# CHLOROTHIAZIDE—ITS MODE OF ACTION AND ITS USE IN PATIENTS WITH OEDEMA

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The development of an effective oral diuretic is an important step forwards in therapeutics. To date the most effective diuretic agents have been the organic mercurial compounds administered by intramuscular injection. These have been associated with remarkably few side-effects. The very small mortality rate has occurred generally with intravenous administration.[1-4] Undesirable effects of the mercurial diuretics are the development of the salt-depletion syndrome and of hypokalaemic alkalosis, but the major disadvantage is the necessity of intramuscular injections. These compounds when given by mouth are less effective diuretics while increase in the dosage results in toxic effects, particularly in respect of the gastro-intestinal system. Axelrod and Pitts[5] have suggested that the mercurial diuretics specifically block the renal tubular reabsorption of chloride. There is an associated loss of sodium and water but not of bicarbonate. The potassium loss is variable.

A completely different biological approach was used with the introduction of acetazoleamide,* a heterocyclic unsub-

* Diamox.

stituted sulphonamide. It inhibits carbonic-anhydrase activity. This enzyme normally catalyses the conversion of carbon dioxide and hydrogen to carbonic acid. When this action is inhibited in the renal tubule there is depression of sodium and hydrogen-ion exchange resulting in an increased excretion of bicarbonate, while titratable acidity and ammonia diminish or disappear. In addition, potassium normally competes with hydrogen for excretion and during acetazoleamide administration the reduction in hydrogen-ion secretion is associated with an increased tubular secretion of potassium.[6, 7] Acetazoleamide administration therefore results in the excretion of an increased volume of alkaline urine rich in bicarbonate without an increase in chloride. *Pari passu* a state of hyperchloraemic acidosis develops. Since there is a reduction in the amount of bicarbonate filtered by the glomeruli,[8] with continued administration acetazoleamide soon loses its effect in so far as bicarbonate excretion is concerned. The reduced capacity to exchange hydrogen for sodium, however, persists, thus preventing the correction of the acidosis. In our own experi-

ence and that of others[9, 10] it has been an unsatisfactory diuretic.

Yet another series of diuretic agents in current use is the amino-uracils. Aminometradine† is an oral diuretic which is considered to act by directly interfering with the tubular reabsorption of sodium and/or chloride. Anorexia, nausea and vomiting are frequent effects.[11] More recently amisometradine‡ has been on trial.[12] It appears to be less liable to produce gastro-intestinal effects, but in our limited experience has not been as effective as the organic mercurials.

Chlorothiazide¶ is 6-chloro-7-sulphamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide—a substituted benzothiadiazine compound with a free sulphonamide group (Fig. 1). It was first synthesized by Novello and Sprague.[13] It was found to be
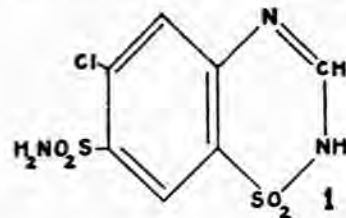


Fig. 1. Chlorothiazide (6.choro-7-sulphamyl-1, 2, 4-benzothiodiazine-1, 1-dioxide). The detailed structure of the heterocyclic ring of chlorothiazide is not known with certainty, although available evidence favours a structure with the 3, 4 double bond as the predominant form.

a potent carbonic-anhydrase inhibitor *in vitro*, yet the drug in animals has produced a large and almost equimolecular excretion of sodium and chloride without producing acidosis or alkalosis.[14]

In a preliminary report[15] we confirmed that the mode of action of chlorothiazide was similar to that of the organic mercurial compounds inasmuch as its major action was a tubular one increasing the urinary excretion of chloride. Despite its known *in vitro* action as an inhibitor of carbonic anhydrase, the slight increase in urinary excretion of bicarbonate indicated but slight activity in this respect in man. Several favourable reports on its use as an oral diuretic have appeared.[16-21]

This communication is concerned with (i) detailed short-term studies on the mode of action and (ii) the results of clinical experience in 33 patients with oedema.

### I. SHORT TERM STUDIES ON MODE OF ACTION

*Methods*

Studies were carried out in 3 patients. They included one with hypertensive congestive heart failure (No. 18, Table II) and 2 cases of the nephrotic syndrome (Nos. 22, 23, Table IV). All 3 patients had long-standing oedema.

After adequate control periods 2 g. of chlorothiazide were given by mouth. The effect on the glomerular filtration rate and the renal excretion of the electrolytes was followed for $2\frac{1}{2}$ hours in one patient, for $4\frac{1}{2}$ hours in another, and for 7 hours in the third. The duration of the periods was approximately 20, 30 and 60 minutes respectively. Urine was collected by means of indwelling catheters. The bladder was washed out with a known volume of sterile distilled water and air insufflation ensured complete emptying of the bladder. The urine was collected under toluol and then frozen. Blood was drawn $2\frac{1}{2}$ minutes before the mid-point of each period. Serum under oil was centrifuged and separated immediately and then analysed promptly or stored frozen. In the first 2 patients the glomerular filtration rate was measured as the clearance of

\* Mictine.    ‡ Roliscton.    ¶ Chlotride, Saluric and Diuril.

insulin, constant serum levels being maintained by means of a constant infusion apparatus. In the third patient endogenous creatinine clearance was used as a measure of the glomerular filtration rate.

