Summary

Factors which contribute to salt and water retention in congestive heart failure are reviewed, with particular reference to the endocrine system.

Clinical observation of 14 patients with chronic congestive heart failure suggested an initial coexistent endocrine overactivity followed subsequently by adrenocortical insufficiency.

This premise was supported by the presence of hyponatraemia, a normal or elevated serum-potassium level with an increased blood urea in 14 patients with chronic heart failure which had become resistant to therapy with digitalis, a low-salt diet, and diuretics.

The urinary excretion of 17-ketosteroids was estimated in four of these patients, and in two the corticoid excretion was also assessed. Subnormal values were obtained in each instance, and in one patient were consistent with a diagnosis of Addison's disease. Following corticotrophin administration the urinary excretion of these steroids increased in each patient and was accepted as evidence that hypoadrenocorticism was due to anterior pituitary rather than adrenocortical failure.

Replacement therapy, using prednisolone, induced a greatly enhanced response to diuretics in all 13 patients who received this treatment. All were relieved of congestive heart failure and also, when coexistent, of left ventricular failure. Two patients died following pulmonary emboli.

A hypothesis is advanced regarding the endocrine adjustments which occur in heart failure and which could lead to the formation of oedema. The importance of these adjustments is described in relation to the treatment of heart failure.

The possible mode of action of prednisolone is discussed.

Parallels are drawn between the oedema of late-stage congestive heart failure, nephrotic oedema, and starvation oedema.

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CHLORMERODRIN: CLINICAL EFFECTIVENESS AND ABSENCE OF TOXICITY IN CONGESTIVE HEART FAILURE

REPORT OF A FOUR-YEAR STUDY

BY

WILLIAM A. LEFF, M.D.

AND

HARVEY E. NUSSBAUM, M.D.

From the Cardiac Service, Hospital of St. Barnabas and for Women and Children, Newark, N.J.

Organomercurial diuretics are widely recognized as the most potent and reliable of available diuretic agents. Until recently, satisfactory organomercurial preparations were available only for administration by injection, limiting their acceptability to patients. From the clinical standpoint, a need also existed for an oral organomercurial which could be administered frequently in relatively small doses. Such an agent would provide continuous diuresis, rather than the seesaw of dehydration and rehydration that occurs with the less frequent higher doses ordinarily employed when a diuretic is given by injection. Chlormerodrin ("neohydrin"*) ; 3-chloromercuri-2-methoxypropyl-urea, a non-ionic crystalline compound introduced in 1952, showed early promise of meeting this need. Our

*Neohydrin supplied through the courtesy of Dr. H. L. Daiell, Lakeside Laboratories, Inc., Milwaukee, Wis.

own preliminary clinical study (Leff and Nussbaum, 1953) indicated that most patients who had previously required meralluride ("mercuhydrin") injections at least once a week did as well or better on three or four tablets of chlormerodrin daily. Side-effects were few and not of a serious nature. Similar findings have been presented by other investigators (Moyer *et al.*, 1952; Finch, 1952; Mauriello and Re, 1953; Kaplan *et al.*, 1953; Bresnick and Abramson, 1953; Lawrence *et al.*, 1954; Doherty *et al.*, 1954; Kuchmeister and Kristal, 1955; Ginefra, 1955; Hvidsten, 1955; Moyer and Hughes, 1955; Evans and Massumi, 1956).

The observations over a four-year period now presented were made with particular attention to the relative safety of chlormerodrin. Whenever organomercurials are used as therapeutic agents, fear of their possible toxicity is likely to be expressed. Although we consider this fear to be unwarranted when modern organomercurial preparations are used, we remained aware that the following questions regarding the safety of these agents have not been fully answered: What are the possibilities that *inorganic* mercury will be deposited in the tissues during the course of therapy with *organic* mercurials? How much mercury can be quantitatively demonstrated in the kidney and other vital organs after extensive use of mercurial diuretics? Does impairment of renal function or permanent renal damage result from their use?

Over the period of study our patients were taking very large amounts of chlormerodrin by mouth following many years of treatment with parenteral meralluride. In pursuing our investigation we therefore laid great emphasis on obtaining kidney-function tests on the patients. Clinically, attention was focused for any evidence of renal insufficiency or renal damage. The overall plan also included histological study of tissues obtained at necropsy for evidence of mercurial damage, and quantitative tissue analysis for "metallic mercury" in the whole organs.

Clinical Results

During a four-year period 48 patients in chronic congestive heart failure have been maintained in fluid balance with the use of chlormerodrin, maintenance digitalis, and low-salt diet. Five additional patients developed gastro-intestinal symptoms—nausea, loss of appetite, vomiting, and diarrhoea—and could not tolerate the drug, regardless of rest periods or reduced dosage. These five cases were regarded as failures, and are not included in this long-term report.

