Chlorothiazide is probably contraindicated in patients with cirrhosis (Read *et al.*, 1958).

The problems associated with long-term mercurial therapy are well known (DeGraff and Nadler, 1942; Ben-Asher, 1946), but from a practical point of view their extensive use over many years has shown them to be safe and effective. If further studies confirm the efficacy of oradon as an oral mercurial with a low incidence of gastro-intestinal irritation it should provide a safe and adequate oral treatment for the maintenance of mild or moderately severe cases of oedema, particularly in the conditions of general practice, where frequent electrolyte determinations are not possible. It should be given for five to six days in each week, and this intermittent therapy will not interfere with digitalis or antihypertensive therapy.

Combined therapy should be restricted to resistant cases and preferably be carried out in hospital.

The control of fairly severe cases may be attained with the alternate use of the two drugs, giving chlorothiazide for three days in each week and oradon with potassium for the other four. This might well give maximum control with minimum electrolyte imbalance.

Summary

Oral diuretics in the form of chlorothiazide and 3-hydroxy - mercuri - 2 - methoxy - 1 - succinimidopropane, theophylline hydrate (oradon), a new oral mercurial, have been carefully studied alone and in combination in a small series of patients with oedema.

The potency of each diuretic was shown, and a potentiation was demonstrated when the drugs were used in combination. This combination was of particular value when tolerance had developed to the individual agents.

An average of 36.6% of the ingested organic mercury was recovered from the urine, showing it to be much more potent than existing oral mercurials.

The effect of chlorothiazide on the renal excretion of potassium is discussed, and suggestions for various therapeutic regimes are made.

We thank Professor A. Kekwick for his stimulation and encouragement and for providing the facilities for research; Dr. T. Chalmers for his constant help and criticism; Mr. Pawan and Miss Warne for assistance with electrolyte estimations; Mr. Stephens and Mr. Jenkins for mercury and chlorothiazide estimations; and the nursing staff and dietitians for their patient help. Supplies of oradon were kindly supplied by J. Wyeth and Brother, Limited.

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CLINICAL EVALUATION OF HYDROCHLOROTHIAZIDE

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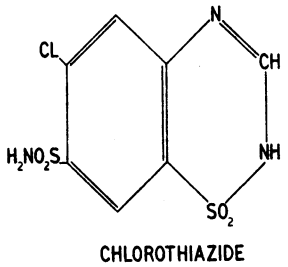
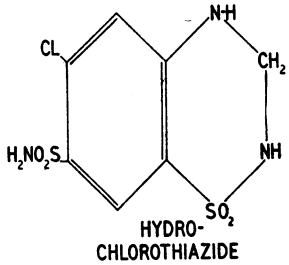
Chlorothiazide ("chlotride," "diuril," "saluric") has over the past twelve months become established as a powerful and useful oral diuretic. Its primary action is to increase the rate of chloride excretion (Slater and Nabarro, 1958), and in this respect it resembles the action of the mercurial diuretics (Pitts and Sartorius, 1950). *In vitro* studies have demonstrated that chlorothiazide has a carbonic anhydrase inhibitory effect (Beyer *et al.*, 1957), and this action has been demonstrated in short-term studies *in vivo* (Slater and Nabarro, 1958). This secondary action has been suggested as an explanation for the considerable hypokalaemia with which the administration of this drug may be associated (Slater and Nabarro, 1958). Certainly hypokalaemia is the most important side-effect of chlorothiazide, and when used in the treatment of cirrhosis hepatis it is so common as to be almost inevitable (Read *et al.*, 1958); furthermore, the hypokalaemia may not be corrected by giving as much as 6 g. of potassium chloride by mouth daily, which is as large a dose as the average person can tolerate.

Hydrochlorothiazide* (6 - chloro - 7 - sulphamyl - 3,4 - dihydro-1,2,4,-benzothiadiazine-1,1,-dioxide), which is closely related chemically to chlorothiazide, is a new oral diuretic that has recently become available (see



CHLOROTHIAZIDE



HYDRO-CHLOROTHIAZIDE

Formulae). Animal experiments have suggested that this drug is well tolerated by mouth, is of unusually low toxicity, and is ten to twenty times more potent than chlorothiazide. Little inhibitory activity to carbonic anhydrase has been demonstrated *in vitro*, and it has been reported to have less effect on the diuresis of

*Generic name approved in U.S.A.

potassium (de Stevens *et al.*, 1958). An oral diuretic of this potency without the side-effect of hypokalaemia would obviously be a major advance in the therapeutic management of patients with oedema. As the diuretic effect of chlorothiazide is already established, we have undertaken a clinical trial to compare the effects of hydrochlorothiazide and chlorothiazide.

