TREATMENT OF CHRONIC RENAL OEDEMA*

BY

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Chronic renal oedema may be defined as a very persistent oedema associated with gross proteinuria, a fall in the level of plasma albumin, and a rise in the plasma cholesterol. Renal function may or may not be impaired and hypertension may or may not be present. Oedema of this type is protracted, lasting months or years. It causes discomfort and some risk of death from infection of the oedematous tissues (especially in children), although this hazard is much less than it used to be since the introduction of antibiotics. Oedema such as this is most often due to Bright's disease, but may also develop in the course of diabetic glomerulosclerosis, amyloidosis involving the kidneys, diffuse lupus erythematosus, and even thrombosis of the renal veins.

This review of treatment is concerned mainly with oedema due to Bright's disease, but some of the measures advocated are applicable to the relief of the other varieties. Recent work has suggested that the steroid hormones cortisone and corticotrophin (Luetscher *et al.*, 1953; Heymann *et al.*, 1955), and particularly the synthetic forms, prednisolone (Arneil, 1956) and prednisone, may cause not only diuresis but also cessation of proteinuria. With these possible, and as yet unconfirmed, exceptions treatment of chronic renal oedema is symptomatic and does not lead to cure. The lines of treatment available are summarized in the Table.

Treatment of Chronic Renal Oedema

General measures:	
Diet	Sodium restriction: cation-exchange resin High-protein diet
Diuretics	Mersalyl Others
Plasma volume expanders	Acacia Blood products Polyvidone: dextran
Steroid hormones	Corticotrophin Cortisone Prednisolone: prednisone
Stress producers	Nitrogen mustard
Tapping	

General Measures

Where oedema is considerable, patients are inconvenienced by its mere weight and are more comfortable in bed. On the other hand, slight oedema is quite compatible with a sedentary occupation, and there is no evidence that staying in bed influences the course of the disease. Too much should not be expected to follow removal of septic foci, but an antibiotic should be used at once for even mild infections.

Diet

Fluid Intake.—Provided the sodium content of the diet is adequately restricted, it has become common practice to allow patients to drink as much as they wish. I prefer myself to limit fluids to 1,800 ml. in 24 hours if there is no fever and no azotaemia. This causes no particular inconvenience and allows of more accurate assessment of fluid balance.

Sodium Restriction.—This has been widely practised since the time of Widal and Javal (1903). To be of any value the salt content of the diet must be less than 2 g. in 24 hours. With such a diet it is unusual to observe disappearance of oedema or even marked improvement, but addition of salt to the diet invariably aggravates oedema. The tastelessness of the food may be mitigated by the use of pepper, vinegar, lemon, or garlic, and, for those who demand it, salt substitutes are available which owe their flavour to potassium. Salt substitutes which contain sodium are, of course, equivalent to salt and are valueless.

Cation-exchange Resin.—This may be used to reinforce the effect of salt restriction. It should in theory be particularly valuable when the salt-poor diet is required also to be rich in protein, as proteins contain much sodium. The cation resin clings to sodium in the gut, hydrogen ions being liberated in exchange and absorbed. Accordingly when renal function is impaired, as indicated by azotaemia, resin should not be used as it increases any existing tendency to acidosis. Excessive loss of potassium and less commonly of calcium may also occur in the faeces and lead to symptoms of deficiency, but the risk of hypokalaemia has been diminished by the incorporation of resin in the potassium phase in amounts up to 25% of the total dose. Supplements of potassium may still be required, and close biochemical control is always necessary. The dose of resin is 15–30 g. three or four times a day, best given in chilled fruit juice which contains potassium (50 mg. in an oz. (175 mg. per 100 ml.) of orange juice). In my experience a high proportion of patients refuse to continue with resin because of nausea, heartburn, or the unpleasant taste. Others have recorded better results (Lippman, 1951). Severe constipation is common and faecal impaction may occur. A mild purgative such as senna should be given daily. Even when none of these difficulties was encountered the results of treatment with a cation-exchange resin have not been spectacular (Fig. 1). (In Figs. 1–9 the patients all received a high-protein salt-poor diet, and the fluid intake was limited to 1,200 ml. or to 1,800 ml. a day.)

