

THE MERCURIAL DIURETICS.

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Before commencing a discussion on diuretics a few words on oedema and its causation, so far as that is understood, will perhaps not be out of place. I propose, therefore, briefly to consider the modern view generally thought to offer the most satisfactory explanation.

Oedema may be defined as a condition in which there is an abnormal accumulation of fluid in the tissue spaces. In cardiac failure the sequence of events is probably as follows. In consequence of the failing right heart the normal venous pressure of 10-15 cms. of water becomes very considerably raised sometimes apparently to as much as 30-35 cms. As a result stasis occurs in the capillaries and it is suggested that this is one of the principal factors in the onset of cardiac oedema. Associated with such a rise in the venous pressure there must of course also be a rise in the capillary pressure which in the presence of malnutrition of the walls of the capillaries leads to their increased permeability and the passage of fluid into the tissue spaces. Such malnutrition is secondary to the stasis of the blood in the capillaries and not only are the capillary walls suffering from the effects of starvation but certain products of metabolism, which in the absence of more precise knowledge of their composition have been named metabolites, accumulate in the tissues and raise their osmotic pressure. This additional factor still further serves to increase the tendency for fluid to pass into the tissue spaces and above all to be retained there. Lastly the effect of the raised venous pressure upon the kidneys is to reduce the flow of blood through them, and with under-nutrition playing its part in the later stages their secretory activities become more and more severely impaired. The albumen and blood which so often appear in the urine in cardiac oedema—the blood frequently only in microscopic amounts—are allowed to escape by the damaged glomeruli because anoxæmia produces changes in the epithelium of these altering their permeability. The dependent parts of the body are the first to be effected since in them the hydrostatic pressure is greatest. It is in this form of oedema that the mercurial diuretics have proved themselves of the utmost value. The diminution in the quantity of fluid present in the tissues after the diuresis assists cardiovascular efficiency and such improvement is probably due to a decreased peripheral resistance and a smaller blood volume.

A further factor of some importance is the raised basal metabolic rate which has been shown to be present in cardiac failure. In effect this means an increased aeration of the lungs and more work for the heart in distributing the oxygen to the tissues. Friedman (quoted by Poll & Stern 1937) has therefore suggested that the improvement occurs in two ways:—

1. A diminished load for the heart effected by reducing the quantity of blood flowing through the oedematous tissues in proportion to their metabolism, the resulting decline in the venous return and the venous pressure tending to decrease the cardiac output.
2. An increase in the ability of the heart to carry the load by reducing myocardial oedema and so increasing the contractile power of the heart.

In other oedematous conditions the principal failure lies not in the pump but in the filter. Oedema is a very constant feature of acute glomerulonephritis but this is of little interest to us since any form of mercury is absolutely

contra-indicated. The main function of a diuretic drug is to increase the volume of urine and naturally this pre-supposes an adequate amount of functioning renal tissue.

However, it will be worth while to consider briefly one form of chronic nephritis—the nephrotic type of chronic glomerulo-nephritis. In this condition the glomerular changes are slight but there is a marked degeneration of the tubular epithelium. There is no evidence of renal insufficiency as tested by the urea concentration and urea clearance tests, but the amount of protein in the urine may be enormous. It is supposed that the glomerular permeability is in some way altered to permit the passage of the smaller albumen molecules while retaining the larger globulin molecules in the plasma. As one of the chief factors responsible for the retention of water in the tissues, Epstein in his study of nephrosis has laid special emphasis upon this loss of plasma proteins. In consequence there is a relative rise in the osmotic pressure of the tissues as compared with that of the plasma. That this hypothesis is probably correct is shown by the striking diuresis which sometimes follows an increase in the protein of the diet in these patients. It is recommended that protein should be given to the amount of one gramme per kilo weight over and above the amount of protein lost in the urine during the day.

It has been truly stated (East & Bain 1936) that irrespective of the cause, the presence of gross œdema is bad for the individual—improvement is always obvious when the œdema has been dispersed and therefore every effort should be made to achieve this end.

To assist us in the treatment some more or less non-toxic forms of mercury were introduced in the early part of the last decade. In the succeeding years these have been modified—decreasing their toxicity and augmenting their diuretic action. The toxic effects have been rendered almost negligible and those dangers which in the past were always such a drawback to the use of this drug have been eliminated. For many years the diuretic action of mercury has been recognised and for its virtue in this respect it was used during some four centuries. As a component of Guy's pill it is still much used and a marked diuretic effect may follow the exhibition of mercury in this form even when failure attends the administration of the organic preparations.