Material and Methods

The response of 21 in-patients with oedema to four-day courses of chlorothiazide and hydrochlorothiazide (" esidrex ") has been studied. The cause of the oedema was as follows:

	No. of Patients
Congestive cardiac failure	11
Laennec's (portal or post-necrotic) cirrhosis complicated by ascites and peripheral oedema	4
Cardiac cirrhosis secondary to rheumatic heart disease with tricuspid incompetence	1
Nephrotic syndrome secondary to nephritis	1
Constrictive pericarditis	1
Acute nephritis and carditis with congestive cardiac failure	1
Obstruction of inferior and superior venae cavae as a result of metastases from a carcinoma of kidney	1
Oedema of uncertain aetiology (? induced by cortisone replacement therapy following adrenalectomy)	1

The trial was introduced by a four-day control period of bed rest and salt restriction alone. The initial drug chosen to begin therapy was alternated so that half the cases started treatment with chlorothiazide and the other half with hydrochlorothiazide: thus after the initial control period half of the patients received four days' diuretic therapy with chlorothiazide in a dose of 0.5 g. twice daily. This was followed by an interval of two to four days during which no diuretic was given. A four-day course of hydrochlorothiazide in a dose of 50 mg. twice daily then followed. In the remaining cases hydrochlorothiazide was chosen to begin therapy so that the order of treatment was reversed. This was done because it is well known that in a sequential comparison of diuretics the first drug given has an inevitable advantage.

In a few instances the preliminary period of observation had to be curtailed on account of the severity of the patient's condition. No potassium supplements were given during the period of study. The sodium intake of all patients was restricted to 25 mEq a day (1.5-g. salt diet) and the daily fluid intake was constant at 1,500 ml. The patients were weighed daily and 24-hour collections of urine were made throughout the period of observation. In all patients the urinary electrolytes (sodium, potassium, and chloride) were measured daily, and the serum electrolytes (sodium, potassium, chloride, and bicarbonate) twice weekly. Weekly estimations of haemoglobin, differential white count, blood urea, and tests of hepatic function were made. The sodium and potassium levels were measured by flame photometry and the chlorides by potentiometric titration, using a silver electrode.

Tables I and III show the therapeutic response to the two diuretics, as judged by reduction of weight (probably the best single index of progress), increase of urine flow, diminution of oedema, and a general clinical assessment. The patients have been segregated into two groups on the basis of the results.

Group 1

Group 1 (Table I) comprised 12 patients, nine of whom were in heart failure. The group was characterized by the fact that in all cases the oedema was of comparatively recent onset, and none of the patients had previously been subjected to dietary salt restriction. The therapeutic response was good, without exception, to both hydrochlorothiazide and chlorothiazide. The mean daily weight loss during hydrochlorothiazide therapy was 2 lb. (907 g.); that during chlorothiazide was 1.6 lb. (725 g.). Sodium and chloride ion excretion was much increased with both drugs, and these two substances were present in the urine in roughly equivalent amounts. (Table II shows mean values of electrolyte and water output.) Urinary potassium excretion was not materially increased. There was no biochemical disturbance of the serum