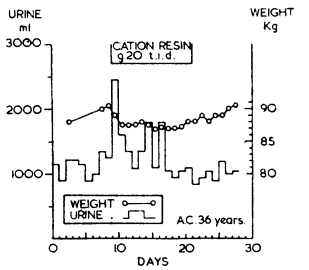

FIG. 1.—Failure of cation resin.

High-protein Diet.—This was introduced by Epstein (1917) in the hope that it would counterbalance the loss of protein from the body in the urine, and permit restoration of the plasma albumin level, with consequent disappearance of oedema. In practice this seldom if ever takes place, and diets containing 200 g. or more of protein a day are no longer used, but it is customary to give a diet containing as much as 100–120 g. of protein because of the prolonged proteinuria. It is essential that the blood urea should be within normal limits initially, and that observations should be repeated at regular intervals. The blood urea may rise slightly, but if it reaches a level of more than 50 mg. per 100 ml. some reduction of protein is called for. As already stated, protein foods contain much sodium, and salt-free butter or margarine, sodium-free flour, and sodium-free concentrates of protein make easier the construction of the diet. Because of the lipaemia which is present in chronic renal oedema, restriction of fat in the diet was commonly advocated. No obvious benefit follows this procedure, which has now been generally abandoned.

Diuretics

The organic mercurials, of which mersalyl may be taken as an example, are sometimes outstandingly successful. Mersalyl acts by preventing reabsorption of chloride in the renal tubule. It should not be used if azotaemia or gross haematuria is present. Some physicians, of whom I used to be one, oppose its use altogether in chronic renal oedema, but after a period of over twenty years I cannot be certain that I have seen renal damage caused by it. On the other hand, I know of two patients who recovered and now show

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no evidence of renal disease sixteen years after the use of a mercurial in childhood. There is no doubt that it is often very effective, and Fig. 2 shows complete disappearance of oedema after one injection of mersalyl in a boy of 10 who had been oedematous for months. This result cannot be regarded as typical, and indeed mersalyl may fail to produce diuresis, possibly most frequently in those with very severe hypoalbuminaemia. It is probably advisable always to supply chloride from the start by giving 2 g. of ammonium chloride four times a day in emplets or capsules during the period when mersalyl is being given. Even this plan does not always result in adequate diuresis (Fig. 3). Intravenous injection of 0.25 g. of aminophylline (which increases glomerular filtration) two hours after administration of mersalyl has not produced material diuresis when I have used it in the treatment of chronic renal oedema (Fig. 3). The alternate use of mersalyl with ammonium chloride and of acetazolamide ("diamox") has also been unsuccessful. The addition of mersalyl in patients who had no diuresis with cation resin alone may give some response (Fig. 4).

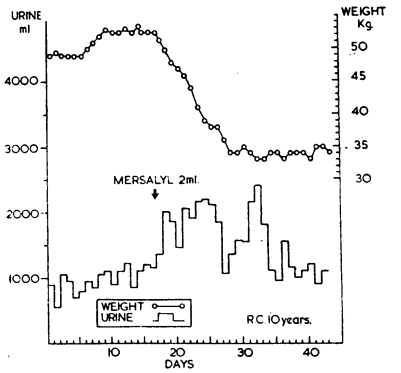

FIG. 2.—Diuresis after a single dose of mersalyl.

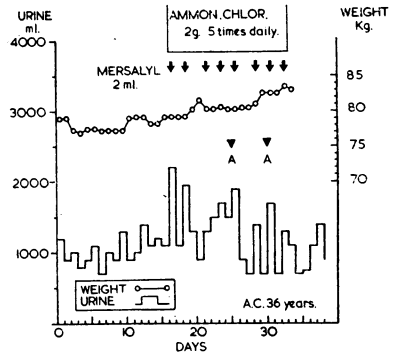

FIG. 3.—Failure of mersalyl and ammonium chloride along with aminophylline.