There appears to be little doubt that the main action of the mercurial diuretics is a direct one upon the kidneys rather than any extra-renal effect, for instance by decreasing the water binding powers of the tissues. In proof of the former view it has been shown that the injection of Salyrgan—one of the most popular of the mercurial preparations—into the left renal artery of the dog was succeeded by a diuresis solely from the injected kidney. Apparently the action of the mercury is upon the epithelium of the tubules diminishing their power of absorption. That there are nevertheless some extra-renal factors involved has recently been shown by an Italian worker. It had been noted that the weight lost by a patient after the injection of a diuretic was much greater than the total weight of the excreted urine. This led Rocchini (1937) to investigate the loss of water through the skin. By enclosing a portion of the skin under a vessel containing calcium chloride and determining after a time the increase in the weight of the vessel he found that there was a marked difference before and after the administration of a diuretic—in this case Novasurol. The excretion of water by the œdematous skin is considerably less than that of the normal skin, but a marked rise followed the injection of Novasurol. This increase was coincident with the rise in the excretion of urine and from his investigations this worker concludes that the mercurial diuretics have a direct action on œdematous tissue.

It was not long before it was realised that the diminution in the absorptive powers of the tubules did not produce a sufficiently great diuresis so long as the inevitable venous stasis impaired the filtering capacities of the glomeruli. For some time the xanthine compounds, Theobromine, Theophylline, Euphylline, etc. have been employed for their diuretic action and it was known that these drugs obtained their effect by directly increasing the rate of filtration of the glomeruli. Furthermore it has been shown that the presence of theophylline at the site of injection of these new preparations tends to prevent any latent toxic action of the mercury on the tissues. The xanthine compounds, theophylline in particular, have therefore been combined with the organic mercurial preparations and in such combination a much enhanced diuresis is obtained.

Following the injection there may be an enormous increase in the volume of urine and the resultant dehydration may be the direct cause of a syndrome with which I propose to deal later when discussing the toxic effects. Actually the amount of urine is sometimes from 2-5 times as much as on the preceding day (Stewart & Wheeler 1937). On the other hand an injection which at one time may result in a powerful diuresis will on another occasion be rather less effective. In some instances the response seems to vary according to the amount of excess fluid available for mobilisation, though it is not always possible to attribute the variations in response to this cause. Sometimes it appears that if, through some cause, the patient is anxious or worried a diminution in the amount of urine occurs. It is of interest to note that in dogs it has recently been shown (Rydin, H. & Verney, E. B. 1938) that emotional stress resulted in a striking inhibition of secretion by the kidneys.

The preparations in common use are

1. Salyrgan
2. Novurit
3. Neptal

and amongst the older ones are Mersalyl and Novasurol. These drugs are made up either in ampoules for intra-muscular and intra-venous injection or in the form of suppositories. In general, Salyrgan is used for the intra-venous and intra-muscular route and Novurit is administered per rectum in the suppository form. In the presence of large effusions the mercurial diuretics have been injected directly into the pleural and peritoneal cavities and they have also been given orally but the resulting diuresis was considerably less. It is maintained by many authorities that the intra-venous route gives the greatest diuresis and it is probably the most popular. The objections to this mode of administration are the initial discomfort caused by the injection and the maximal diuresis which, occurring on the same day will probably be the cause of a sleepless night and much discomfort not calculated to improve the condition of an already debilitated patient. There is the additional risk of subcutaneous leakage followed sometimes by sloughing and always by much local irritation of the superficial tissues which manifests itself by erythema, localised oedema and burning pain. The dosage for an adult is 1-2 c.cms. of the 10 per cent. solution though it is advisable to commence with an initial dose of $\frac{1}{2}$ c.c.m. to test the sensitivity of the patient to mercury. The injections should not be given more often than twice weekly. Where the injections are given over a long period of time and are repeated at short intervals the vein may ultimately become sclerosed. To minimise the tendency for such complications to occur it has been recommended that 1-2 c.cms. dose of the drug be given diluted to 10 c.cms. in normal saline.

In this connection it may be of interest to quote the case reported in the proceedings of the staff meetings of the Mayo Clinic (Noth 1937). The patient, a sufferer from constrictive pericarditis had received since 1928 no less than 450 injections of these preparations of mercury. In 1934 he reported at the clinic on account of the difficulty in finding a place to inject the Salyrgan because all the superficial veins were sclerosed. He was therefore treated with suppositories instead and occasional intra-muscular injections with which he had since continued. At the time of reporting (1937) the patient was carrying on his usual daily occupation—that of banker—and by avoiding strenuous exertion leading a fairly normal existence. In another case (Norbury 1937) which eventually came to autopsy the patient received 32 injections of Salyrgan and 58 injections of Novurit. During life the kidney function tests showed no evidence of renal damage and this was confirmed by macroscopic and microscopic examination at post-mortem.