TABLE I.—*Clinical Details and Response to Therapy of* 12 *Patients in Group I*

Case	Diagnosis	Response to Treatment	Remarks
		Group 1	
1	Pulmonary heart disease	Good. No weight loss during initial 4-day control period; 20 lb. (9·1 kg.) lost in 12 days' diuretic therapy	Equimolecular diuresis of sodium and chloride on both drugs. Hydrochlorothiazide used first and produced the major diuresis (see Fig. 1)
2	,, ,,	Good	Fourfold increase in urinary volume on hydrochlorothiazide. Patient lost 5 lb. (2·27 kg.) in 4 days. Trial then abandoned on account of haemorrhage from carcinoma of bladder, requiring blood transfusion
3	,, ,,	Good. 16 lb. (7·25 kg.) lost in 12 days' diuretic treatment	Equimolecular diuresis of sodium and chloride. Chlorothiazide used first with fair response. Hydrochlorothiazide used during second period produced greater diuresis
4	,, ,,	Good. 34 lb. (15·4 kg.) lost in 10 days	Similar response. No initial control period possible on account of severity of patient's condition. Major diuresis produced during first trial period on chlorothiazide
5	,, ,,	Good. 17 lb. (7·7 kg.) lost in 12 days	Similar response. Slightly greater diuresis during first trial period on chlorothiazide
6	Rheumatic heart disease	Good. 16 lb. (7·25 kg.) lost in 8 days	Equimolecular diuresis of sodium and chloride
7	Pulmonary heart disease	Good (see Discussion)	Equimolecular diuresis of sodium and chloride: potassium loss appreciable but less than when on mersalyl
8	Hypertensive heart disease	Good. 15 lb. (6·8 kg.) lost	Equimolecular diuresis of sodium and chloride
9	,, ,,	Good. 10 lb. (4·5 kg.) lost in 8 days' diuretic treatment	Similar. Weight loss not marked as patient had only slight oedema
10	Nephrotic syndrome	Good. 34 lb. (15·4 kg.) lost in 14 days	Similar equimolecular diuresis of sodium and chloride. Major diuresis occurred during the first trial period on hydrochlorothiazide
11	Acute nephritis and carditis	Good. 15 lb. (6·8 kg.) lost in 8 days	Disproportionate water diuresis on hydrochlorothiazide (see text)
12	Cortisone-induced oedema	Good. 18 lb. (8·16 kg.) lost in 8 days' diuretic treatment. No weight lost in control period	Significantly better response to hydrochlorothiazide although this drug was used in second trial period (see text)

TABLE II.—*Mean Effect of Hydrochlorothiazide* (100 *mg./day*) *and Chlorothiazide* (1,000 *mg./day*) *on Urinary Excretion of Sodium, Potassium, Chloride, and Water in* 10 *Patients in Group* 1 (*Nos.* 1 *and* 4–12 *in Table* I). *Data Not Adequate for Strict Comparison in Cases* 2 *and* 3. *Six Patients Received Hydrochlorothiazide First, and Four Chlorothiazide First*

Treatment	Daily Urinary Electrolyte Excretion (mEq)			Urine Flow (Litres/ 24 Hours)
	Na+	K+	Cl−	
Control (27)	55	50	62	1·225
Hydrochlorothiazide (38)	134	74	150	2·060
Chlorothiazide (35)	107	65	111	1·755

Figures in parentheses indicate total number of observations.

electrolytes. Fig. 1 shows details of a representative subject (Case 1).

The general trend of the results shows that 100 mg. of hydrochlorothiazide evokes a diuresis equivalent to that of 1,000 mg. of chlorothiazide, with a similar pattern of urinary electrolyte excretion. In two instances, however (Cases 3 and 12), hydrochlorothiazide proved more effective than chlorothiazide, in spite of being the second drug administered.

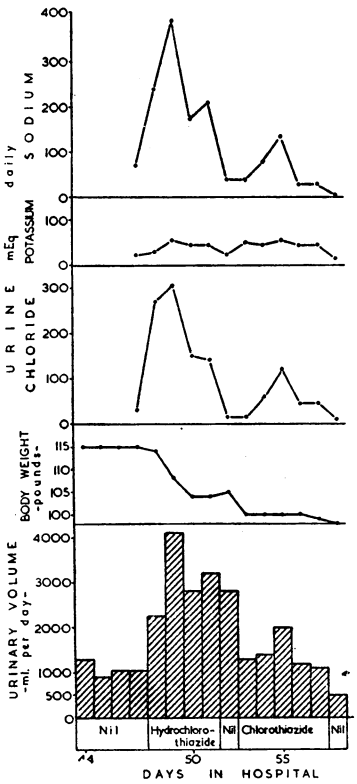


FIG. 1.—Case 1. Patient aged 68 with pulmonary heart disease. Shows electrolyte excretion pattern typical of patients with oedema of recent onset. Note equimolecular diuresis of sodium and chloride with little potassium loss, which occurs as a result of both hydrochlorothiazide and chlorothiazide therapy.

Case 7 is of interest. A man aged 50 first developed cor pulmonale eight years previously and had been treated with weekly injections of mersalyl (2 ml.) ever since. He was admitted to this hospital with an exacerbation of a chronic bronchitis and was in mild congestive cardiac failure. The diuresis following twice-weekly injections of mersalyl was excellent, but it was of interest to note that whilst equimolecular concentrations of sodium and chloride were excreted there was in addition a large diuresis of potassium (160 mEq in 24 hours). This pattern of electrolyte excretion was again reproduced when chlorothiazide and hydrochlorothiazide were used. The weight loss during the trial period was limited to 6 lb. (2.7 kg.), as the major diuresis had already been produced by mersalyl.

Case 11 was complicated by the coincident resolution of an acute focal nephritis.

