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CHLOROTHIAZIDE IN THE MANAGEMENT OF CARDIAC ŒDEMA*

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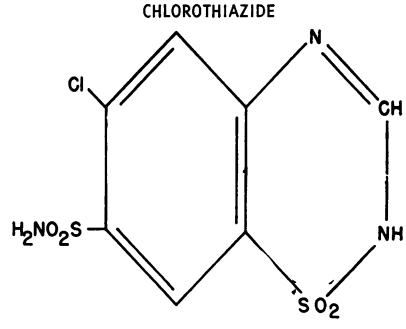
INTRODUCTION

IN THE MANAGEMENT of œdema in congestive heart failure, it would be highly desirable to have a non-toxic, non-mercurial oral diuretic which would act as effectively as parenterally administered mercurial diuretics.

In 1956, Novello and Sprague[1] in their search for a new non-mercurial oral diuretic synthesized the compound chlorothiazide (Fig. 1). The latter is



6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide

Fig. 1.—Structural formula of chlorothiazide.

pharmacologically unique, in that it has the structure of a carbonic anhydrase inhibitor and an enhancing effect on salt and water excretion resembling that of a potent organomercurial diuretic agent. Preliminary observations in animals and in man have shown this drug to be relatively non-toxic and highly potent as an oral diuretic.[1-5]

Accordingly, in March 1957, this study was undertaken to evaluate the diuretic effect of chlorothiazide in hospitalized patients with congestive heart failure and also to study the effects of the drug in long-term treatment of ambulatory patients with chronic congestive heart failure.

MATERIALS AND METHODS

The clinical material is presented in Table I. Twenty-five patients were studied, 16 men and 9 women, ranging in age from 47 to 86 years. Eleven patients had rheumatic heart disease, eight had arteriosclerotic heart disease, including recent and remote myocardial infarctions, four had cor pulmonale and two had hypertensive heart disease. Six of the patients were hospitalized during a period of the study, and four of these were later followed up in the out-patient cardiac clinic along with 19 other ambulatory patients with heart failure.

Hospitalized Cases

These patients were admitted with classical signs and symptoms of congestive heart failure. In all instances the severity of the failure was increasing despite various therapeutic measures, including the use of mercurial injections. In all instances, on admission, there was evidence of pulmonary congestion, an enlarged and tender liver, and leg œdema. In three cases ascites was present. In one patient the ascites was so marked that therapy with chlorothiazide was started eight days before admission (Fig. 2).

On admission the following data were recorded: degree of œdema, weight, and symptoms of congestion such as cough, dyspnœa or orthopnœa. The venous pressure and arm-to-tongue circulation time were recorded before, during and after therapy. The total blood volume and plasma volume using radioactive albumin (RISA) were also determined in three cases before and after treatment.[6]

The serum sodium, chloride, potassium and CO_2 combining power were determined before and during therapy with chlorothiazide. Blood studies also included estimation of the serum total proteins, albumin/globulin ratio and nonprotein nitrogen (NPN) at frequent intervals. Daily urine specimens were collected at 24-hour intervals and analyzed for sodium, potassium and chloride, both in control periods and during the whole study period. In two patients, fractional urine specimens were studied at six-hourly intervals for part of the study in order to determine the duration of action and degree of response to single doses of chlorothiazide.

The sodium and potassium concentrations in both serum and urine were determined with a direct reading flame photometer (Evans Electroselenium, England). Serum and urine chloride were determined by mercurimetric titration.[7] The CO_2 combining power of the plasma was determined by the volumetric Van Slyke method after equilibration of the plasma sample with a mixture of 5.5% CO_2 and 94.5% air.

Blood non-protein nitrogen was determined colorimetrically on digests of blood filtrates after nesslerization. Total serum proteins and albumin-globulin levels were determined by the biuret procedure.[8]

Similar studies were also completed in one case of cirrhosis of the liver with ascites and peripheral œdema, three cases of nephrotic syndrome and one case without heart failure, convalescing after a coronary thrombosis.

The patients were given diets containing 2-4 g. of NaCl. Fluids were given *ad lib.* and total daily intake of water varied from 1400-2000 c.c. All patients were digitalized.

After a suitable control period of 2 to 4 days, chlorothiazide was administered in 250-mg. tablets twice or three times daily after meals. In order to evaluate a dose-response effect, the dosage used ranged from 250 to 4000 mg. daily. However, on the average, the dose used was 500 to 1000 mg. daily. The duration of study with this drug in the hospitalized patients ranged from 7 to 45 days, with an average of 14 days.

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Ambulatory Group Attending the Cardiac Clinic

This group of 23 cases, including four which were studied in the hospital, had been treated for chronic congestive heart failure in the cardiac clinic for periods ranging from 1 to 8 years (Table I). These cases were considered to be in moderately severe congestive heart failure requiring from 1 to 6 mercurial injections per month along with the daily use of digitoxin and oral diuretics, mainly chloromerodrin (Neomerettes) and moderate salt restriction, approximately 4 to 6 g. of salt daily. At the onset of the study, most of the patients were fairly comfortable, but on examination, 18 of the 23 cases had some residual signs of heart failure (Table I).

Visits to the clinic were made once weekly, and the following data were recorded: weight, degree of œdema, signs and symptoms of congestive failure or leg œdema, basal rales, ascites, pleural effusion, cough, dyspnœa or orthopnœa. Serum electrolyte studies were made in all patients before and during therapy with chlorothiazide, including determination of sodium, potassium, chlorides and CO_2 combining power. Other blood studies include total serum proteins, A/G ratio and NPN.