The initial functional classification of the patients varied from class II to class IV, under the criteria of the New York Heart Association. Those in class IV were reduced to class II or III by active treatment with parenteral meralluride before changing to the oral regimen with chlormerodrin. It should be noted that continuance of the improved cardiac function was dependent on continued diuretic therapy. Most of the patients had received parenteral diuretic for several years before the change to chlormerodrin was made.

The aetiology of heart disease was varied (Table I). The ages ranged from 29 to 80 years (Table II), 65% being in the sixth and seventh decades. Dosage of chlormerodrin varied with response and tolerance of the patients (Table III).

Of the 48 patients, 43 were maintained free from any signs or symptoms of congestive failure, and did not

TABLE I.—*Aetiology in 48 Cases*

Arteriosclerotic heart disease (A.S.H.D.)	22
Hypertensive cardiovascular disease (H.C.V.D.)	9
Arteriosclerotic heart disease (H.A.S.H.D.)	2
Rheumatic heart disease (R.H.D.)	10
Luetic heart disease (L.H.D.)	5

TABLE II.—*Age and Sex*

	29	30–39	40–49	50–59	60–69	70–79	80	Total
Male	0	1	5	12	7	1	0	26
Female	1	2	4	6	6	2	1	22

TABLE III.—*Dosage*

Chlormerodrin	Mercury Equivalent	No. of Patients
2 tablets a day	20 mg.	11
3 " " " "	30 "	29*
4 " " " "	40 "	8†

* Includes 2 patients maintained on 1 tablet a day after the first 6 and 9 months, respectively.

† Includes 1 patient who occasionally took 6 tablets a day.

require additional parenteral mercurials. Five did require occasional booster injections of meralluride in addition to the daily chlormerodrin. After several weekly injections of meralluride, these patients were again able to be maintained on the daily oral mercurial for as long as three to seven months before requiring additional meralluride. Three patients developed diarrhoea taking four tablets daily. They were kept off the drug for two weeks, and then resumed, taking one tablet a day for a week and increasing the dose each week until three tablets a day were being taken after meals. One of these three patients developed soft stools about every fourth month during a three-year period. The remaining two developed diarrhoea in a single instance only. Evans and Massumi (1956) have pointed out, in this connexion, that the patient with heart failure and hepatoportal congestion often has gastro-intestinal symptoms, similar to those produced by drug irritation, which may clear up as the liver and intestines are unburdened of oedema. None of the patients developed any symptoms of mercurialism, or any similar reactions ascribable to hypersensitivity to mercurials.

Our experience with chlormerodrin has conclusively proved its effectiveness as a thoroughly safe and potent "continuous diuretic" agent. Once the dry-weight level was achieved with parenteral meralluride, the seesaw of accumulation and dehydration was rarely seen. The steady diuretic effect of chlormerodrin was in sharp contrast to the intermittent diuretic effect of periodic injections. In several patients, however, an occasional booster shot of the parenteral agent seemed to enhance the steady action of the oral organomercurial. The 48 patients included in this report showed no evidence of mercurial toxicity, as manifested by skin reactions, allergic phenomena (hypersensitization to mercury), renal damage, cardiovascular reactions, bone-marrow depression, or systemic reactions.

Effectiveness in the older age groups was striking. It is obvious that men and women in myocardial failure are now living much longer, owing to more accurate diagnosis, newer glycosides, sodium-restricted diets, and the use of effective non-toxic organomercurials. It should be emphasized that the aged can tolerate oral organomercurials effectively and without renal toxicity.

In the four years of our study the combined total of mercury contained in both parenteral and oral organo-

mercurials given to 48 patients ranged from 6,240 to 78,560 mg. The majority of the patients—34 (71%) received a combined dosage ranging from 20,000 to 60,000 mg. of bound mercury.

In none of the 48 patients was there any clinical or laboratory evidence of renal impairment or permanent renal damage due to the massive quantities of parenteral and oral organomercurial given over the entire four-year period. In spite of the tremendous total dosages, it will be noted (Table IV) that there were practically no abnormal urinary findings. Seven patients exhibited occasional (1+ to 4+) albuminuria, but it is not unreasonable to suppose that this was due to renal passive congestion, and not to any effect of the diuretic. Race *et al.* (1956), at the Mayo Clinic, reported that albuminuria existed in 88% of a group of 161 patients

with congestive failure who had come to necropsy without clinically obvious causes for albuminuria, and who showed no histological changes which would account for albuminuria. There was a tendency for the albuminuria to parallel the severity of the cardiac failure.