A man aged 38 presented two weeks after an attack of tonsillitis with microscopic haematuria and evidence of renal failure (blood urea 85 mg./100 ml.) associated with acute carditis and signs of congestive cardiac failure: the cardiac condition was acute enough to demand therapy. During the first trial period with hydrochlorothiazide there was a fourfold increase in the urinary volume without a corresponding loss of sodium. During the second trial period there was an increased diuresis of sodium with little rise in the urinary volume. The disparity of electrolyte and water diuresis is probably related to the resolution of the nephritic episode. During this trial period the blood urea fell to 51 mg./100 ml. and there was a decrease in the number of casts in the urine; within two weeks the blood urea was 25 mg./100 ml.

Group 2

Group 2 comprised nine patients with chronic oedema of many months' or even years' duration (Table III): their dietary sodium intake had been restricted for periods ranging from nine months to ten years, and all had received previous diuretic therapy in the form of mersalyl or chlorothiazide. This group provides a stringent test for any diuretic. The pattern of electrolyte excretion is quite different from that seen in cases with oedema of recent onset. The daily excretion of sodium during the control period was less than the dietary intake (25 mEq) without exception. Some of the patients lost potassium in the urine in appreciable quantities, and during the periods of diuretic therapy the urinary excretion of potassium exceeded that of sodium in all instances except Case 13. The other characteristic feature of this group was the way in which the urinary potassium loss reflected the loss of chloride. There did not appear to be any significant difference between the electrolyte excretion pattern following hydrochlorothiazide and that following chlorothiazide.

TABLE III.—*Clinical Details and Response to Therapy of Nine Patients in Group 2*

Case	Diagnosis	Duration of Previous Salt Restriction	Response to Treatment	Remarks
13	Cirrhosis hepatis	9 months	Good. No weight lost during control periods: 30 lb. lost in 16 days' diuretic treatment. Complete disappearance of ascites	Serum albumin 3·5 g.%, globulin 3·2 g.%. Diuresis comprised predominantly a loss of sodium and chloride: response to each drug was similar. Urinary potassium loss less than 60 mEq/day, but serum potassium fell to 2·3 mEq/l.
14	,,	12 ,,	Good. No weight loss during control periods: 8 lb. lost in 8 days' diuretic treatment	Serum albumin 3·3 g.%, globulin 3·2 g.%. Consistently larger diuresis of potassium than sodium. Serum potassium fell to 2·5 mEq during short period of trial (see Fig. 2)
15	,,	5 years	Poor response. Weight constant during trial period	Serum albumin 1·5 g.%, globulin 4·5 g.%. No sodium diuresis (less than 5 mEq/day) on either drug. Initial slight potassium diuresis on chlorothiazide
16	,,	18 months	Poor response. Steady reaccumulation of ascites	Serum albumin 3·1 g.%, globulin 4·0 g.%. No sodium diuresis (less than 5 mEq / day). Slight potassium diuresis with each drug, accompanied by fall in serum potassium and rise in blood urea
17	Rheumatic heart disease and cardiac cirrhosis	10 years	No response	Serum albumin 5·1 g.%, globulin 2·1 g.%. No sodium diuresis (less than 5 mEq/day) on either drug. Persistent loss of potassium in urine (50–60 mEq/day), with fall in serum potassium and rise in blood urea
18	Constrictive pericarditis	2½ ,,	Poor response. No weight loss	Serum albumin 3·8 g.%, serum globulin 2·2 g.%. No sodium diuresis on either drug. Initial potassium diuresis, with fourfold increase in urinary volume and fall in serum potassium on hydrochlorothiazide
19	Obstruction to inferior vena cava	9 months	No response	Oedema resistant to all diuretics
20	Rheumatic heart disease	3 years	Good response to hydrochlorothiazide	No response to chlorothiazide after one week: good response to hydrochlorothiazide with sodium diuresis covered entirely by chloride (see Fig. 3)
21	,, ,,	1 year	Poor response	Sodium diuresis did not exceed dietary intake. Loss of water accompanied mainly by potassium and chloride

Hepatic Cirrhosis

Four of these patients suffered from Laennec's portal cirrhosis with ascites and oedema: these were all advanced cases that had become refractory to conservative treatment and had been referred to this hospital (Mr. Alan H. Hunt) for consideration of a portocaval anastomosis. The serum albumin levels were low in all cases (see Table III). In all these patients the sodium excretion during the control period was less than 5 mEq/day (the details of urinary electrolyte excretion are shown in Table IV). In two patients the response to diuretic therapy was good. In Case 13 there was a loss of 30 lb. (13.6 kg.) in body weight, which was almost entirely due to the resolution of ascites. The response to hydrochlorothiazide and chlorothiazide was similar: there was a fair sodium diuresis, but this was associated with an appreciable loss of potassium on both drugs; this was accompanied by a fall in the serum potassium (to 2.3 mEq) and a state of drowsiness. In Case 14 the diuresis of potassium exceeded that of sodium with an associated fall (to 2.5 mEq) in the serum potassium level (see Fig. 2).