Chlorothiazide was added to the regimen in doses of 250 to 3000 mg. in divided doses. However, with trial, it was quickly observed that the optimal dose was usually 250 to 500 mg. daily. If additional diuresis was required, the patient was instructed to increase the dose to 1000 mg. for two days of each week and then continue again with 500 mg. daily. Injections of a mercurial diuretic were added when the signs and symptoms of congestive heart failure could not be controlled by chlorothiazide alone.

Potassium chloride in doses of 3 g. daily was added for several days, whenever the serum electrolytes revealed a low serum potassium. Ammonium chloride 60 grains daily was added in many cases to correct low serum chlorides and later to prevent the occurrence of hypochloræmia with the prolonged use of chlorothiazide. The duration of therapy with chlorothiazide ranged from three weeks to six months (Table I).

RESULTS

The results of the study are tabulated in Table I and Figs. 1-6. From the data it can readily be noted that chlorothiazide has been useful both in starting a prompt and effective diuresis and also in the long-term maintenance of the œdema-free state in patients with heart failure.

In the hospitalized patients (Figs. 2-7) the diuresis was prompt and was associated with a marked increase in the 24-hour urine volume. Although no attempt was made to control the fluid intake, in every instance the 24-hour urine volume was significantly increased over the control periods. The maximum diuresis occurred in 2 to 6 hours after a single oral dose. Studies of electrolyte excretion in the 24-hour urine collections revealed a definite and marked increase in the output of sodium, potassium and chlorides. The excretion of chlorides almost paralleled the excretion of sodium. The potassium excretion was not increased to the same extent.

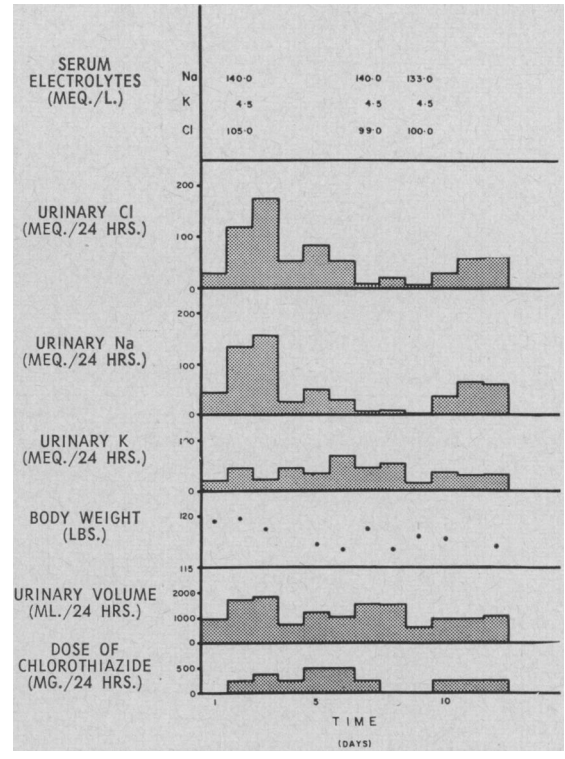

Fig. 2.—Woman, aged 47, in failure for 2 years after a mitral commissurotomy. Chlorothiazide was started 8 days prior to admission to hospital with marked loss of ascites and leg œdema. Note increase in 24-hour urine volume and electrolyte excretion with doses of 250-500 mg. daily.

This increase in water and electrolyte response was always accompanied by an improvement in the patient's clinical condition, as was evident by the loss in weight, loss of œdema and disappearance of pulmonary rales. In two patients, after therapy, total blood volume was also reduced by 12% and

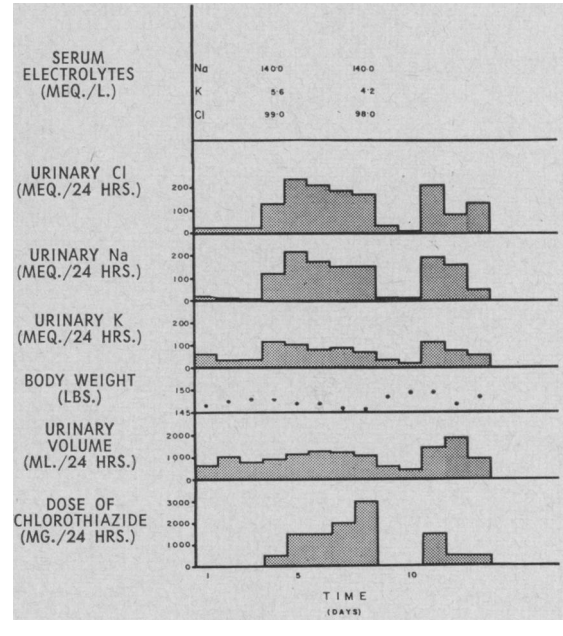

Fig. 3.—J.G., aged 55, rheumatic heart disease (see Case 5, Table I). Note increase in diuretic response with increase in dose of chlorothiazide up to 1500 mg. daily—no further increase with 2000-3000 mg. daily. Note the marked decrease in urinary electrolyte and urinary volume excretion with cessation of the drug and the prompt response when the drug was again given.