*Biochemical Methods.* For sodium and potassium, flame photometry with a Barclay flame photometer using lithium as an internal standard. For chloride, Schales and Schales' method.[22] For carbon dioxide, urinary ammonia, and titratable acidity, Peters and Van Slyke's method.[23] For insulin, Schreiner's method.[24] For creatinine, Bonsnes and Taussky's method.[25] Blood urea and serum proteins were determined by standard laboratory methods of the Department of Chemical Pathology, University of Cape Town.

*Results*

In all 3 cases the administration of chlorothiazide produced marked alterations in the electrolyte pattern of the urine. The changes in cases 18 and 23 are illustrated graphically in Figs. 2 and 3. The most striking alterations are in the urinary excretion of sodium and chloride, the chloride excretion exceeding the sodium. Fig. 4 illustrates the events in case 18. The increase in urinary chloride begins within $\frac{1}{2}$ hour and there is a stepwise increase until a peak is reached $2\frac{1}{2}$ hours after the administration of chlorothiazide. Thereafter the excretion continues at a high though gradually decreasing level throughout the duration of the experiment. Sodium behaves similarly, but potassium increases to a lesser extent (Fig. 5). Urine volume shows a similar increase. Further observations have shown that this enhanced excretion continues for a variable period of time, which is commonly up to 8 hours. In case 18, the glomerular filtration rate remained unchanged (Fig. 4), while in case 23 there was a slight rise in the glomerular filtration rate during the first and second periods following chlorothiazide. Case 22 was followed for 7 hours with hourly periods, and similar electrolyte changes
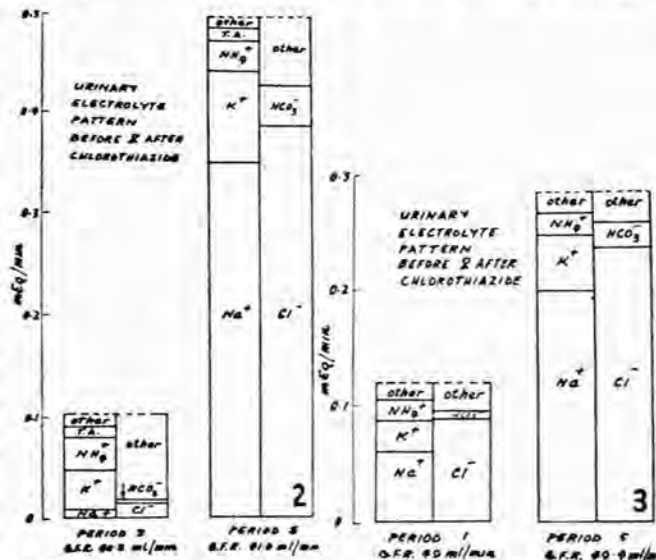


Fig. 2. Case 18. This illustrates the marked changes in urinary electrolyte excretion after 2 g. of chlorothiazide in a patient with hypertensive heart failure. The glomerular filtration rate is comparable in the two periods.

Fig. 3. Case 23. The changes in urinary electrolyte excretion are less pronounced in this case of the nephrotic syndrome. The glomerular filtration rate is comparable in the two periods.

were encountered without significant alteration in the glomerular filtration rate.

Fig. 6 illustrates the changes in case 18 in the bicarbonate titratable acidity and in urinary ammonia following the administration of chlorothiazide. There was a rise in the urinary pH by the second period in case 18 and a temporary rise during the first period in case 23

Thus of the cations, apart from sodium, there was a lesser increase in potassium while there was little change in ammonia and a slight fall in titratable acidity. Of the anions the striking chloride increase completely overshadowed the slight rise in urinary bicarbonate. There was no increase in phosphate excretion in case 18.

*Conclusion.* These figures illustrate that the mode of action of chlorothiazide is primarily on the renal tubule, resulting in an increase in the excretion of chloride, sodium, and water. The excretion of sodium and chloride is almost equimolecular although chloride usually exceeds sodium. The potassium excretion increases to a lesser extent. There is a slight increase in the urinary bicarbonate and an associated rise in the pH of the urine.