Of greater significance in our own laboratory data were the consistent findings of normal blood urea nitrogen throughout this study. In fact, urea nitrogen improved in some patients—a manifestation of improved cardiovascular-renal dynamics. In addition, there were the noteworthy normal findings of blood creatinine, N.P.N., and urea-clearance tests.

Deaths During Study

Eight deaths occurred among the 48 patients, none of which was related to mercury (Table V). Three patients

TABLE IV

Case No.	Age and Sex	Race	Aetiology	Chlormerodrin			Meralluride			Total Mercury Oral and Parenteral (mg.)	Laboratory Studies				
				Daily Dose (Tablets)	Duration (Mths)	Total Mercury (mg.)	Weekly Dose (ml.)	Duration (Years)	Total Mercury (mg.)		Urine	Urea Nitrogen	Creatinine	N.P.N.	Urea Clearance
1	59 M	C	H.C.V.D.	2 b.i.d.	21	23,520	2	10	40,000	63,520	Normal	12.3 25.0 14.4	1.3	25.0	95%
2	62 M	C	R.H.D.	1 "	15	8,400	2	1	4,000	12,400	"	8.4	1.0	17.4	101%
3	57 F	C	R.H.D.	1 "	19	10,640	4	3	24,000	34,640	"	9.0	0.8	18	94%
4	53 M	C	H.C.V.D.	1 "	20	11,200	2	3	12,000	23,200	"	"	0.4	22	"
5	67 F	C	H.C.V.D.	1 t.i.d.	19	15,960	"	None	13,330	15,960	"	10.4	"	21	100%
6	30 M	C	R.H.D.	1 "	36	30,240	2	3 1/3	13,330	43,570	"	12.0	"	15.0	"
7	80 F	C	A.S.H.D.	1 "	24	20,160	"	None	"	20,160	"	"	"	"	"
8	59 F	C	H.A.S.H.D.	1 b.i.d.	24	13,440	2	1	4,000	17,440	"	"	"	"	"
9	45 M	C	L.H.D.	1 t.i.d.	36	30,240	2	2	8,000	38,240	Alb.; few casts	14.3 12.9	1.4	32.4	155%
10	62 M	C	H.A.S.H.D.	1 "	22	18,480	4	1	8,000	26,480	Normal	13.5	1.3	28.2	193% 177%
11*	29 F	W	R.H.D.	1 o.d.	6	12,600	2	2½	10,000	22,600	"	11.5	1.0	20	"
12	59 M	W	A.S.H.D.	1 t.i.d.	30	25,020	1	1	2,000	27,020	"	12	1.2	12	"
13	45 M	W	R.H.D.	1 q.i.d.	24	26,880	4	3	24,000	50,880	"	11.3	"	"	88.4%
14	40 F	W	R.H.D.	1 b.i.d.	16	8,960	1	3	6,000	14,960	Occ. alb.	10	1.6	22	"
15	54 M	W	A.S.H.D.	1 t.i.d.	24	20,160	2	1	4,000	24,160	Normal	15.0	"	"	"
16*	50 M	C	R.H.D.	1 "	24	20,160	2	½	2,000	22,160	"	10.6 19.2	1.4	30	"
17	46 F	C	H.C.V.D.	1 b.i.d.	18	10,080	2	5	20,000	30,080	Alb. trace	15.0	1.2	"	"
18	48 M	W	A.S.H.D.	1 t.i.d.	24	20,160	2	2	8,000	28,160	Normal	12.4	1.1	"	"
19	62 M	C	L.H.D.	1 "	24	20,160	"	None	"	20,160	Alb. 4+ prior to oral diuretic therapy	"	"	"	"
20*	67 F	W	A.S.H.D.	1 b.i.d.	30	16,800	2	2	8,000	24,800	Normal	16.5	2.0	"	"
21*	48 M	C	L.H.D.	1 t.i.d.	36	30,240	2	4	16,000	46,240	"	15	1.8	28.1	92%
22	58 M	C	H.C.V.D.	1 "	42	35,280	2	7	28,000	63,280	"	22.0	2.0	"	"
23*	67 M	W	H.A.S.H.D.	1 b.i.d.	4	2,240	2	1	4,000	6,240	"	14.4	1.8	"	"
24	72 M	C	A.S.H.D.	1 t.i.d.	12	10,080	2	2	8,000	18,080	"	"	"	"	"
25	68 F	C	A.S.H.D.	1 "	24	20,160	2	2	8,000	28,160	Alb. 4+	10.9	1.8	"	"
26	47 M	W	A.S.H.D.	1 "	42	35,280	1	2	4,000	39,280	Normal	11	1.2	24	"