TABLE I.—CLINICAL DATA

Case No.	Age & Sex	Diagnosis	Duration of heart failure	Degree of failure at outset of study: pulm. rales	leg œdema	ascites	pleural effusion	No. of mercurial inj. before	Type of treatment before	Type of treatment after: KCl	NH4Cl	Dose of chlorothiazide	No. of mercurial inj. after	Duration of treatment	Wt. bef. (lb.)	Wt. after (lb.)	Date	Serum electrolytes: CO_2 in	Na mEq./l	K	Cl	NPN Mg%	Total protein G.%
1	48 F	H.C.V.D.	7 years	+	++	+	0	0	Neomerettes (Chloromerodrin) Serpasil Digitoxin	0	+	500 mg. daily	0	6 mths.	138½	136½	May 8		140.0	4.8	98.0	29.0	
																	May 15	21.8	137.0	4.5	97.0	—	
																	June 15		140.0	4.9	102.4	42.5	
																	July 10		136.8	5.1	101.8	33.0	
																	Sept. 6		140.2	4.9	98.0	30.8	
																	Oct. 24	30.5	141.4	4.4	97.5	39.5	
2	69 M	Parkinson's disease R.H.D. H.C.V.D.	2 years	++	++	0	0	1/week	Raudixin Neomerettes Digitoxin	0	0	500–1500 mg. daily	0	5 mths.	157	149	May 2	30.0	145.0	4.7	95.0	50.0	
																	May 22		140.0	4.5	105.0	—	
																	June 26		145.0	4.7	106.0	43.0	
3	45 M	Cor pulmonale	1 year	+++	+++	0	0	1/week	Digitoxin	+	+	1000–1200 mg. daily	0	6 mths.	194½	178	June 12	26.9	138.5	5.1	106.3	49.1	7.53
																	June 19	32.2	136.0	3.8	98.0	55.4	—
																	July 10	30.0	142.0	4.7	98.0	29.8	—
																	Aug. 7	30.0	138.0	4.8	104.0	23.1	7.22
																	Oct. 4	—	140.2	5.4	98.1	29.0	7.31
4	57 M	R.H.D.	1 year	+	+	+	0	1/week	Digitoxin	0	0	500–2000 mg. daily	1/week	9 weeks	145	146	Apr. 28	25.0	144.0	4.5	100.0	41.0	
																	May 10	—	137.0	4.3	102.0	39.8	
																	Aug. 9	—	138.5	5.0	102.0	36.0	
																	Sept. 19	—	140.2	5.2	101.0	—	
																	Oct. 2	29.7	138.5	5.3	101.0	—	
5	55 M	R.H.D.	3 years	+	+	+	0	0	Neomerettes Digitoxin	0	+	750–1000 ↓ 500–1000 mg. daily	0	6 mths.	164	159	June 27	—	146.2	4.8	106.7	41.2	
																	Oct. 24	32.0	141.4	4.9	98.0	—	
6	57 F	R.H.D.	12 years	+	0	+	0	1/week	Neomerettes NH_4Cl Digitoxin	0	+	1000–1500 ↓ 500–750 mg. daily	0	7 mths.	121	109	May 9	35.0	133.0	3.3	97.0	66.0	
																	May 23	28.0	133.0	4.7	99.0	59.0	
																	June 24	26.0	140.0	5.2	106.0	—	
																	July 12	—	142.0	—	97.6	39.3	
																	Nov. 1	28.6	143.6	4.7	93.5	—	
7	58 F	R.H.D.	5 years	++	+++	+	+	2/week	Neomerettes NH_4Cl Digitoxin	+	+	750–1500 mg. daily	1/week	7 mths.	130	129	May 2	—	147.0	3.6	98.0	34.0	
																	June 27	32.2	143.6	4.1	98.5	40.0	
																	Aug. 23	—	143.6	4.8	93.9	53.3	
																	Oct. 24	28.6	140.2	4.7	93.1	39.8	
8	47 F	R.H.D. post-commissurotomy	2 years	+	+	+++	0	0	Diamox Neomerettes Digitoxin	0	0	250–500 mg. daily	0	7 mths.	129	121	May 8	29.0	140.0	3.8	96.0	30.0	
																	June 28	26.2	145.3	4.8	106.7	61.8	
																	Aug. 8	—	140.0	4.1	105.0	30.0	
																	Oct. 24	32.0	140.2	4.9	98.6	29.0	
9	49 M	R.H.D.	3 years	+	+	0	0	1/week	Neomerettes Digitoxin	0	0	250 mg. daily	0	6 weeks	125½	125	Mar. 21	—	134.0	5.0	93.0	43.0	
																	Aug. 16	—	133.4	5.5	94.4	45.0	
10	61 M	R.H.D.	3 years	+	+	0	0	2–4/mth.	Neomerettes NH_4Cl Digitoxin	0	+	500–1000 mg. daily	0	6 mths.	147	140	May 9	27.0	132.0	5.0	101.0	44.0	
																	May 23	24.0	132.0	5.1	102.0	—	
																	June 20	24.0	138.0	5.6	101.0	58.2	
																	July 11	28.0	133.4	5.7	98.1	37.4	
																	Aug. 8	—	136.8	5.2	100.0	27.1	
																	Oct. 24	27.7	132.0	5.2	101.0	—	
11	62 M	R.H.D.	2 years	+	+	0	0	1/week	Neomerettes Rolicton NH_4Cl Digitoxin	0	0	500–1500 mg. daily	0	6 mths.	119	118	May 9	26.0	138.0	4.5	99.0	43.0	
																	May 23	30.0	135.0	4.7	103.0	—	
																	May 28	—	—	—	—	32.0	
																	June 20	32.0	138.0	4.6	98.0	60.0	
																	Aug. 8	—	138.5	5.0	96.2	43.0	
																	Nov. 1	28.6	141.9	5.3	93.5	40.0	

(Continued on page 596)

16% respectively, and venous pressure and circulation time decreased. In the third patient in whom blood volume was measured, there was no change after use of chlorothiazide (Fig. 6), and this patient was also found to be resistant to other forms of therapy.

