneys as urine; thus the tubular water reabsorption does not amount to more than 34 per cent. of the glomerular filtration, at the peak of the diuresis. Similar findings were made on dogs (Dicker[146]). With infusions of mannitol the tubular water reabsorption fell to about 50 per cent. of the glomerular filtration rate (Wesson and Anslow[144]). It is a pity that Schou did not investigate the excretion of chloride or sodium.

It is clear that if the generalisation of Wesson and Anslow[144] were true, the osmotic diuresis following sodium sulphate injection would have to be explained as follows : the absorptive capacity of the tubules to reabsorb sodium sulphate is exceeded after intravenous injection of the salt, and its clearance approaches that of inulin or creatinine[47,148,149,150]; this excess of sodium sulphate creates an osmotic pressure which restricts water reabsorption, with the result that more than the ordinary amount of water flows through the proximal tubule in a unit time; hence more than the ordinary amount of water flows into the distal tubule, flooding its mechanism of T^dmH_2O, and more than the ordinary amount of water is excreted finally. However, according to Wesson and Anslow's explanation the restriction of water reabsorption by the proximal portion of the tubule would lead to concentration of the filtrate and ultimately to its increased rate of excretion. But during sodium sulphate diuresis there is no excess sodium in the urine which is not neutralised by the sulphate[145]. This question remains unanswered.

An interesting interpretation of the mechanism of action of diuretics like sodium sulphate, urea and sucrose has been given by Winton[151,152], as a result of his studies on the relations among renal pressures (Eggleton, Pappenheimer and Winton[136]). The intrarenal pressure of isolated kidneys (normally 10 mm. Hg.) is raised by diuretics. At the same time the volume of the kidney increases; this increase of volume may be produced by increase of blood flow, ureteral pressure, venous pressure or by a decrease of extrarenal pressure. There is evidence that intrarenal pressure obstructs the outflow of urine by exerting a pressure on some parts of the tubules and that urine flow increases proportionately with the reduction of extrarenal pressure[153]. Winton[151,152] has shown that a rise in the pressure of the ureter has no effect on urine flow or urine composition until the rise reaches 10 mm. Hg. approximately. This is attributed to an intrarenal pressure exerted on the tubules, keeping them collapsed until they are forced open by urine which has reached a pressure just greater than that in the renal tissue. This is accompanied by an inhibition of tubular water reabsorption[154].

It is difficult to explain the chloruresis following injection of mannitol and its absence during sulphate diuresis by any of these separate series of experiments. However, a reinvestigation of Wesson and Anslow's findings in the light of Winton's may lead to some interesting, and maybe

unexpected, explanation of the mechanism of osmotic diuresis. In the meantime, it is clear that there are numerous questions which must receive satisfactory answers before a comprehensive mechanism of osmotic diuresis can be considered as established, and that Rapoport's claim that all osmotic diuretics act in an "identical fashion" is a dangerous oversimplification.

The Use of Diuretics

Nothing will be said about acidifying diuretics, as they have been reviewed in some detail by Pitts and Sartorius[1]. It is felt, however, that this review should end with some indications about the practical aspects of those groups of diuretics which have been discussed.

Water. As an agent producing an increased flow of urine, water is a diuretic "par excellence." There is evidence that water is also capable of removing the excess of water from the body. When normal subjects ingest from 20 to 200 ml. of water every 10 minutes for 3 to 7 hours, the total urinary output of water may exceed intake by up to 8 per cent. (Wolf[2]). Including some 50 ml. per hour additional extrarenal water loss through insensible perspiration, it is clear that water, under these circumstances, has a dehydrating effect (Pitts and Sartorius[1]). It has further been shown by Marshall[155], Wolf[2], and Steward and Rourke[156] that the ingestion of very large water loads increases the excretion of salt. As, according to Wolf[2], the "regulation of concentration of plasma chloride takes precedence over the regulation of body volume," it can be expected that the elimination of increased quantities of water to compensate for the loss of salt will occur as a means of minimising the change of osmotic pressure of the body fluids. This mechanism depends almost certainly upon the inhibition of secretion of the antidiuretic factor of the posterior pituitary hormone. Application of these findings has been advocated by Schemm[157] in his treatment of oedema. In all fairness, and in spite of Schemm's claims[157], it must be made clear that the most important feature of his regimen is not so much the high fluid intake as the limitation of salt intake. The fact, however, remains that high water load will lead to substantial urinary loss of salt, though little information exists as to its mechanism. According to Pitts and Sartorius[1], the "increased rate of transport of fluid through the distal tubular segment in consequence of reduced water absorption would interfere with mechanisms of base absorption and lead to increased salt excretion." According to results of experiments on rats (Dicker[43]), it would seem that increasing the water load increases the glomerular filtration rate; this would result in increased quantities of water and electrolytes delivered to the distal tubule, and ultimately an increased quantity of salt escaping in the urine. This conception is also supported by Shannon's observation on the dog[158,159].