## II. CLINICAL EXPERIENCE IN 33 PATIENTS WITH OEDEMA

All patients, except 2, were admitted to the wards of Groote Schuur Hospital. Judgment of the effectiveness of chlorothiazide was made by clinical assessment, by observation of change in weight, and by urine output in relationship to fluid intake. In some cases sodium, potassium and chloride excretion was measured. A careful watch was kept on the familiar pitfalls of routine ward collections of 24-hour urine samples. In assessing the action of a diuretic, the effects of bed rest, diet and previous therapy had to be considered; for example, considerable diuresis and loss of weight while at rest was
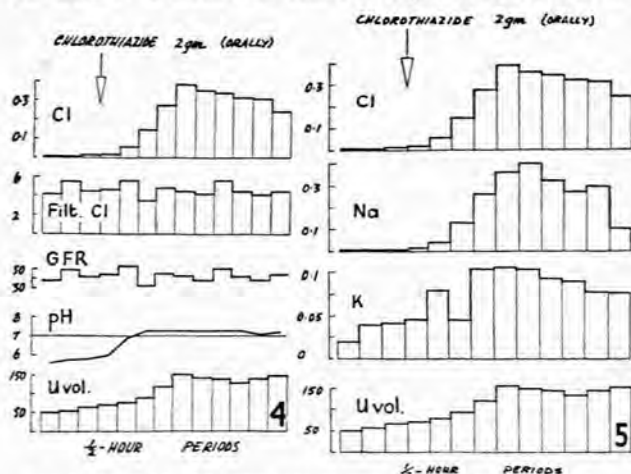
*Fig. 4.* Case 18. Cl=chloride in urine, mEq./min. Filt. Cl= Filtered load, mEq./min. GFR=glomerular filtration rate (CIN), ml./min. U vol.=urine volume, ml. The chloride excretion increases in stepwise fashion after the administration of 2 g. of chlorothiazide. The glomerular filtration rate and the filtered load of chlorine remain relatively constant. The rise in pH is illustrated on this chart. (The true urine volume is less 40 ml./period—the volume of bladder rinse.)

*Fig. 5.* Case 18. Cl=chloride in urine, mEq./min. Na= sodium in urine, mEq./min. K=potassium in urine, mEq./ min. U vol.=urine volume, ml. The sodium and chloride excretions follow each other. There is a slight increase in potassium excretion as well. The potassium scale is larger than that of the sodium and the chloride.
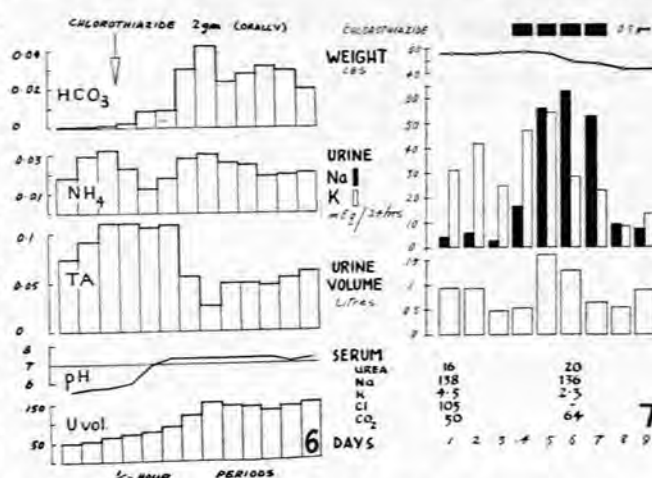
*Fig. 6.* Case 18. $HCO_3$=$HCO_3$ in urine, mEq./min. $NH_4$= ammonia and amino acids in urine, mEq./min. TA=titratable acidity, mEq./min. U vol.=urine volume, ml. This illustrates the slight changes in urinary bicarbonate, ammonia and titratable acidity following chlorothiazide.

*Fig. 7.* Case 28, nephrotic syndrome: Prompt increase in urinary sodium and potassium followed 0·5 g. of chlorothiazide. On the first day potassium loss exceeded sodium loss. Note the rapid development of hypokalaemia.

noted in one patient before the administration of chlorothiazide. The diet was salt-restricted ($\pm 30$ mEq. per 24 hours) except in case 4, where the salt intake was unrestricted.

The daily dosage used is indicated in Tables II, III and IV. Varying dosage schemes were used. The results in the 33 patients are summarized in Table I. The relevant clinical

### TABLE I. RESULTS OF TREATMENT

| Aetiology | | No. of Patients | Good Response | Fair Response | Doubtful Response | No Response |
|---|---|---|---|---|---|---|
| Cardiac Oedema (Table II) | .. | 21 | 13 | 2 | 2 | 4 |
| Renal Oedema (Table III) | .. | 10 | 4 | 2 | — | 4 |
| Hepatic Oedema * (Table IV) | .. | 2 | 2 | — | — | — |
| Total | .. | 33 | 19 | 4 | 2 | 8 |

* One with associated constrictive pericarditis

features and the response in the patients with cardiac, hepatic and renal oedema are summarized in Tables II, III and IV. Examples of effective chlorothiazide therapy are illustrated in Figs. 7, 8, 9 and 10.