In one patient with ascites (Fig. 2), because of the urgency of her condition the chlorothiazide was given for one week before admission to hospital. After a dose of 250 mg., she reported a profound diuresis and noted that she had lost 4 lb. in weight in the first 24 hours. During the next seven days, while awaiting admission to hospital, she took 250 to 500 mg. chlorothiazide daily and during this time her weight dropped from 129 lb. to 120 lb., with a marked decrease in the size of her abdomen (loss of ascitic fluid) and disappearance of leg œdema. During her stay in hospital (Fig. 2) her œdema-free state could be maintained with 250 to 500 mg. daily. This patient has now been followed up for six months in the clinic on a daily dose of 250 to 500 mg. and has remained free of œdema and ascites, although her salt intake has been more liberal (Case 8, Table I).

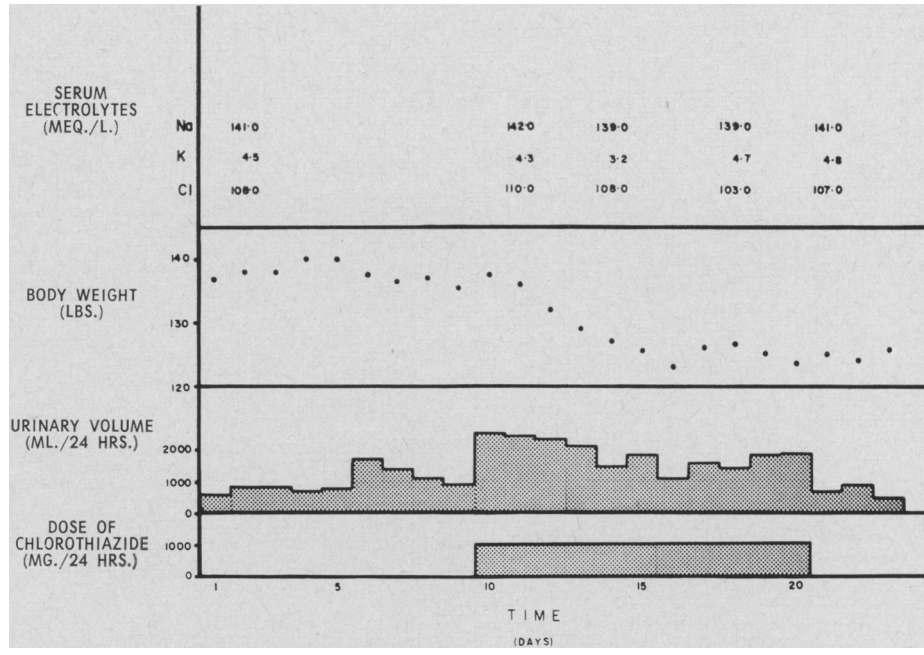

Fig. 4.—J.F., man aged 55, rheumatic heart disease. Note prompt and continued response to 1000 mg. of chlorothiazide daily, after poor response to 9 daily mercurial injections, and daily use of 20 mg. of Meticorten and 250 mg. of Diamox.

In another patient with severe rheumatic heart disease, pleural effusion, cardiac cirrhosis and ascites, and leg œdema (Fig. 6), although doses of chlorothiazide up to 4 g. daily did cause an increase of water and electrolyte diuresis as compared to the control period, the clinical status was not appreciably altered. It should be noted, however, that the response to chlorothiazide in this case was slightly superior to that of parenteral mercuhydrin in 2-c.c. doses daily although neither rendered the patient free of œdema.

From the data in Figs. 3, 6 and 7, it can readily be seen that the diuretic response increased sharply with doses up to 1 g. daily, and only a slight increase occurred in some patients when the dose was raised to 2 g. daily. The maximum optimal dose appeared to be about 1000 to 1500 mg. daily for the initiation of a good diuresis, while the optimal daily dose for maintenance ranged between 250 and 500 mg. In three patients (including one without heart failure) (Figs. 6, 7) where attempts were made to compare the potency of chlorothiazide with other known oral diuretics and parenteral mercuhydrin in 2-c.c. doses, chlorothiazide appeared to be the most potent oral diuretic employed, and in doses of 1000-2000 mg. equalled or exceeded in diuretic potency 1 c.c. to 2 c.c. of mercuhydrin.

In four of the six hospitalized patients, when the drug was discontinued, there was a prompt decrease in the 24-hour urine and electrolyte diuresis associated with a slight increase in body weight. When the chlorothiazide was again administered, the 24-hour urine volume and electrolyte excretion quickly increased above control values in association with a slight decrease in body weight (Figs. 2, 3 and 4).

The data in Table I show that, in the ambulatory group of patients with congestive heart failure, chlorothiazide was effective both in the initiation of water diuresis and in the prolonged maintenance of the œdema-free state. As would be expected, the diuresis was most marked in patients with peripheral œdema at onset of study. In Cases 3 and 13, after seven days of chlorothiazide in doses of 750 to 1200 mg. daily, the patients experienced a prompt diuresis which was associated with a drop of 12 and 14 lb. in weight, respectively. At the end of the week, the patients could breathe easier, there were no pulmonary rales and only a trace of leg œdema persisted.