TABLE IV.—*Mean Effect of Hydrochlorothiazide* (100 *mg./day*) *and Chlorothiazide* (1,000 *mg./day*) *on Urinary Excretion of Sodium, Potassium, Chloride, and Water in Four Patients with Hepatic Cirrhosis* (*Nos.* 13, 14, 15, 16 *in Table III*). *Two Patients were Given Chlorothiazide First and Two Hydrochlorothiazide First*

Treatment	Daily Urinary Electrolyte Excretion (mEq)			Urine Flow (Litres/ 24 Hours)
	Na+	K+	Cl−	
Control (10)	3	37	24	0·98
Hydrochlorothiazide (16)	36	69	84	1·200
Chlorothaizide (16) ..	42	69	66	1·205

Figures in parentheses indicate number of observations.

In Cases 15 and 16 there was no response to treatment. The body weight remained constant (Case 15) or was increased (Case 16); a slight potassium diuresis was associated with a fall in the serum level and a deterioration in the patient's general condition. In Case 16 the hypokalaemia was associated with a rise in the blood urea (69–108 mg./100 ml.): as the blood pressure remained unchanged this may be considered to be a manifestation of the impaired renal function associated with potassium depletion (Relman and Schwartz, 1956).

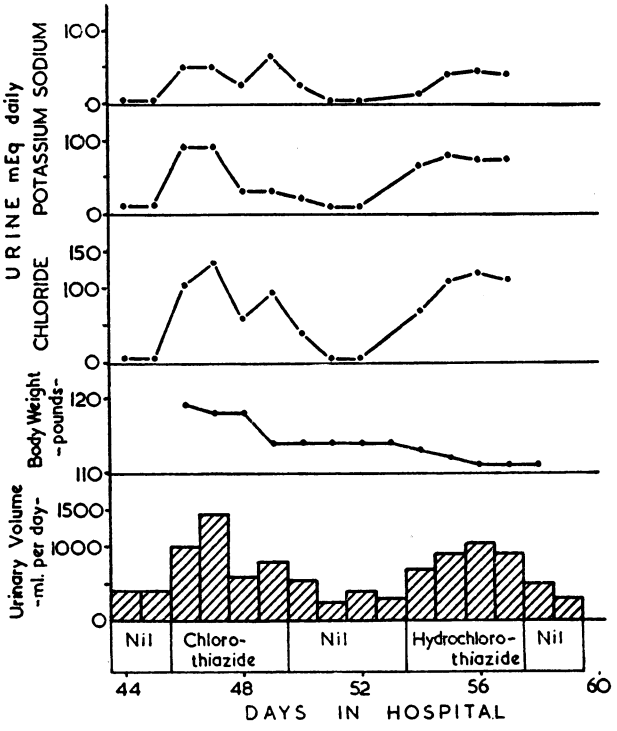


FIG. 2.—Case 14. Patient aged 59 with cirrhosis hepatis. Electrolyte excretion pattern resulting from chlorothiazide and hydrochlorothiazide therapy in a patient with chronic ascites and sodium retention. Note the similar potassium loss produced by each drug.

Cardiac Disease

Case 17.—A woman aged 40 with rheumatic heart disease, mitral stenosis and incompetence, and tricuspid incompetence had been treated with salt restriction and mersalyl for 10 years; over the preceding 12 months she had developed a cardiac cirrhosis with ascites which had proved refractory to conservative measures. No diuresis of sodium was achieved in this patient on chlorothiazide or hydrochlorothiazide (less than 5 mEq daily). Potassium was lost in the urine in quantities of 50–60 mEq daily, and this was associated with a fall in the serum potassium and a rise in the blood urea (46–72 mg./100 ml.). A small increase in sodium excretion was achieved (50 mEq daily) by the addition of "thiomerin" to each of the oral diuretic drugs.