Mercurial derivatives. Reports on the completion of excretion of therapeutic doses of mercurials give estimates ranging from 60 to 100

per cent. excretion of a single dose in 24 hours[1]. Little is known as to whether mercury is filtered by the glomerulus and is subsequently reabsorbed by the tubules or whether it enters the tubular cells directly from the blood and is secreted by them, or whether it is both filtered and secreted. The time of onset and the duration of diuresis vary according to the route of administration. Both onset and duration are shortest after parenteral injection. Most workers agree that, with parenteral injection, diuresis commences within 3 hours, reaches a maximum in 9 hours and is complete in 12 to 18 hours (see Pitts and Sartorius[1]). In elderly people, however, the diuresis may last up to 48 hours[160]. When the diuresis starts, the fluid eliminated during the first 2 or 3 hours is almost entirely at the expense of the circulating plasma[1]; later on the fluid excreted is up to 90 per cent. of extracellular origin; only 10 per cent. is of intracellular origin[76]. This explains the variability of the diuretic response to a standard dose of mercurial: 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 generalised oedema responded to the administration of 1 ml. of a mercurial derivative with a 24-hour diuresis of 14·22 litres[161].

It is not intended to review the literature concerned with the amount of mercurial to administer. Let it be said, however, that dosage of mercurials should be based on the weight of the patient rather than on accepting 1 or 2 ml. as a standard dose. There can be little doubt that the use of standard doses of 1 or 2 ml. has been actually the cause of death in children: if the dose had been calculated on a basis of mg./kg. as it should have been, it would have been realised that the dose administered to these children was equivalent to 6 to 8 ml. for an adult.

The toxicity of organic mercurials can be considered under two headings: the toxic action of mercury itself and the toxic manifestations due to excessive loss of salt and water: the toxic action of mercury can be subdivided into 2 sub-headings: general and renal toxicity. Sudden death may result from the intravenous injection of mercurial derivatives[162,163,164,165]. Such accidents occur in 1 to 3 minutes after the injection: the patient gasps, shows cyanosis and pallor alternatively and dies as a result of ventricular fibrillation[163,165]. Other manifestations of mercurialism include gastro-intestinal disturbances, salivation and colitis. More interesting are the renal lesions produced by the repeated administration of mercurial diuretics. Whether filtered by the glomerulus or secreted by the tubules, there is evidence that mercury enters the cells at a fairly quick rate, where it inhibits susceptible enzymatic systems rather slowly. According to Jowett and Bróoks[166], the ionised mercury is adsorbed by the enzyme and forms with it a stable chemical bond. Patients receiving therapeutic doses of organic mercurials have sometimes developed oliguria, anuria and œdema followed by death. At autopsy, varying degrees of proximal tubular degeneration with areas of necrosis were found: in one of these cases mercury was recovered from the kidney in a concentration of 5 mg. of mercury per 100 g. of tissue[167].

While toxic reactions may be prevented by injection of dimercaprol if it is administered sufficiently early, it is evident that dimercaprol cannot restore viability to a necrotic cell. The importance of early treatment in mercurial poisoning in man has been discussed and reviewed by Longcope *et al.*[168].

Loss of water and salt following an unusually marked diuretic response may also lead to coma: 4 fatal cases in patients subjected to a regimen of salt restriction and salt diuresis have been reported recently[169]. Signs of dehydration usually become evident in 6 to 12 hours after injection of the drug; they are most commonly observed in elderly patients. Dehydration may be a contributing factor in the production of renal insufficiency. The results of salt depletion have been reviewed by McCance[170].

While the above data indicate that mercurial derivatives can be toxic, there is plenty of evidence to indicate that damage or accident need not necessarily occur. Mercurial derivatives have been most successfully used in patients with congestive heart failure after full digitalisation and in ascites due to hepatic disease. The action of mercurials can be enhanced by the administration of acidifying salts. It has been suggested that this effect may be due to the greater dissociation of mercury in an acid urine, thus increasing its absorption by the renal tubules[171]. However, more work is needed to clarify this point.

Xanthine derivatives. The efficiency of xanthine derivatives, especially of theophylline compounds as diuretics in congestive heart failure is a well-established fact. It is interesting to note that in œdema of extracardiac origin the diuretic response to xanthine derivatives is usually absent. This has been observed also in rats fed on a protein deficient diet: as soon as tissue œdema developed, the diuretic response following administration of theophylline sodium acetate disappeared (Dicker[146]).

As with other diuretic drugs, the diuretic response to the administration of xanthine varies with both dosage and amount of extracellular fluid available[76,172]. It varies also with the compound used: caffeine is the poorest diuretic of the group, and is therefore of no practical use in medicine as a diuretic. Equally useless are theobromine and theobromine sodium salicylate: their diuretic action is only slightly more effective than that of caffeine[99,115,172]. Theophylline and its conjugated forms (theophylline ethylenediamine, theophylline methylglucamine, theophylline sodium acetate) are decidedly the best of the xanthine derivatives[60,76,173,174,175]. They are, however, inferior to mercurials in their diuretic potency[60,176]. Their usefulness is really valuable in cases where mercurials alone do not produce the desired diuretic effect: the administration of a theophylline compound will raise both the glomerular filtration and the effective filtration pressure, and allow the mercurial drug to have an effect. (For explanation, see above.)