The five patients (Cases 1, 5, 8, 14, 17) who were maintained on daily oral mercurial diuretics or Diamox without additional parenteral mercurial therapy improved still further when placed on chlorothiazide, with disappearance of the residual pulmonary rales and leg œdema and a further slight decrease in body weight.

Of the remaining 17 patients, who were treated with other daily oral diuretics as well as 1 to 8 mercurial injections per month, all but three (Cases 4, 7, 20) were able to be maintained with chloro-

TABLE I. (continued)—CLINICAL DATA

Case No.	Age & Sex	Diagnosis	Duration of heart failure	Degree of failure at outset of study: pulm. rales	leg œdema	ascites	pleural effusion	No. of mercurial inj. before	Type of treatment before	Type of treatment after: KCl	NH4Cl	Dose of chlorothiazide	No. of mercurial inj. after	Duration of treatment	Wt. bef. (lb.)	Wt. after (lb.)	Date	Serum electrolytes: CO2 in mEq./l	Na mEq./l	K	C	NPN Mg%	Total protein G.%
12	68 M	A.S.H.D.	5 years	0	0	0	0	0–1/week	Neomerettes Digitoxin	0	0	250 mg. daily	0	2 weeks	162	160	May 22	—	135.0	5.1	108.0	50.0	
																	July 10	29.0	138.5	5.2	106.2	40.6	
																	Aug. 9	—	141.9	4.9	106.9	57.7	
13	86 M	A.S.H.D.	4 years	++	+++	0	0	Untreated	Digitoxin	+	0	250–1000 mg. daily	0	6 mths.	196	175	Oct. 31	29.4	147.1	3.6	104.6	—	
14	69 M	A.S.H.D.	4 years	+	+	0	0	0	Neomerettes Digitoxin	0	+	500–1000 mg. daily	0	6 mths.	155	153	July 3	—	140.0	6.0	100.8	—	
																	July 10	—	142.3	5.2	100.9	40.4	
																	July 21	—	140.2	4.7	103.2	—	
																	Aug. 21	—	—	—	—	32.8	
																	Nov. 1	30.3	143.6	6.5	99.1	42.0	
15	55 M	Cor pulmonale	7 years	++	+	0	0	0-2/mth.	Rolicton	0	0	500–750 mg. daily	0	4 mths.	176	163	July 11	—	138.5	5.7	99.0	53.1	
																	Aug. 23	—	141.9	5.3	95.8	64.3	
16	68 M	A.S.H.D.	6 years	++	+++	0	0	1/week	Neomerettes NH4Cl Digitoxin	0	+	500–1000 mg. daily	0	5 mths.	175	168½	May 9	—	138.0	4.3	106.0	30.0	
																	May 23	29.0	140.0	4.5	105.0	—	
																	Aug. 7	—	138.5	4.3	106.9	23.5	
																	Sept. 20	—	140.2	4.1	100.8	24.8	
17	61 M	A.S.H.D.	1 year	+	++	0	+	0	Rolicton Digitoxin	0	0	250 mg. daily	0	12 wks.	164	159	Mar. 29	—	147.0	4.9	101.0	23.7	
18	77 F	A.S.H.D.	6 years	+	++	0	0	2/week	Digitoxin	0	+	500–750 mg. daily	0	6 mths.	124	121	June 20	30.0	144.0	4.8	103.0	43.0	
																	July 11	—	140.9	5.1	103.4	37.5	
																	Aug. 16	—	143.6	5.1	103.2	27.3	
19	62 M	Cor pulmonale	4½ yrs.	+	++	0	0	1–2/week	Diamox Digitoxin	0	0	1000 mg. daily	0	3 wks.	202	203	May 23	30.0	135.0	4.0	99.0	46.0	
																	July 5	—	136.8	4.8	92.5	53.0	
20	75 F	A.S.H.D.	6 years	+	+	0	0	2/mth.	Neomerettes Digitoxin	0	+	750 mg. daily	1/mth.	12 wks	191	193	Apr. 18	27.0	144.0	4.7	100.0	51.0	
																	May 9	28.0	137.0	4.0	104.0	46.0	
																	Aug. 29	—	136.8	4.5	103.2	—	
21	49 F	R.H.D.	7 years	0	+	0	0	2/week	Neomerettes NH4Cl Digitoxin	0	+	1000–1500 mg. daily	0	8 wks	179	172	Apr. 20	25.0	144.0	3.8	97.0	53.0	
																	May 9	27.0	140.0	3.3	99.0	50.0	
																	May 30	24.0	144.0	4.5	105.0	30.0	
																	July 10	30.0	142.0	4.5	102.1	40.0	
																	Oct. 24	26.0	142.0	5.1	105.9	40.0	
22	62 F	A.S.H.D.	4 years	+	+	0	0	0–1/week	Neomerettes Digitoxin NH4Cl	0	+	500–1000 mg. daily	0	4 mths.	145	139½	Apr. 28	28.0	144.0	4.5	92.0	42.0	
																	May 23	—	133.0	4.5	100.0	44.0	
																	June 22	—	133.0	5.7	98.0	—	
																	July 22	28.0	136.8	5.1	100.6	37.2	
																	Aug. 2	28.0	147.1	5.6	101.0	35.5	
																	Sept. 19	—	136.8	5.5	101.0	—	
23	59 F	H.C.V.D.	4 years	+++	++	+	0	2/week	Neomerettes Rolicton NH4Cl Digitoxin	+	+	500 mg. daily	0	6 mths.	129	120	July 5	—	135.1	5.3	99.5	—	
																	July 19	30.0	140.2	5.3	100.0	38.8	
																	Aug. 1	24.0	145.3	4.0	104.0	45.3	
																	Aug. 27	—	143.6	4.9	100.0	—	
																	Nov. 10	—	140.0	4.0	96.0	—	

A.S.H.D. = arteriosclerotic heart disease; H.C.V.D. = hypertensive cardiovascular disease; R.H.D. = rheumatic heart disease.