Case 18.—A man aged 34 with constrictive pericarditis had been oedematous for three years; he had shown some initial improvement on salt restriction and diuretics, but, despite this regime, repeated acupunctures and abdominal paracenteses had become necessary over the previous 10 months. There was no sodium diuresis on either hydrochlorothiazide or chlorothiazide, but on hydrochlorothiazide there was a potassium diuresis which was associated with a fourfold increase in urinary volume: this was accompanied by a fall in the serum potassium level (to 2.2 mEq/l.) and symptoms of lethargy. It would have been of interest to see if the diuresis could have been maintained by potassium supplements, but his general condition gave cause for anxiety, and it was felt that pericardectomy should be delayed no longer.

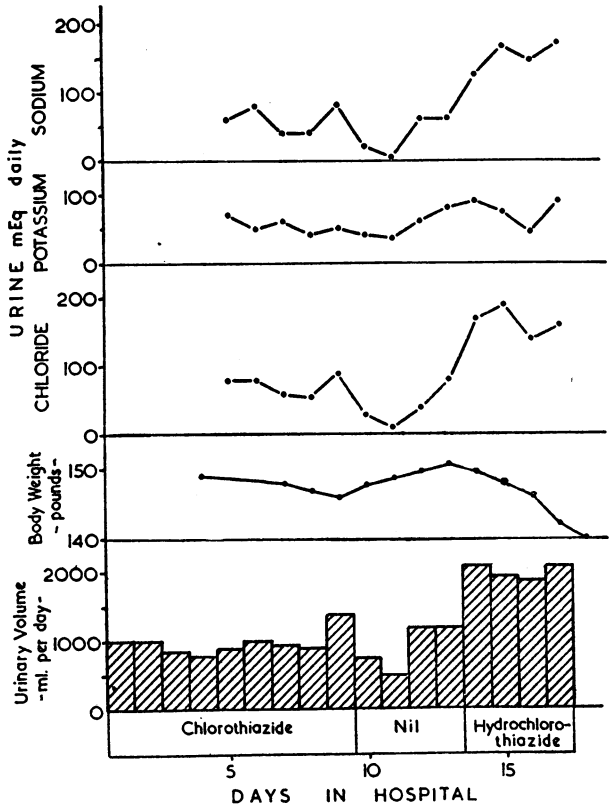


FIG. 3.—Case 20. Patient aged 58 with rheumatic heart disease. A good response to hydrochlorothiazide after eight days' treatment with chlorothiazide had proved ineffective.

Case 20, that of a woman aged 58 with rheumatic heart disease, is of interest. She had been admitted to hospital on 12 occasions with congestive cardiac failure. For three years she had been treated with a low-salt diet, digitalis, and injections of mersalyl twice weekly. She was admitted to this hospital in severe congestive cardiac failure. The heart rate was, however, well controlled and no alteration in the dose of digitalis was made. Chlorothiazide given over a period of nine days produced no response, but an immediate and impressive diuresis resulted from hydrochlorothiazide therapy, and a loss of 10 lb. (4.5 kg.) in body weight was achieved in four days (see Fig. 3).

Discussion

Hydrochlorothiazide differs from chlorothiazide only in the presence of two hydrogen atoms in the thiadiazine ring of the molecule. Because of this small modification in structure one might anticipate that the diuretic action of hydrochlorothiazide would differ only quantitatively and not in any important qualitative aspect. The results of this trial indicate that the diuretic response of 100 mg. of hydrochlorothiazide is approximately equal to that of 1 g. of chlorothiazide and that the pattern of electrolyte excretion is the same. While chlorothiazide resembles the organic mercurials in its action on the excretion of chloride, it differs in the much greater tendency to produce hypokalaemia (Slater and Nabarro, 1958). This secondary effect on potassium excretion has been ascribed to the inhibitory activity of the drug to carbonic anhydrase. It was of special interest, therefore, to observe the effect of hydrochlorothiazide on potassium excretion, because it has been reported that the drug was less inhibitory *in vitro* to carbonic anhydrase, and in animal experiments it was less active in promoting potassium excretion (de Stevens *et al.*, 1958). Our results have been unable to confirm that hydrochlorothiazide produces a smaller urinary potassium loss than chlorothiazide.