Of the 21 cases with cardiac oedema (Table II) 11 were due to rheumatic heart disease, 3 to each of ischaemic heart disease and hypertensive heart disease, and 1 to each of syphilitic aortic incompetence, subacute cor pulmonale, chronic cor pulmonale, and right heart failure in a grossly obese subject with pulmonary hypoventilation. There was a good response in 13 patients; this was assessed by significant weight loss, by a diuresis of up to 3 litres in the succeeding 24 hours, sodium loss of up to 400 mEq. over the same time, and clinical improvement. In 2 the response was assessed as fair, in 2 doubtful. In 4 patients there was no response at all; 3 of these had chronic rheumatic valvular disease with gross congestive heart failure (8, 9 and 11) and the 4th (16) had intractable congestive failure following myocardial infarction. Cases 9 and 11 were moribund at the time of treatment. Case 8, who was in acute congestive heart failure,

## TABLE II. CARDIAC OEDEMA

| No. | Race | Sex | Age | Diagnosis | Oedema | Duration of oedema | JVP cm. above angle of Louis | Creps. at bases | Liver enlargement, fingerbreadths down | Serum albumin g./100 ml. | Blood urea mg./100 ml. | Dose, g. 24/hr | Maximum sodium loss mEq./24 hr | Loss or gain in weight lb./days | Response | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | E | F | 42 | Rh., MI | ++ | 2 yr | 10+ | + | 3 | 3·8 | 51-23 | 1-2 (b) | 160 | -7½/12 | Good | Previously refractory to Mersalyl. |
| 2 | C | M | 44 | Rh., MS | ++ | mths | 5 | + | 2 | 3·7 | 40-? | 2x | — | -12/10 | Good | Poor response to Mersalyl before adm. |
| 3 | E | M | 58 | Rh, MI, AI | + | 5 mth (a) | 10+ | + | 3 | 3·8 | 43-35 | 1 | — | -7½/8 | Good | Refractory to Mersalyl before adm. |
| 4 | E | F | 47 | Rh, MI, AI | + | mths | 6 | ++ | 2 | 4·3 | 33-12 | 2 (c) | 166·6 | -7/8 | Good | Complicating S.B.E. suspected. |
| 5 | C | M | 48 | Rh, MS, AS, AI | ++++ | 1 wk | 15 | + | 1 | 3·1 | 67-60 | 1 | — | -8/4 | Good | Complicating S.B.E. suspected. |
| 6 | C | M | 54 | Rh, MS, MI | ++++ | 8 mth | 10+ | — | 4 | 2·8 | 16-32 | 2 (b) | 433 | -11/7 | Good | See Fig. 8. |
| 7 | E | M | 52 | Rh, MI, AI | ++++ | mths | 10+ | ++ | 5 | 3·4 | ?-130 | 2-1 | — | -4½/3 | Good | Later refractory to 5 g. daily. |
| 8 | C | M | 13 | Rh, MS, MI | ++++ | 2 wk (a) | 10+ | ++ | 5 | — | 18-50 | 1-2 (b) | 56 | 0/4 | None | Responded better after Mersalyl. |
| 9 | E | F | 40 | Rh, AS | ++ | 1 mth + (a) | 4 | ++ | 2 | 3·6 | 35-91 | 2 (c) | — | +2/10 | None | Refractory to all treatment. |
| 10 | E | M | 44 | Rh, AI | ++++ | yrs | 5 | ++ | 4 | 2·2 | 102-158 | 2 (d) | — | -2½/7 | Fair | Refractory to all treatment. |
| 11 | C | F | 67 | Rh, MI | ++ | 2 mth (a) | 10+ | ++ | 2 | 3·8 | 81-32 | 2 (c) | — | +1½/9 | None | Previously poor response to Mersalyl. |
| 12 | C | M | 51 | S. AI | + | 2 wk | 5 | + | 3 | — | 103-39 | 2 (c) | — | -2½/11 | Fair | |
| 13 | E | M | 49 | Chron. CP | ++++ | 3 yr | 10+ | ++ | 4 | — | 61-37 | 1 | — | -7/6 | Good | Previously poor response to Mersalyl. |
| 14 | E | F | 53 | PE, CP | + | 1 wk | 4 | ++ | 3 | 3·8 | 10-20 | 1 | — | -2½/7 | Good | Possible underlying fibro-elastosis. |
| 15 | E | M | 54 | M Inf. | ++ | 1 yr | 4 | — | 1 | 4·4 | 55-52 | 1 | — | -6/14 | Good | Claimed better than Mersalyl. |
| 16 | E | M | 60 | M Inf. | ++ | mths | 10+ | ++ | 3 | 4·4 | 38-? | 1 | — | +2/7 | None | Refractory to Mersalyl. |
| 17 | E | M | 54 | IHD | + | 2 wk | 6 | ++ | 2 | 3·9 | 58-51 | 1 (d) | — | -5½/5 | Good | Poor response to Mersalyl. |
| 18 | E | M | 51 | EH | ++++ | mths | 10 | ++ | 3 | 3·7 | 30-50 | 2 (d) (b) | — | -10½/6 | Good | No effect on hypertension. |
| 19 | C | M | 12 | MH, URD | ++++ | mths | 10+ | ++ | 3 | — | 28-? | 2 | — | -1/2 | Doubtful | Later nephrectomy performed. |
| 20 | C | F | 46 | MH | ++ | 4 mth | 4 | ++ | 3 | 3·8 | 33-34 | 1 | — | -1/2 | Doubtful | Diuresis 3 litres after single dose. |
| 21 | E | M | 51 | HS, O | ++ | 8 yr | 6 | ++ | ? | 3·9 | 41-51 | 2 (d) | — | -11/8 | Good | KCl therapy because long administration. |