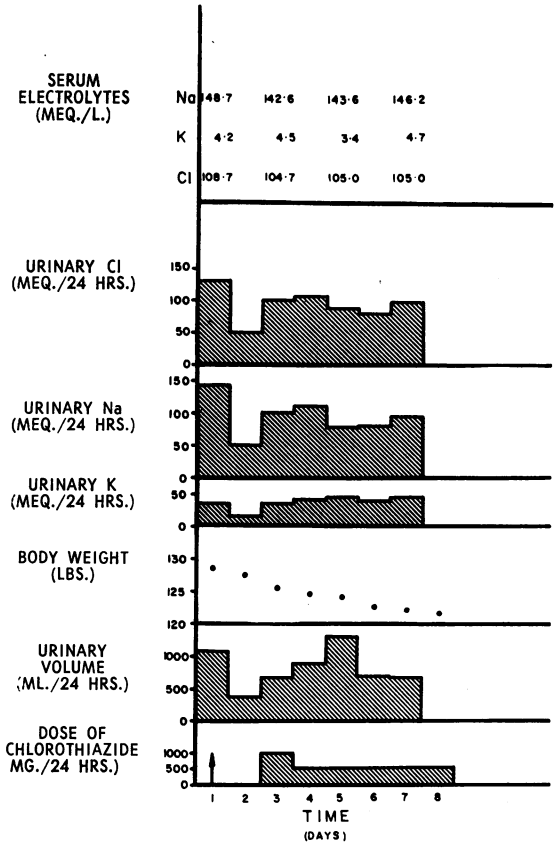

Fig. 5.—A.D., woman aged 59, hypertensive heart disease (Case 23, Table I). Note that response to 500 mg. daily in this case is as good as to 1000 mg. daily, and the latter approximates the response to mercurial injection (see arrow). The hypopotassæmia was quickly corrected by addition of 1 g. potassium chloride orally 3 times a day and without interruption of therapy with chlorothiazide.

thiazide alone. These three had been in severe heart failure for many years and had an enlarged, firm, tender liver with probably some degree of cardiac cirrhosis. Although they could not be treated with chlorothiazide alone, the frequency of mercurial injections was reduced, but at no time has it been possible to rid these patients completely of the peripheral œdema. In these cases equivalent clinical improvement could not be obtained merely by increasing the dose of chlorothiazide to 1½ to 2 g. daily for two days weekly. In the 14 cases which did respond to the use of chlorothiazide alone without the addition of mercurial injection, further improvement in their clinical state was associated with further reduction in body weight.

From the data in Table I, it can be seen that the daily maintenance dose ranged from 250 to 1000 mg., the average being about 500 mg. daily. However, when the patient was seen in the clinic, it was frequently noted that at times the daily maintenance dose was not adequate and there was a slight return of leg œdema or pulmonary rales associated with perhaps a gain of 1 to 2 lb. in weight over the previous week. Such patients were then treated with 1000 mg. in two doses of 500 mg. after breakfast and dinner for two days of each week, and instructed to continue with 500 mg. daily for the balance of the week. With such a modification in the treatment schedule, parenteral injections of mercurial diuretics were never required to maintain the œdema-free state.

In eight of these patients, omission of the chlorothiazide for several days (2 to 11 days) when patients would not attend clinic to obtain an additional supply of the drug, promptly resulted in a return of some of the signs and symptoms of heart failure with a gain in weight of from 2 to 7 lb. When treatment with chlorothiazide was again started, clinical improvement was again achieved quickly.

It should be noted that throughout this study, especially in the last four months, a more liberal salt intake was encouraged. Some patients returned to almost normal salt intake while on daily chlorothiazide therapy and were still able to be free of œdema.

Electrolyte Studies

The electrolyte disturbances noted occurred mainly at the onset of this study when the potency of this diuretic agent was not fully appreciated and much higher daily doses were employed than were actually required. The disturbances encountered were hypochloræmia, hyponatræmia, and hypokalæmia. These were never serious and were usually associated with clinical symptoms of weakness, lassitude, and some drowsiness.

Hyponatræmia occurred in only four cases where the serum sodium levels dropped to 132-135 mEq./l.; hypochloræmia was noted in two patients with serum levels below 95 mEq./l. and hypopotassæmia occurred in six cases where serum levels dropped to 3.3-3.8 mEq./l. No changes were noted in the CO_2 combining power. The symptoms as well as the serum electrolyte levels were quickly corrected by the addition of potassium chloride and/or ammonium chloride, as required.