As Bayliss *et al.* (1958) have pointed out, potassium depletion may develop during treatment with any diuretic which primarily increases the excretion of chloride, and the more potent the diuretic the more likely is this to occur. Normally the increased excretion of chloride will be accompanied by an approximately equimolecular amount of sodium, but rigid dietary restriction or avid renal tubular absorption will reduce the amount of sodium available for excretion, and potassium may then be excreted as the cation. The hypokalaemia is particularly apt to occur in cirrhosis hepatis and certain cases of congestive cardiac failure where there may be an additional factor of increased production of aldosterone (Chart and Shipley, 1953 ; Singer and Wener, 1953 ; Axelrad *et al.*, 1955). It seems uncertain at the present time to what extent the increased aldosterone production is related to the previous dietary restriction of sodium. The apparently clear-cut segregation of our patients into two groups, according to their renal electrolyte response to both drugs, seems to be due, in part at least, to the preceding salt intake. While sodium restriction has long proved to be a useful therapeutic measure in its own right, there may be grounds for reappraising its value and hazards when used in conjunction with powerful diuretics of the hydrochlorothiazide and chlorothiazide type, especially over long periods.

Until the introduction of chlorothiazide the occurrence of potassium deficiency as a complication of therapy with the mercurial diuretics, although reported (Cort and Matthews, 1954), had escaped general recognition. Nevertheless a large urinary loss of potassium may occur after the administration of mercurials, especially when there is marked restriction of dietary sodium (Lesser *et al.*, 1952). No comparative study of the diuresis following the mercurial compounds has been made during this trial, but the incidental observation in Case 7 of a 24-hour excretion of 160 mEq of potassium following 2 ml. of mersalyl is of interest. This figure was exceeded on only one occasion throughout this trial by either chlorothiazide or hydrochlorothiazide. The greater toxicity of the mercurial diuretics prevents their daily administration so that the cumulative effect of a constant potassium diuresis less often progresses to a fall in the serum level. The hypokalaemia that is now recognized as a complication of chlorothiazide treatment is possibly the result of a more prolonged rather than a dissimilar action. In this respect it is worthy of note that Davies and Evans (1958) gave short and intermittent courses of chlorothiazide to 20 patients with heart failure. Although no potassium supplements were given, a slight fall in serum potassium was noted in only five cases. These authors suggest that potassium supplements may be unnecessary if an intermittent dosage regime is employed.

Although the pattern of electrolyte excretion following chlorothiazide and hydrochlorothiazide is similar, we have encountered three instances when hydrochlorothiazide appeared more efficacious. On one of these occasions (Case 20) a good diuresis followed hydrochlorothiazide when there had been no response to chlorothiazide. We cannot relate this to any other aspect of the patient's progress and make no attempt to explain it.

We have not encountered any toxic reactions after the use of either of these oral diuretics. Recently, six cases of thrombocytopenia (Nordqvist *et al.*, 1959) and one of agranulocytosis (Zuckerman and Chazan, 1958) have been recorded after giving chlorothiazide: the similar chemical structure of hydrochlorothiazide would suggest that this drug, too, may not be immune from these occasional hazards, although the smaller dosage may be advantageous.

Summary

The value of the new oral diuretic hydrochlorothiazide has been assessed: its effect is compared with that of chlorothiazide in 21 oedematous patients. A dose of 100 mg. of hydrochlorothiazide produced a similar quantitative and qualitative response to that following 1 g. of chlorothiazide. In three patients hydrochlorothiazide appeared to produce a better diuresis.

Although hydrochlorothiazide is less inhibitory than chlorothiazide to carbonic anhydrase *in vitro*, the diuretic action appears to be similar and potassium loss in the urine occurs just as readily. Patients with oedema of recent origin respond with an equimolecular diuresis of sodium and chloride and little potassium is lost, but patients with chronic oedema and sodium retention may lose considerable quantities of potassium in the urine and are especially liable to hypokalaemia.

We thank Dr. A. W. Spence for his constant help and encouragement ; Dr. T. Hanley for much helpful criticism ; the consultant staff of St. Bartholomew's Hospital who allowed us to study patients under their care ; Mrs. E. M. Akers for many of the electrolyte determinations ; Mr. N. K. Harrison for preparing the figures ; and Ciba

Laboratories Ltd. for generous supplies of hydrochlorothiazide (" esidrex ").

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HYDROCHLOROTHIAZIDE, A NEW ORAL DIURETIC

BY

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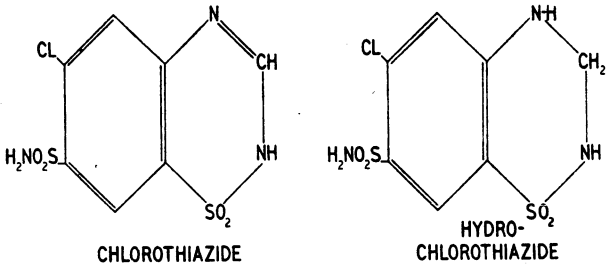
Chlorothiazide is a potent oral diuretic which is relatively free from toxic effects. Its main disadvantage is that it often causes potassium depletion (Tapia *et al.*, 1957; Bayliss *et al.*, 1958; Slater and Nabarro, 1958; Harington and Kincaid-Smith, 1958). Hydrochlorothiazide, which is a hydrogenated derivative of chlorothiazide, has recently been synthesized (de Stevens *et al.*, 1958) and has been shown to be a more potent diuretic than chlorothiazide on a weight-for-weight basis (Brest and Likoff, 1959; Ford, 1959; Moyer *et al.*, 1959). This study compares the diuretic potency of these two drugs and their effect on electrolyte excretion in normal persons and in patients with congestive heart failure.