## TABLE III. HEPATIC OEDEMA

| No. | Race | Sex | Age | Diagnosis | Oedema | Duration of oedema | JVP cm. above angle of Louis | Creps. at bases | Liver enlargement, fingerbreadths down | Serum albumin g./100 ml. | Blood urea mg./100 ml. | Dose, g. 24/hr | Maximum sodium loss mEq./24 hr | Loss or gain in weight lb./days | Response | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 32 | C | M | 30 | Cirrhosis of the Liver | ++++ | 3/12 | 9 | + | 1 | 2·7 | 26 | 2 (d) | 160 | -4½/7 | Good | Liver biopsy confirms diagnosis. |
| 33 | C | M | 21 | Parenchymatous Liver Disease with Constrictive Pericarditis | ++++ | 3/12 | 12+ | ++ | 3 | 2·0 | 12 | 2-1-2 (d) | 122·5 | -7/6 | Good | |

## TABLE IV. RENAL OEDEMA

| No. | Race | Sex | Age | Suspected Aetiology | Oedema | Duration of oedema | Hypertension | Serum albumin g./100 ml. | Serum cholesterol mg./100 ml. | Haematuria microscopic | Blood urea mg./100 ml. | Dose, g./24 hr | Maximum sodium loss mEq./24 hr | Loss or gain in weight lb./days | Response | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 22 | B | F | 29 | Type II | ++++ | 1 yr | No | 2·5 | 682 | No | 78-43 | 2 (d) | 116 | -11¾/14 | Initially good | Later refractory to all therapy. |
| 23 | E | F | 41 | Type II | ++++ | 4 mth | No | 2·3 | 480 | No | 48-50 | 2 | 93·1 | -5/7 | Initially good | Later refractory to all therapy. Fall in serum potassium from 4·2 to 3·2. |
| 24 | E | F | 12 | Type II | ++ | 5 mth | No | 2·7 | 357 | No | 21-? | 1-2 (d) | — | +½/12 | None | Refractory to steroid therapy. |
| 25 | C | F | 53 | Type II | ++++ | 1 mth | No | 2·7 | 605 | No | 40-? | 2 (b) | — | +1½/7 | None | Refractory to all therapy. |
| 26 | E | M | 2 | Type II | ++++ | 3 wk | No | 0·6 | 760 | No | 25-42 | ½ (d) | — | +1½/6 | None | Refractory to all therapy. |
| 27 | E | F | 2 | Type II | ++++ | 4 mth | No | 1·9 | 550 | No | 17-53 | 1 (d) | — | -½/5 | None | Refractory to all therapy |
| 28 | E | F | 6 | Type II | ++ | +1 yr | Yes | 0·9 | 840 | Yes | 20-40 | ½ | 63·1 | -6½/6 | Good | Hypokalaemic alkalosis developed. |
| 29 | C | M | 32 | Type I | ++ | 10 mth | Yes | 2·3 | 370 | No | 47-94 | 1 (e) | — | -3½/7 | Good | Confirmed by renal biopsy. |
| 30 | C | M | 29 | Type I | ++++ | 1 mth | No | 2·8 | 395 | Yes | 253-255 | 1 | — | -2½/5 | Fair | Autopsy confirms diagnosis. |
| 31 | E | M | 53 | Dissd. lupus eryth. | ++++ | 9 mth | Yes | 2·3 | 567 | Yes | 50-64 | 2 | 52·5 | -1½/4 | None | Died 3 months later with massive oedema. Refractory to all treatment. |

(a) = Previously in CCF. (b) = Intermittent omission of daily dose. (c) = Every third day (d) = In 2 doses, a.m. and p.m. (e) = Alternate days.

JVP = Jugular venous pressure. Rh = Rheumatic heart disease. MI = Mitral incompetence. MS = Mitral stenosis. AI = Aortic incompetence. AS = Aortic stenosis. S = Syphilis. CP = Cor pulmonale. PE = Pulmonary embolism. M Inf = Myocardial infarction. IH = Ischaemic heart disease. EH = Essential hypertension. MH = Malignant hypertension. UR = Unilateral renal disease. HS = Hypoventilation syndrome. O = Obesity, Types I and II = Types I and II nephritis. SBE = Subacute bacterial endocarditis. Under Race, E = European, C = Coloured, B = Bantu.
Where 2 blood-urea figures are given they refer to values before and after treatment.

showed no weight alteration, an unimpressive diuresis, but a sodium loss of 58 mEq. in 24 hours.

Of 10 cases with the nephrotic syndrome (Table IV) 7 were due to type-II nephritis, 2 to type-I nephritis, and 1 to disseminated lupus erythematosus. The response was good in 4 and fair in 2. In 4 there was no response at all; there was no obvious reason for this; the serum-electrolyte concentrations were normal but measurements of the glomerular filtration rate were not available in most of these patients.