Sclerosis of the vein is avoided by using the intra-muscular route and the risk of subcutaneous infiltration is greatly lessened. The maximal effect is somewhat delayed and spread over a longer period of time so that the discomfort caused is rather less. The injections are best made into the gluteal region and the dosage and preparation is the same as for the intravenous method.

From the point of view of general practice there is no question that the suppository is the preparation of choice. It is the route which gives the patient the minimum of discomfort and does not require the presence of the doctor for its administration. The use of suppositories is also particularly indicated for those patients in whom the condition of the tissues by reason of oedema would render an injection most inadvisable. The following rules for the administration of Novurit suppositories have been suggested by Engel (1937):—

1. The suppositories should not be given at an interval of less than five days. Adherence to this rule renders the patient tolerant of repetitive suppositories over a period of years without the production of a chronic inflammatory reaction in the rectal mucosa.
2. On the administration the rectum must be empty otherwise the presence of the suppository may provoke defæcation with the subsequent expulsion of the drug.
3. The administration should not immediately follow on the enema for the suppository may then be badly tolerated as the mucosa of the rectum will be in an irritable condition. An interval of at least two hours should elapse.
4. Occasionally after the insertion of the suppository a patient may complain of a burning sensation in the rectum and even tenesmus has been reported as a sequel. In such cases a small dose of 5-7 minims of Tr.Opii is indicated immediately before the insertion of the suppository. The opium in no way diminishes the resultant diuresis.

The effect of the suppositories is less rapid than either of the other two routes. The diuresis is more evenly distributed and the smaller volume of urine during the first hours after administration possesses several advantages. The effect is not so fatiguing for a weakened patient and the administration in the afternoon or evening does not give the patient that disturbed night which so often follows an injection. The diuresis may be prolonged even to the third day after administration. The only disadvantage is the rather smaller diuresis produced, though in one patient at least treated in this hospital the resultant diuresis was such as almost to cause anxiety.

In those patients in whom there is much oedema and respiratory distress which is not ameliorated by one weekly injection satisfactory results may be obtained by

prescribing a suppository later in the week. This prevents the unpleasantness and attendant risks of too many injections and still keeps within the rules suggested by Engel.

The effect of all the mercurial diuretics is considerably enhanced by premedication with acid producing salts. Of these ammonium chloride is the salt generally used though calcium chloride and ammonium nitrate have also been used. The resultant acidosis leads to the withdrawal of base in the form of sodium and potassium from the body tissues. With the increased excretion of these basic radicles the water held in the tissue spaces is liberated and diuresis results (Steele 1937). The dose of the chloride is 60-90 grains daily for two to three days preceding and on the day of the injection of the diuretic. Sometimes these salts produce nausea and they are then best prescribed in the form of capsules. That digitalis might appreciably affect the action of the organic mercurial preparations towards an increase of the diuresis one would naturally assume, but such has not been found to be the case (Thomson 1937). However, this must not be taken to contra-indicate the use of digitalis for although digitalis may not directly assist the mercurial diuretics, the two drugs are without doubt complementary.

The indication for the mercurial diuretics is unquestionably the œdema of cardiac failure. Engel goes so far as to recommend the use of the Novurit suppository in what he terms the pre-œdematous state marked only by dyspnoea on exertion. In an investigation on the vital capacity of a group of nine patients with congestive heart failure and breathlessness it was found that there was an average increase of 290 c.cms. twenty-four hours after the injection of a mercurial diuretic (Alsever & Levine 1938).

Nevertheless it has been pointed out that in elderly people these preparations should be employed with caution. There is some difference of opinion regarding the use of the organic mercurial diuretics in renal disease though most observers agree upon their use in the nephrotic syndrome. Mercurial diuretics are definitely contra-indicated in acute nephritis and indeed in any condition in which there is impairment of the concentrating capacity of the kidney. Some authorities state that they may be used in subacute and chronic nephritis but only with the exercise of great caution and provided that the renal efficiency is not greatly impaired. The use of so potentially dangerous a preparation in such circumstances would appear to be the antithesis of good treatment.

In ascites irrespective of the cause the mercurial diuretics are always worth a trial. The results are not so dramatic as those in the œdema of cardiac insufficiency but often the diminution in the amount of fluid may be surprisingly great. In passing it may be mentioned that the suppository has not been found to give good results in the ascites due to cirrhosis of the liver (Flexner 1938).

The contra-indications may be enumerated as:

1. Severely impaired renal efficiency.
2. Hæmaturia and the hæmorrhagic diathesis.
3. Advanced cachexia.
4. Colitis, enteritis and diarrhœa.
5. Fever.