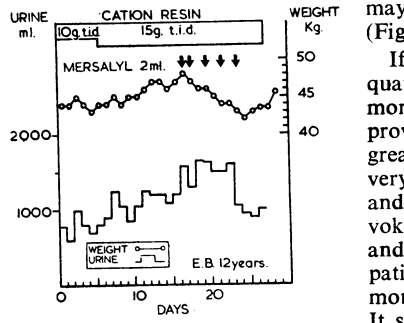

FIG. 4.—Failure of cation resin alone. Diuresis with addition of mersalyl.

If taken in large quantities, 60 g. or more a day, urea will provoke diuresis. The great difficulty is its very unpleasant taste and tendency to provoke nausea, vomiting, and diarrhoea, and few patients can stand it for more than a few days. It should only be given if the blood urea is normal at the start of the treatment, and frequent observations are necessary. In my experience it is much less effective than mersalyl.

Purines, acetazolamide, and aminometradine ("mictine") in my hands have been of no value in chronic renal oedema.

Plasma Volume Expanders

In the first world war acacia in 6% solution was given intravenously in the treatment of shock, the plasma volume being increased by tissue fluid drawn into the blood stream through the osmotic effect of the acacia. When used subsequently in the treatment of chronic renal oedema it was found that diuresis followed in a fair proportion of cases. Acacia is not metabolized, however, and ceased to be used when it was found to remain indefinitely in the reticulo-endothelial system of experimental animals.

Blood products were next tried. Blood itself and plasma were found to be of no value, but concentrated serum gave better results. As might be expected, 25% concentrated salt-free human albumin proved to be better than any. Its effect is temporary, it is very expensive, and it is unobtainable in this country.

Polyvidone was developed in Germany during the war as a substitute for plasma, but has not been adopted extensively elsewhere because there is doubt about its fate in the body. I have not used it in the treatment of oedema.

Dextran is a polysaccharide formed by the condensation of the glucose moiety of sucrose by the action of the organism *Leuconostoc mesenteroides*. Commercial dextran is prepared by hydrolysis and fractional precipitation of this crude dextran. When given to man it is in part excreted in the urine and faeces or fully metabolized. Spectacular diuresis often follows its use (Fig. 5), when 540 ml. of 10% salt-free solution is given intravenously by continuous drip over at least four hours on up to five consecutive days (Mollison and Rennie, 1954). Dextran is claimed to be non-antigenic after numerous trials in Scandinavia, the United States, and this country on patients suffering from shock and/or under anaesthesia. With growing personal experience of its use as a diuretic, however, I have noted headache, nausea, backache, urticarial rash, and, less commonly, vomiting and bronchospasm. Some of these manifestations are due to rapid increase of blood volume and can be prevented or mitigated by slow infusion. It must be concluded that symptoms such as urticarial rash, shivering, and bronchospasm are due to sensitivity. Tests for sensitivity before injection have so far not proved reliable. If symptoms do occur the drip should be stopped and 0.5 ml. of adrenaline given subcutaneously. Diuresis is poor or absent when a reaction occurs (Fig. 6). In this patient an urticarial rash developed with the last injection of dextran and later became haemorrhagic. There was also some fever, headache, and backache. This was the most severe reaction encountered in over 100 infusions of dextran. In all, reactions believed to be allergic have been observed on nine occasions. I believe that dextran should not be given when there is hypertension, and I have not given it to anyone with significant azotaemia.

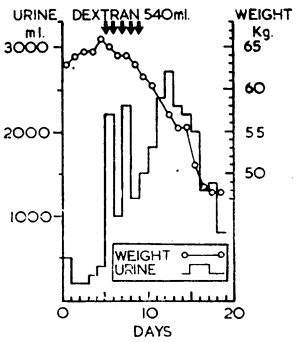

FIG. 5.—Spectacular diuresis after 540 ml. of 10% salt-free solution given by continuous drip for at least four hours on five consecutive days.

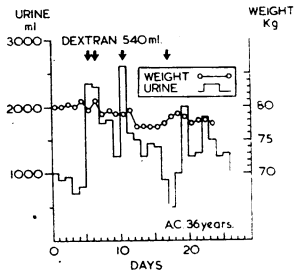

FIG. 6.—Failure of dextran due to sensitivity.