One patient with cirrhosis of the liver responded well, and another with constrictive pericarditis and cirrhosis of the liver also responded well (Table III).

Two cases with the nephrotic syndrome (22 and 23) and 2 with cardiac oedema (7 and 15) responded initially and later became refractory. Four patients with cardiac oedema (1, 2, 3 and 13) were clearly resistant to mersalyl and responded well to chlorothiazide. Case 25 with the nephrotic syndrome had responded to mersalyl but did not respond to chlorothiazide. Case 8 with cardiac oedema responded moderately well to mersalyl but had had chlorothiazide on the previous day— during which he excreted 56 mEq. of sodium. A potentiating action is a possible explanation. This also might have been the case in one other patient.

There were no side-effects. No patients complained of anorexia, nausea or vomiting and there was no evidence of leucopenia or liver or renal damage except for a rise in blood-urea concentration in some of our patients. Two of these patients, with congestive heart failure, were moribund and the 3rd had disseminated lupus erythematosus. In 3 patients with the nephrotic syndrome daily measurement of the protein loss in the urine showed no alteration during chlorothiazide therapy.

Studies of serum electrolytes in most of the patients before and after treatment showed little change. A fall in serum potassium concentration was noted in 9 patients and was moderate except in cases 28 and 32, where levels of 2·3 and 2·6 mEq. per litre were recorded at the end of therapy.

(Apart from the use of chlorothiazide in patients with oedema we have administered the drug to one patient with periodic paralysis and a few patients with hypertension. In the case of periodic paralysis the administration of 1 g. of chlorothiazide after 42 days on a low-sodium diet (26 mEq. per day) resulted in the loss of 270 mEq. of sodium in the urine. The administration of 0·5 g. of chlorothiazide to 3 normal subjects on a similarly sodium-restricted diet resulted in a loss of sodium, potassium and chloride in the urine.[28] The sodium loss in the 3 subjects amounted to 64, 155 and 69 mEq. respectively.

Our experience with the use of chlorothiazide in the management of hypertension is too limited to state any definite conclusions. In 6 patients with essential hypertension the drug alone appeared to be associated with a significant fall in blood pressure in only one and, in that instance bed rest and a low-sodium diet had been maintained for only 1 week. In 2 other patients receiving mecamylamine the administration of chlorothiazide was associated with a further fall in blood pressure and the dose of mecamylamine had to be reduced. Harrington et al.[27] have ascribed this effect to possible diminution in excretion of mecamylamine.)

### DISCUSSION

Beyer et al.[14] have stated that in vitro studies have shown that chlorothiazide is 30 times more potent a carbonic-anhydrase inhibitor than acetazoleamide and therefore it is surprising to find that in man its action in this respect is extremely poor. It resembles the mercurial group of drugs in that its prime effect is on the renal tubule with excretion of chloride and sodium. Others have confirmed these effects. In addition we have noted the rapid development of hypokalaemic alkalosis following chlorothiazide therapy, an effect which again resembles the action of the mercurial diuretics.

There are, however, points of difference. We have noted possible potentiation of the action of the mercurial diuretics, and, more important, in some cases chlorothiazide was effective when mersalyl had failed. While the effects on the
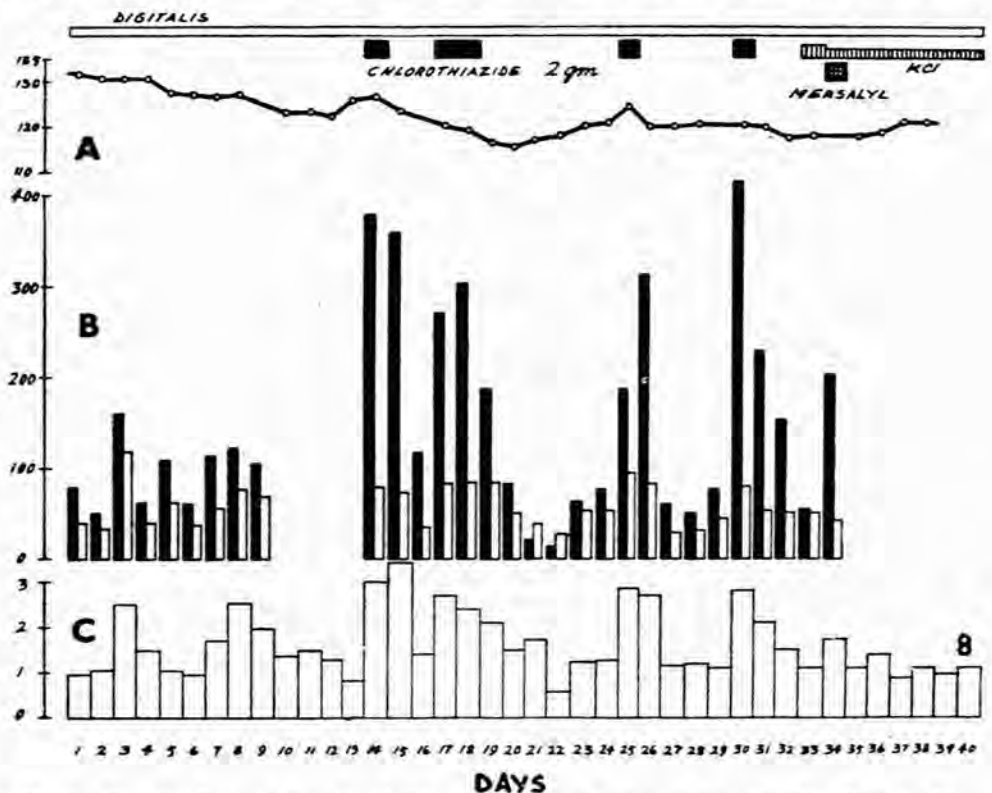