The danger of giving mercury in a condition in which the number of functioning nephrons is gravely reduced is obvious even when the mercury is in a comparatively

innocuous form. There is always the possibility that the remaining portion of the kidney is in an abnormally sensitive state and in the circumstances even mild toxic effects might produce a fatal anuria. In the hæmorrhagic diathesis the effects of the drug might be such as to cause a dangerous hæmorrhage either into the bowel or from the kidneys. Colitis, enteritis and diarrhoea may be aggravated by the administration of a drug which in poisonous doses already produces such results.

Lastly, pyrexia which is a contra-indication only when it is unduly high and probably secondary to some other complication. The mercurial diuretics have been used in patients with a small rise of temperature without noting any deleterious effects.

The ordinary case of congestive failure in the early stages is much benefited by the diuresis. The drug must be given with greater caution, however, when the patient happens to be a hypertensive of long standing in whom the condition is very advanced and associated with passive congestion and secondary degenerative changes in the kidneys. In such a patient a sudden diuresis may precipitate the onset of uræmia (Barker 1937).

Earlier, the dangers involved in too rapid dehydration were mentioned. The unfortunate effects of dehydration occur mainly when salt and water are lost from the body in excessive amounts and it has been shown that in the diuresis due to salyrgan and its allies an enormous excretion of sodium chloride and water results. The syndrome described by American authors (Poll & Stern 1937) is characterised by a preliminary restlessness associated with great prostration. There are in addition extreme thirst, a dry tongue and sunken shrivelled features likened by these authors to the terminal condition seen in the algid form of cholera. In the later stages delirium and apathy frequently occur. The condition is directly attributed to the loss of sodium and has been compared with Addison's disease in which there is a similar sodium deficiency. These authors advise particular care when administering the organic mercurial preparations to patients in an advanced state of athero-sclerosis and cachexia. When these symptoms develop the following measures should be adopted:—

1. Oral administration of water.
2. Oral administration of sodium chloride in capsules.
3. Intravenous administration of sodium chloride solutions when the oral route is not available.

Signs of mercurial poisoning have on occasion been reported and these are thought to be a sequel to failure of elimination when, as sometimes happens diuresis does not occur. The effects which manifest themselves are stomatitis, diarrhoea, vomiting, hæmaturia and purpuric symptoms. Nevertheless even when the first injection is not successful a second may safely be given after 48 hours. Reference has already been made to the unpleasant results which may sometimes follow leakage into the subcutaneous tissues and to these may be added wrist drop as a late sequel.

The toxic effects are mentioned only for the sake of completeness and in general one may say that such effects when the mercurial preparations are used in their correct dosage, are for all practical purposes negligible and the benefits obtained far outweigh any potential dangers.

It is in the treatment of cardiac oedema that these new preparations are of most value. Not only in those patients in whom there is obvious evidence of oedema but also in the early stages of cardiac failure when the presenting signs at the most may be merely a diminished exercise tolerance. In no circumstances should the mercurial diuretics displace digitalis but rather they should be used in conjunction with it, the digitalis sustaining the failing heart, the diuretics assisting the kidneys in the elimination of the surplus fluid. Whether the mercurial diuretics do in fact lengthen the life span of the cardiac patient is not decided. One author (Hynes 1938) is of the opinion that the duration is shortened by the use of the mercurial diuretics whereas in the experience of another (Lyons 1937) these drugs will often prolong life. Further careful investigation is required to elucidate this problem but in the present state of our knowledge it would not be right to withhold a drug which so often brings relief and comfort to the patient.

REFERENCES.

- Alsever, J. B. & Levine, S. A. (1938) *Am. Heart Journ.* 15:201.
Barker, M. H. (1937) *Illinois M.J.* 72:313.
East & Bain, *Recent Advances in Cardiology*, J. & A. Churchill, London, 1936.
Engel, C. (1937) *Bruxelles-med* 17:1311.
Flexner, J. (1938) *Ann. Int. Med.* 2:1962—1972.
Hynes, L. (1938) *J.A.M.A.* 110:202.
Lyons, R. (1937) *New Orleans M. & S. J.* 90:188.
Norbury, F. G. (1937) *J. Lab. & Clin. Med.* 23:156.
Noth, P. H. (1937) *Proc. Staff Meet. Mayo Clinic* 12:513.
Poll, D. & Stern, J. E. (1937) *M.Clin. North America* 21:1973.
Rocchini, G. (1937) *Clin.med ital.* 68:443.
Rydin, H. & Verney, E. B. (1938) *Quart. Journ. Physiol.* 27:343.
Steele, C. W. (1937) *Maine M.J.* 28:236.
Stewart, H. J. & Wheeler, C. H. (1937) *Am. Heart Journ.* 14:526.
Thomson, W. A. R. (1937) *Quart. Journ. Med.* 6:321.