Steroid Hormones

Cortisone and corticotrophin are claimed to promote diuresis in 60 to 80% of patients and to be more successful in children than in adults. The mode of action is uncertain but has been ascribed to a relative insufficiency of the adrenal cortex after withdrawal of the hormone. This can hardly be the full explanation, as in a fair proportion of cases diuresis starts before withdrawal, this being particularly true regarding the new synthetic preparation prednisolone. Disappearance of proteinuria and apparent cure have been

attributed to these hormones, and recent work appears to indicate that this happens most often with prednisolone.

If cortisone or corticotrophin is used in the initial stage because of its action in promoting retention of water and sodium, there is often increase of oedema, which can be ignored. Patients who have been on a strict salt-free regime, however, may have a disproportionate retention of water with symptoms of water intoxication—weakness, headache, oliguria, azotaemia, and occasionally mental confusion and convulsions. A low level of plasma sodium would be a contraindication to the use of these hormones. Hyperkalaemia from their anti-anabolic effect is also sometimes seen, while later, when diuresis develops, excessive loss of potassium or sodium may occur. The dose of cortisone is 200 mg. by mouth in divided doses, and of corticotrophin 100 mg. by intramuscular injection, both for ten days. The gel may be used. Prednisolone is given by mouth in doses of 60–80 mg. for ten days, then 40–60 mg. for ten days, and so on, tapering off gradually. With this substance there is claimed to be no tendency to retention of sodium and water. Phenoxymethylpenicillin should be given as protection from intercurrent infection during the treatment. If there is hypertension or azotaemia hormones should not be used. A further course should be given if relapse occurs.

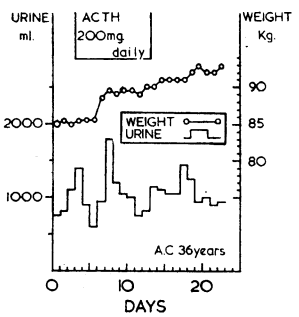

FIG. 7.—Failure of corticotrophin (A.C.T.H.).

My experience is limited to nine courses given to four patients, ranging in age from 14 to 36 years. With cortisone and corticotrophin no striking diuresis ensued. Fig. 7 shows failure of corticotrophin in a man of 36 years. Good diuresis followed the administration of prednisolone in a boy of 14 (Fig. 8), but there was no change in blood chemistry or in proteinuria. (During treatment fever developed and the dose of phenoxymethylpenicillin was increased from 125 to 250 mg. six-hourly. Diarrhoea with incontinence followed and the urinary output could not be measured for a time.) A second course has also produced a good diuresis. After two periods of treatment with prednisolone in the same 14-year-old patient neither cure nor alleviation of proteinuria has occurred. Various other dosage schedules with cortisone and corticotrophin have been recommended, including "continuous" treatment with a smaller dose and treatment on three days a week for prolonged periods. The results seem no better.

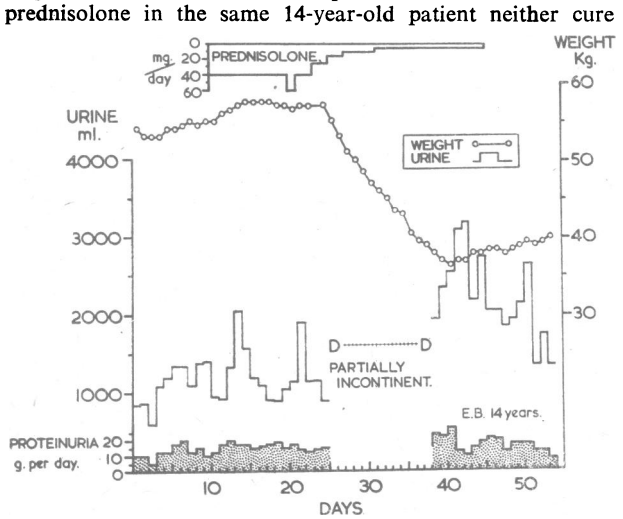

FIG. 8.—Diuresis during administration of prednisolone.