Fig. 8. Case 6. Congestive cardiac failure—mitral valve disease. A=weight, lb. B=urine Na (black columns) and K (white columns), mEq./24 hrs. C=urine volume, litres. Digitalis therapy was associated with a loss of sodium, but the addition of chlorothiazide in 2·0 g. dose was associated with a striking increase in urinary sodium to as much as 400 mEq. per day. The sodium loss from single doses appeared to continue for at least 48 hours. Potassium excretion was relatively unaffected although serum potassium had fallen to 3·6 mEq. per litre.

excretion of water, sodium, chloride and potassium are very similar to those which are encountered after the administration of the organic mercurial diuretics the rise in urinary pH is unlike mercurial action. In addition Beyer[28] states that chlorothiazide is markedly active under experimental conditions of sodium bicarbonate alkalosis, while the mercurial diuretics are essentially ineffective under these conditions. Furthermore 'BAL'* has no effect on chlorothiazide diuresis whereas it markedly depresses the sodium and chloride excretion induced by the mercurial diuretics. Laragh et al.[17] has noted a further point of difference in that 'free' water clearance is increased in mercurial-induced diuresis but not in chlorothiazide-induced diuresis. Apart from these differences we have observed that in case 22, where amisometradine failed to induce a diuresis when given in adequate dosage (up to 3·2 g. daily), chlorothiazide was immediately effective. It is possible that its mechanism of action on the renal tubule differs not only from that of the mercurial diuretics but also from that of the amino-uracil diuretics.

The diuresis starts within 2 hours of administration of the drug and the duration of action usually extends maximally over the next 8 hours, but there seems to be a prolongation of the effect for a full 24 hours and in an occasional case to 48 hours (Fig. 8). While some have recommended that the dose should be divided into a morning and an afternoon dose, this method of administration does not appear to us to have

* British Antilewisite.

any advantage over a single dose administered in the morning. A single dose of 1·0-2·0 g. was administered daily in 12 adult patients. In 8 of them 1·0 g. daily produced an adequate response, while in 4 others 2·0 g. daily appeared to be more satisfactory. However, 1·0-2·0 g. every third day appeared to be an effective therapeutic regime in certain patients and carried less risk of hypokalaemia. The unsupervised prolonged use of this drug may be dangerous; and dosage may well have to be altered repeatedly to suit individual patients.