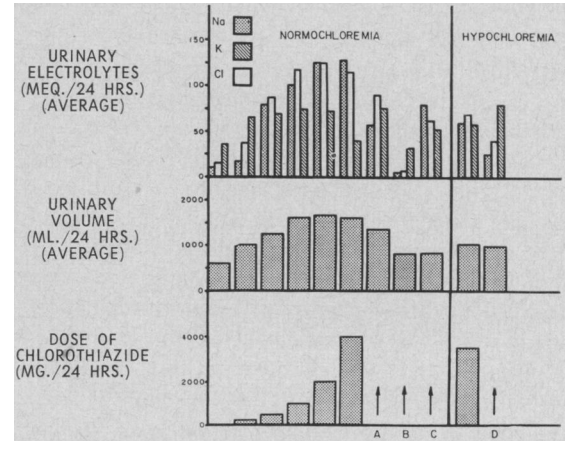

Fig. 6.—L.G., aged 57, male, rheumatic heart disease (Case 4, Table I). Hospitalized with intractable failure. Although chlorothiazide did produce a better diuretic response than other agents, the œdema persisted, with no reduction in blood volume. Compare the diuretic response obtained with intramuscular 2 c.c. of meralluride (A and D), chlormerodrin in daily doses of 3 tablets orally (B), oral aminoisometradine, 3 tablets daily orally (C). Note the decrease in diuretic response to chlorothiazide and meralluride in presence of hypochloræmia.

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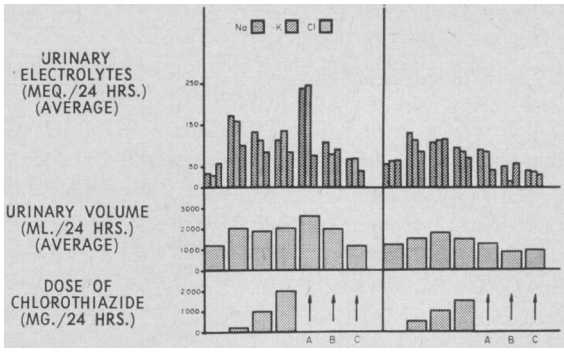

Fig. 7.—L.G., aged 57, male—5 weeks after a coronary thrombosis with no heart failure.
M.S., aged 65, male—4 weeks after a coronary thrombosis, minimal failure, but no peripheral œdema.
Compare the diuretic response of chlorothiazide to 2 c.c. of meralluride intramuscularly (A), 500 mg. of acetazolamide (B) and 3 tablets of chlormerodrin (C).

During the last four months of this study, when the average daily dose of chlorothiazide did not exceed 500 mg., or when larger doses of 1000 to 2000 mg., if required, were not given for more than a few days at a time, serum electrolyte disturbances were rare.

Side Effects

The prolonged daily administration of chlorothiazide seemed to be well tolerated by all the patients and in no instance was it found necessary to discontinue the drug because of any gastrointestinal complaints.

Serum non-protein nitrogen values, estimated at intervals during therapy, showed no significant changes other than would be expected from the disease state itself.

DISCUSSION

From the data it is evident that chlorothiazide is an effective oral diuretic which can be useful in initiating a prompt diuresis and in the long-term maintenance of patients with congestive heart failure, including cases of cor pulmonale.

Although this drug has the structure of a carbonic anhydrase inhibitor, studies of the pattern of sodium and chloride excretion in the 24-hour urine samples confirm the earlier observations of others[1-5] that the pattern closely resembles that obtained after intramuscular injections of mercuhydrin. Although the water intakes were uncontrolled, it is significant that the 24-hour urine output increased in all patients after administration of chlorothiazide. This increased water diuresis was always associated with a loss in body weight and some clinical improvement of the patient.

The degree of diuretic response was, as would be expected, more pronounced in those patients with the most peripheral œdema and was less marked once the patient was well compensated in the œdema-free state. Unlike the action of other carbonic anhydrase inhibitors, the prolonged daily administration of the drug to patients for periods up to six months has not led to the development of a state of drug tolerance.

After a period of study on hospitalized patients it was evident that the 24-hour diuretic response was somewhat proportional to increase in daily dosage from 250 mg. to 1000 mg. With doses of 1500 mg. daily, only a very slight additional diuretic response was evident, and with doses over 2000 mg. daily, no further significant diuretic response could be elicited in the patients studied. The maximum effect appeared to be achieved at a dose of 2000 mg. daily in two divided doses.

Comparison of the "potency" of chlorothiazide with that of mercuhydrin revealed that doses of 1000 to 2000 mg. daily were equivalent to 1 to 2 c.c. of mercuhydrin given intramuscularly (Figs. 4-7). In some patients diuretic response was more pronounced with 1000 mg. of chlorothiazide than with 2 c.c. of mercuhydrin. It was also noted early in the study that daily doses of 250 to 500 mg. were almost as effective as 1000 mg. and were less likely to result in disturbances in serum electrolytes. Accordingly, after the initial diuresis with 1000 to 2000 mg. daily for two days, the patients were maintained in the out-patient clinic with daily doses of 250 to 500 mg. If some residual œdema was still present at the time of the patient's weekly visit to the clinic, instead of giving mercuhydrin as was done previously, the dose of chlorothiazide was raised to 1000 mg. daily for two days followed by 500 mg. daily for the balance of the week. This proved an effective way to treat the long-term cases with chlorothiazide, and disturbances in serum electrolytes were rarely encountered in the last four months of this study.

In cases where there was a slight hypochloræmia, the diuretic response to chlorothiazide was slightly impaired, although still better than control levels. Accordingly, ammonium chloride was added to the regimen in many patients to correct the existing hypochloræmia.