The usual side-effects may follow the use of the steroid hormones, but these are not of much consequence and disappear when the treatment is discontinued. I have, however, seen permanent diabetes develop in one adolescent after eleven days on corticotrophin. A family history of diabetes was not obtained.

Nitrogen Mustard

In view of the hypothesis that glomerulonephritis is due to an abnormal antigen-antibody response following infection with haemolytic streptococci, nitrogen mustard was originally given to patients suffering from chronic glomerulonephritis because it interferes with antibody production (Chasis *et al.*, 1950). No evidence of benefit on the course of the disease was observed, but diuresis was sometimes noted to occur. On this account it has subsequently been used in the treatment of chronic renal oedema, alone (Baldwin *et al.*, 1953) and combined with cortisone or corticotrophin. The consensus of opinion is that nitrogen mustard does no more than produce diuresis occasionally, while it has its usual severe general effects and a depressant action on the marrow. It does not enhance the action of the steroid hormones (Greenman *et al.*, 1955). I have not used nitrogen mustard.

Tapping

By tapping is meant the removal of oedema fluid, commonly by draining it off with Southey's tubes inserted at the ankles or by paracentesis abdominis. The need to do this arises when methods of inducing diuresis have failed or are unsuitable. Before the introduction of antibiotics it carried a not inconsiderable risk of infection locally, and I have seen a fatal cellulitis occur. In Fig. 9 is shown the effect of tapping in a patient in whom all other attempts to dissipate oedema had failed (Figs. 1, 3, 6, and 7). It is particularly interesting to observe that the urinary output increased after many litres of oedema had been removed by tapping.

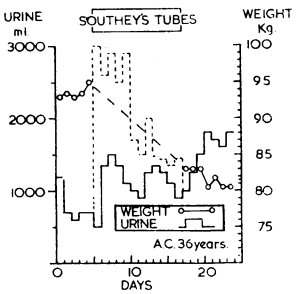

FIG. 9.—Relief of oedema with Southey's tubes.

Summary

It is a useful routine to use a salt-poor diet and, when renal function permits, one which contains 100–120 g. of protein. As a rule this does not cause disappearance of oedema, and in my hands the addition of a cation-exchange resin has not generally resulted in a great increase in diuresis. Mersalyl and ammonium chloride should then be given if the renal status permits. Oedema is at least temporarily dispelled by this form of treatment in over 50% of patients. If no beneficial result is obtained, dextran may be tried or a steroid hormone may be used, and if these fail tapping is done. It should be added that, at the time of writing, striking claims have been made for prednisolone, which, if substantiated, would make it the treatment of choice. With the hormones, and in particular prednisolone, there is some indication that cure and not merely palliation may result.

REFERENCES

Arneil, G. C. (1956). *Lancet*, **1**, 409.
Baldwin, D. S., McLean, P. G., Chasis, H., and Goldring, W. (1953). *A.M.A. Arch. intern. Med.*, **92**, 162.
Chasis, H., Goldring, W., and Baldwin, D. S. (1950). *J. clin. Invest.*, **29**, 804.
Epstein, A. A. (1917). *Amer. J. med. Sci.*, **154**, 638.
Greenman, L., Weigand, F. A., and Danowski, T. S. (1955). *Amer. J. Dis. Child.*, **89**, 169.
Heymann, W., Spector, S., Matthews, L. W., and Shapiro, D. J. (1955). Ibid., **90**, 22.
Lippman, R. W. (1951). *A.M.A. Arch. intern. Med.*, **88**, 9.
Luetscher, J. A., Deming, Q. B., Johnson, B. B., and Piel, C. F. (1953). *J. Amer. med. Ass.*, **153**, 1236.
Mollison, A. W., and Rennie, J. B. (1954). *British Medical Journal*, **1**, 893.
Widal, F., and Javal, A. (1903). *C.R. Soc. Biol. (Paris)*, **55**, 1532, 1639.