Toxic manifestations following the ingestion of xanthine derivatives are mild; they are gastro-intestinal symptoms associated with nausea, anorexia and vomiting. Sometimes there is headache, palpitation or

abdominal pain. The fatal oral dose of xanthine derivatives for man is unknown: however, in terms of LD50 for mice, the lethal dose for a man of 70 kg. would amount to about 40 g. of theophylline sodium acetate. Even when injected intravenously the toxicity of xanthine derivatives is practically nil: only 3 fatal accidents have been reported after intravenous injection of theophylline; all occurred in elderly patients suffering from serious cardiac disease[177].

Osmotic diuretics. The perfect osmotic diuretic should be distributed in the smallest volume in the body, should not be metabolised in the body and should not be reabsorbed by the renal tubules (Rapoport, *et al.*[132]). To these three requisites, one ought to add that it should be given orally without causing any secondary gastro-intestinal or other disturbances. An osmotic diuretic must, however, have a still more important quality: it must promote a substantial loss of sodium and of chloride from the body. An osmotic diuretic which would increase the loss of water from the body only would be clinically ineffective in the treatment of œdema: the patient would suffer a pure water loss with the result that fluid volume would be restored after ingestion of water. For that reason the use of sodium sulphate as an osmotic diuretic cannot be recommended in cases of œdema. Potassium salts are not much better: true, they may produce an enhanced excretion of sodium[178,179]; their action, however, is transient only and the loss of sodium is insignificant[180,181].

Urea is most commonly used as an osmotic diuretic though according to the definition it is not a perfect diuretic. Friedrich (see Pitts and Sartorius[1]) in 1892 first employed urea as a diuretic in patients suffering from liver cirrhosis complicated by congestive heart failure: he used 2 to 14 g. per day and claimed favourable results. Nowadays, between 50 and 60 g. of urea, divided into 3 doses, is administered. It would seem that the diuretic response to adequate doses of urea is somewhat superior to that of theophylline, but less than that of organic mercurials[99]. Between 40 and 70 per cent. of the amount of urea filtered through the glomeruli is returned to the blood stream as a result of passive diffusion (Shannon[159]). During a normal diuresis at least 40 per cent. of the filtered urea diffuses back in the proximal portion of the tubule; however, during severe osmotic diuresis the back diffusion is reduced to about 10 per cent. An additional 10 to 30 per cent. is passively absorbed by the distal segment of the tubules, the proportion varying as an inverse function of urine flow or directly with the degree of concentration of the urine (Shannon[159]). The increased excretion of sodium and chloride which sometimes accompanies urea diuresis is the result of a decreased reabsorption of sodium in the proximal tubules. This has been explained as a consequence of the rapid flow of urine[182] or on the ground of some limiting U/P ratio for sodium[144]. These interpretations have been discussed and criticised above. Various authors, however, have shown that urea does not markedly increase salt output[90,125,132,183] unless salt has been loaded in the body along with urea (Mudge, Foulks and Gilman[182]). In these circumstances, it is questionable whether urea should be preferred to sodium sulphate, as neither of these substances seems to produce clear

chloruresis and natruresis. Two difficulties may be experienced when administering large doses of urea : (i) gastro-intestinal disturbances, with nausea and vomiting, (ii) increasing weakness, lassitude and anorexia. Counterbalancing these difficulties is the fact that urea is not toxic and that its diuretic potency remains unchanged even when administered over a period of years.

A variety of other substances, including glucose, sucrose, mannitol, sorbitol, sorbitan, xylose, etc., are powerful osmotic diuretics. All, except glucose, have to be injected intravenously. They have an evident advantage over other substances like urea, potassium salts or sodium sulphate : they cause a significant loss of body sodium, chloride and water[132,144,184,185]. They have, however, a serious disadvantage : they may lead to functional renal impairment and to histological alterations of the tubular cells[186,187,188,189,190]. If these diuretics are not used too frequently, structural and functional changes are reversible and considered as harmless. According to Dean and McCance[191] and McCance and Wilkinson[140], the administration of hypertonic solutions of sodium chloride or of urea are relatively ineffective in newborn infants and rats, largely because of low rates of glomerular filtration resulting in low loads of osmotically active substances delivered into the urine. Hypertonic solutions of sucrose, however, have a clear diuretic effect in newborn rats (Dicker[141]). The use of hypertonic solution of sodium chloride as an osmotic diuretic (Dean and McCance[191]), has lost much of its value since Winkler, Elkington and Hopper[192] have shown that the resulting dehydration is more cellular than extracellular : the ionic concentration of the extracellular fluid is increased and the water deficit is restored when water is ingested. (See sodium sulphate above.) For that reason, Pitts and Sartorius[1] consider both sodium chloride and sodium bicarbonate as relatively ineffective osmotic diuretics.

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