In order to prevent the occurrence of hypochloræmia, enteric-coated ammonium chloride tablets were given to many patients in daily doses of 60 grains for three to four days of each week as long as they were taking chlorothiazide daily (Table I). The CO_2 combining power remained within normal limits in all patients throughout the period of study.

In comparing chlorothiazide to other oral diuretic agents, it appears to be more effective in causing an increase in 24-hour urine volume and excretion of sodium and chloride than chloromerodrin (Neomerettes), acetazolamide (Diamox) and aminouracils (Rolicton) (Figs. 6 and 7).

Since this study was begun, Freis and Wilkins[10] have called attention to the use of chlorothiazide in the management of patients with hypertension. This series of patients included two cases of hypertension with congestive heart failure. A review of the periodic blood pressure measurements in one patient before and during therapy with chloro-

thiazide revealed a drop in the systolic and diastolic blood pressure from $\frac{200\text{-}220}{95\text{-}110}$ to $\frac{150\text{-}170}{80\text{-}90}$ mm. Hg. In the other patient no significant changes were noted. Studies are now in progress in our cardiac clinic to evaluate the clinical use of chlorothiazide in a large number of patients with hypertension.

Chlorothiazide was also tried in three cases of nephrotic œdema without significant clinical improvement, although the drug did cause a slight increase in 24-hour urine volume and electrolyte excretion over control values. In one patient with cirrhosis of liver, ascites and leg œdema, a good diuretic response was obtained with chlorothiazide.

SUMMARY

The diuretic effects of chlorothiazide have been studied in six hospitalized patients and in 23 ambulatory patients with congestive heart failure for periods up to six months.

Chlorothiazide has been found to be the most potent oral diuretic agent available to date. In doses of 1000 to 2000 mg. daily it is equivalent in action to 1 to 2 c.c. of mercuhydrin intramuscularly.

Recommended dosage to initiate a diuresis is 1000 mg. for two days; this may be followed by a dose of 250 to 500 mg. daily for the long-term maintenance of the œdema-free state in patients with heart failure.

We would like to acknowledge the excellent technical assistance rendered by Mrs. Violet Foldes, and to thank Miss Ruth Hubner for invaluable assistance in helping to prepare this manuscript.

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RÉSUMÉ

L'introduction de la chlorothiazide dans le traitement de l'œdème cardiaque semble être une autre étape sur la route du diurétique idéal. Ce médicament qui possède certains traits d'un inhibiteur de l'anhydrase carbonique fut administré à 25 malades tant alités qu'ambulants, à l'Hôpital général juif de Montréal. Un bilan électrolytique et hémodynamique détaillé fut dressé dans chaque cas avant et pendant la période de traitement. Les doses de chlorothiazide employées varièrent entre 250 et 4000 mg. par jour. Des suppléments de chlorure de potassium et de chlorure d'ammonium furent administrés au besoin.

Le produit s'avéra utile non seulement dans l'entretien d'une diurèse déjà amorcée, mais aussi dans son déclanchement. L'excrétion des chlorures égala presque celle du sodium mais le potassium par contre fut excrété à un taux moindre. L'amélioration clinique suivit la diurèse dans chaque cas. Une femme atteinte d'ascite accusa des résultats surprenants avec des doses quotidiennes de 250 à 500 mg. Le médicament ne fut cependant d'aucune aide aux malades réfractaires aux autres diurétiques y compris les mercuriels.

L'effet diurétique augmenta proportionnellement à la dose jusqu'à concurrence de 1 g. par jour qui semblerait la dose d'attaque optimum dans la majorité des cas alors que 250 à 500 mg. soient suffisants pour poursuivre le traitment. Ce nouveau produit dépassa en efficacité tous les autres diurétiques oraux et se montra au moins l'égal du meralluride (Mercuhydrine) en dose intramusculaire de 1 ou 2 ml. L'administration quotidienne pendant plusieurs semaines fut remarquablement bien tolérée par tous les malades. Certains d'entre eux abandonnèrent même leur diète pauvre en sel sans reprise de leur œdème.

Case Reports

CHRONIC EMPYEMA DUE TO SALMONELLA ORANIENBURG* COMPLICATION OF AN OLD CHEST WOUND

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THE FOLLOWING CASE is of interest because of the unusual localization of *Salmonella oranienburg* in the right chest after a penetrating gunshot wound, and because the correct diagnosis was not made until 11 years after the injury when the patient developed a purulent bronchopleural fistula.

*From the Laboratory Services, Westminster Hospital, London, Ontario.

S. oranienburg was named after a town in Germany where it was first isolated by Kauffmann[1] in 1930. It belongs to group C according to the classification of Kauffmann and White, with its antigenic formula VI, VII: Phase 1, m and t.[2] *S. oranienburg* is frequently found in both animals and man in Canada[3] and the United States.[4, 5] It ranks amongst the five commonest types isolated from human infections in these countries. It has been found mostly in chickens both in the U.S.A.[8] and in Canada.[3] *S. oranienburg* was found in 19% of the animal isolations submitted to the Laboratory of Hygiene, Ottawa, between November 6, 1948, and October 31, 1952.[3] Poultry were the principal source of these strains. Since the introduction in 1941 of dried eggs from the U.S.A., numerous sporadic cases of human infection with this organism together with at least one outbreak have been reported in England.[2, 7–9]