Methods

Three normal adults, who were given a diet of constant fluid and sodium chloride content (7 g. in 24 hours), took single doses of hydrochlorothiazide at intervals of one week. The urinary water and electrolyte excretion were measured and expressed as changes from those occurring during a control period of one or two days.

Twenty-one patients with congestive heart failure were also studied. Nine of these had rheumatic heart disease, eight had ischaemic heart disease or hypertension, two had cor pulmonale, one had severe anaemia, and one had constrictive pericarditis. All these patients drank 1 litre of fluid daily and consumed a diet of constant sodium chloride content (either 0.5 or 3 g. daily). Patients who were critically ill were excluded from the investigation. It was originally planned to give each patient either hydrochlorothiazide or chlorothiazide for three periods of three days separated from one another by a day during which no diuretic was administered. Alternate patients were to be given hydrochlorothiazide or chlorothiazide first; the other drug was to be given during the second three-day period and the first drug administered again during the third period. Thus the effects of six days' treatment with one drug would be available for comparison with the effects of three days' treatment with the other drug in each patient. This programme was completed in 11 patients; five patients deteriorated during the early part of the trial and treatment with mercurial diuretics had to be instituted; and five were treated only with hydrochlorothiazide in order to compare the effects of different doses in the same patient. The daily excretion of water, sodium, potassium, and chloride was measured during the administration of each drug and the results were expressed as changes from the mean daily excretion during the control period of one to five days which preceded each experiment. Treatment with non-diuretic drugs was begun during the control period and usually remained unchanged during the diuretic trial.

Both diuretics were given in equal oral doses at 12-hour intervals. In all patients the dose of chlorothiazide was 1 g. daily; doses of hydrochlorothiazide ranged from 0.1 to 0.4 g. daily.

Chemical Methods.—Sodium and potassium: flame photometry. Chloride: potentiometric titration with silver nitrate (Sanderson, 1952). Ammonia: aeration and titration (Peters and Van Slyke, 1932). Phosphate: colorimetric estimation after combination with molybdic acid (King, 1951). Titratable acid: potentiometric titration of urine to *p*H 7.40 with N/50 NaOH. Urine *p*H: glass electrode at room temperature. Bicarbonate: manometric technique of Van Slyke (Van Slyke and Neill, 1924).

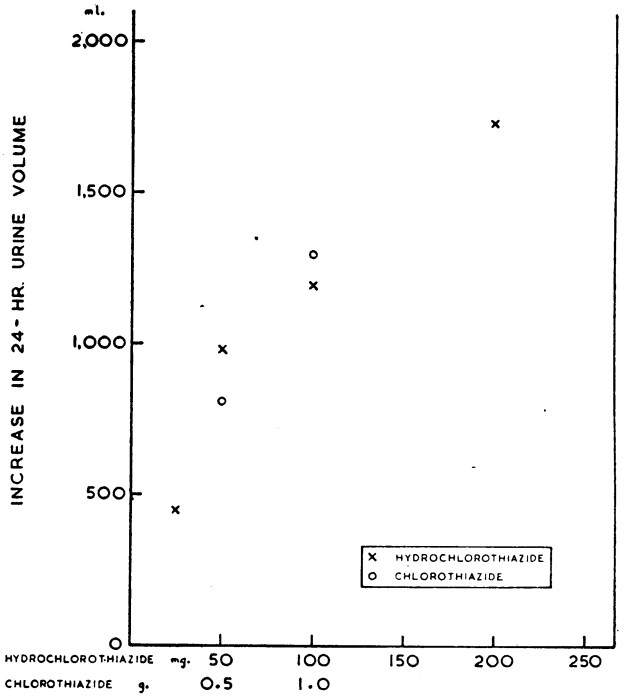


FIG. 1.—Increase in 24-hour urine volume of a normal subject (A) after different doses of hydrochlorothiazide and chlorothiazide.