It is obvious that chlorothiazide is an oral diuretic which is effective in many cases of cardiac, renal and hepatic oedema. In our judgment it is frequently as effective as the organic mercurials administered parenterally in their usual doses. In this series of 33 patients the drug appeared to be devoid of toxic effects. The rapid development of hypokalaemic alkalosis, especially when the drug is given daily, should be borne in mind (Fig. 7). While Laragh et al.[17] noted that mild to moderate hypokalaemic alkalosis developed in most of their 32 patients, this complication was less frequently encountered in our patients. This may be attributed to the fact that, whereas their patients were maintained on a diet rigidly restricted to not more than 12 mEq. of sodium per 24 hours, our patients were receiving not more than 30 mEq. per 24 hours. Sherlock et al.,[29] however, have reported the occurrence of hypokalaemia in patients with cirrhosis of the liver and ascites on a dietary sodium intake of 22 mEq. daily, while Bayliss et al.[30] state that hypokalaemia might develop during intermittent treatment when chlorothiazide is given on 4 consecutive days each week, and could be induced in patients having a sodium intake of 214 mEq. per day! On occasions, however, in some of our patients, potassium loss exceeded the sodium loss (Fig. 10). In cases with marked sodium depletion it is to be expected that the predominant cation excreted would be potassium rather than sodium. Hypokalaemia may be dangerous, not only in itself, but also by increasing sensitivity to digitalis. Hypokalaemia can be corrected by potassium supplementation which, however, should be administered with caution to markedly oedematous patients with hyponatraemia. The wider spacing of doses, viz., 1-2 g. every third day or 1-2 g. daily for, say, 3 days followed by a similar period without treat-
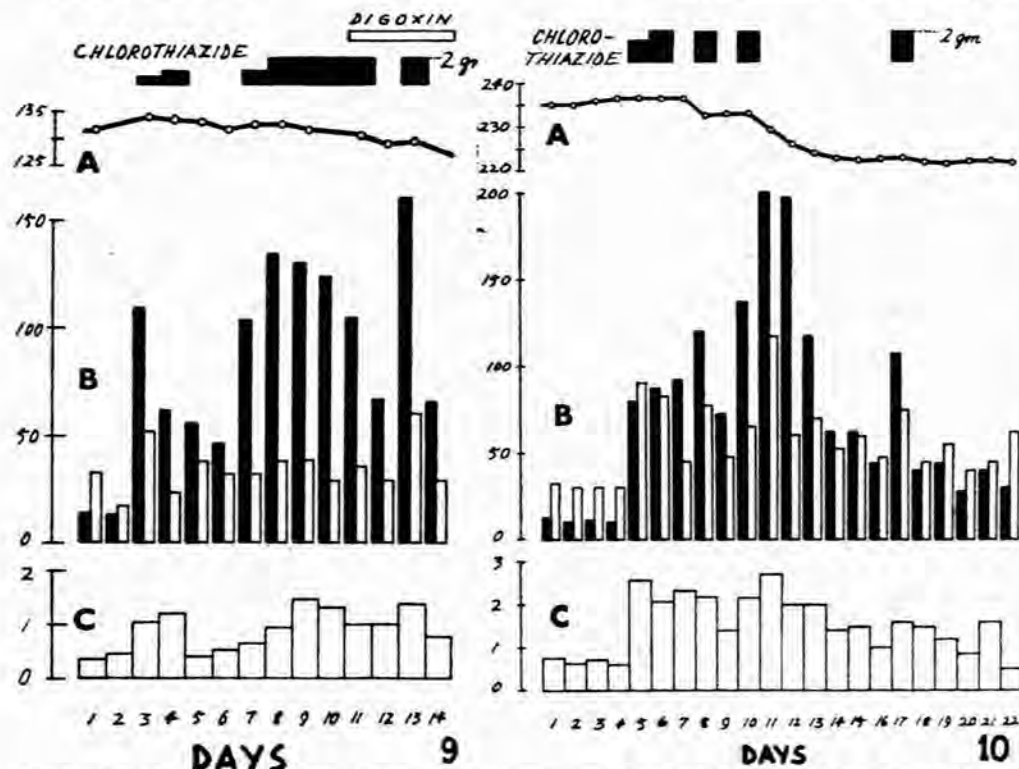


Fig. 9. Case 1. Congestive heart failure—mitral incompetence. A=Weight, lb. B=urine Na (black columns) and K (white columns), mEq./24 hrs. C=urine volume, litres. Even with the initial dose of 0·5 g. of chlorothiazide the marked and prompt increase in the urinary sodium loss is evident. 2·0 g. produced a pronounced naturesis. The potassium excretion increased only slightly.

Fig. 10. Case 22. A=Weight, lb. B=urine Na (black columns) and K (white columns), mEq./24 hrs. C=urine volume, litres. The prompt effect of chlorothiazide on sodium and water excretion in a patient with the nephrotic syndrome is clearly evident. Note, too, the marked increase in potassium loss. This patient later became refractory to chlorothiazide.

ment, may be advisable. In cases receiving protracted heavy dosage the development of listlessness, apathy, weakness and diminution or loss of tendon reflexes should be watched for, serum electrolyte concentrations should be determined, and monitoring with the electrocardiogram for the changes of hypokalaemia is advisable.

There appear to be a few contra-indications to the use of chlorothiazide in oedematous patients, as follows: (1) Pre-existing hypokalaemia and (2) marked elevation of the blood-urea concentration (although several of our patients with blood ureas ranging between 50 and 100 mg.% received chlorothiazide without obvious deterioration). (3) In patients with cirrhosis of the liver and ascites it should be administered with caution. Sherlock et al.[29] have emphasized the development of hypokalaemia in such patients with, in some, the appearance of hepatic foetor, tremor, confusion and, in one case, the loss of consciousness—the usual features of hepatic pre-coma and coma.

It is clear that certain patients with oedema who responded well initially became refractory to treatment. The reasons for this are not apparent. Certain patients who were refractory to all other diuretic therapy did not respond to chlorothiazide even in doses of as much as 5·0 g. daily. We have little reason to recommend a dose above a maximum of 2·0 g. daily.

## SUMMARY

1. Short-term studies in 3 patients suggest that chlorothiazide acts by inhibiting the renal tubular reabsorption of chloride and sodium. In this it resembles the organic mercurial diuretics, but there is a rise in urinary pH and a slight increase in the urinary bicarbonate.

2. Clinical experience in 33 patients with oedema is reported. The results indicate that in a high proportion of cases it is an effective oral diuretic. A maximum daily dose of 1-2 g. is advisable in the adult. This may be given as a single dose or twice daily.

3. In this series of patients chlorothiazide administration was devoid of toxic effects. The main complication is hypokalaemia, and this may necessitate supplementary potassium

chloride and the adjustment of the dosage schedule to the requirement of a particular patient. Prolonged unsupervised use of the drug is to be avoided.

4. Patients may become refractory to chlorothiazide after having previously responded well.

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