27*	48 F	W	R.H.D.	1 q.i.d.	18	20,160	"	None	"	20,160	Alb. 1+	24 21.9	2.1	42 40	"
28	59 M	W	A.S.H.D.	1 t.i.d.	9	10,920	1	2	4,000	14,920	Normal	14	1.4	24	"
29	52 M	W	A.S.H.D.	2 b.i.d.	15	16,800	2	2	8,000	24,800	"	"	"	"	"
30*	71 F	C	A.S.H.D.	1 t.i.d.	7	5,880	2	4	16,000	21,880	Occ. alb.	18.0	2.0	"	"
31	57 M	C	A.S.H.D.	2 b.i.d.	24	26,880	4	1	8,000	34,880	Normal	10.1 12.5	"	24	"
32	57 M	W	A.S.H.D.	1 "	34	19,040	2	2	8,000	27,040	"	15	"	"	"
33	67 F	C	L.H.D.	2 "	17	19,040	2	1	4,000	23,040	"	"	"	"	"
34	73 F	C	A.S.H.D.	1 t.i.d.	48	40,320	2	6	24,000	64,320	"	19.6 10.5	0.9	29.4	109% 125%
35	60 F	W	R.H.D.	1 "	30	25,200	"	None	"	25,200	"	"	"	"	"
36	49 F	C	H.C.V.D.	2 b.i.d.	18	20,160	"	"	"	20,160	"	13.8	"	"	"
37*	65 M	C	A.S.H.D.	1 t.i.d.	12	10,080	2	2½	10,000	20,080	"	15.4	1.4	"	"
38	56 M	W	A.S.H.D.	1 "	24	20,160	2	3	12,000	32,160	"	14	1.2	30	84% 92%
39	60 M	C	A.S.H.D.	1 "	30	25,200	2	1	4,000	29,200	"	"	"	"	"
40	53 F	C	A.S.H.D.	1 b.i.d.	19	10,640	"	None	"	10,640	"	12.4	"	"	"
41	63 M	C	A.S.H.D.	1 t.i.d.	42	35,280	2	1	4,000	39,280	"	9.8	"	"	"
42	64 F	C	A.S.H.D.	2 b.i.d.	38	42,560	2	9	36,000	78,560	"	10.8	1.4	33	129% 44% 66.6% 51.3%
43	58 F	C	H.C.V.D.	1 t.i.d.	36	30,240	"	None	"	30,240	Occ. casts	14.7 22.8	1.2	34.2	"
44	55 F	C	H.C.V.D.	1 "	22	18,480	"	"	"	18,480	Normal	24.0 18.0	1.8	"	"
45	58 M	W	A.S.H.D.	1 "	48	40,320	2	5	20,000	60,320	"	10.7	"	22	90% 94% 80.2% 90% 100% disability
46	38 F	C	R.H.D.	1 b.i.d.	36	20,160	2	4	16,000	36,160	"	15	"	38.7	148% 119%
47	55 F	C	A.S.H.D.	1 t.i.d.	42	35,280	2	2½	10,000	45,280	"	"	"	"	"
48	30 F	C	R.H.D.	1 "	38	31,920	2	1	4,000	35,920	"	11.0 15.0	0.9 1.2	27 38	"

Note.—Complications occurred in the following cases. Case 13: Post-commissurotomy. Case 17: Grade 3 retinopathy. Case 19: Anaemia, luetic nephrosis, and heart block. Case 25: Kimmelstiel-Wilson disease and diabetes. Case 38: An occasional loose stool.

* Died during study. † Necropsy performed. Chlormerodrin contains 10 mg. of mercury per 18.3-mg. tablet. Meralluride contains 39 mg. of mercury per ml. of solution.

died suddenly of coronary thrombosis. They had been completely free of any signs and symptoms of failure up to the day of death. A fourth patient died of toxæmia and acidosis following amputation of a leg necessitated by saddle embolism. She was not in failure at the time of the embolic accident. Another patient had syphilitic heart disease with aneurysmal dilatation of the aorta, and aortic insufficiency, with marked hypertrophy

TABLE V.—Deaths During Chlormerodrin Study

Duration	Case No.	Age	Aetiology	Cause of Death
7 months	30	71	A.S.H.D.	Acute coronary thrombosis
4 "	23	67	H.A.S.H.D.	" " "
12 "	37	65	A.S.H.D.	" " "
30 "	20	67	A.S.H.D.	Embolism " to femoral artery; amputation
36 "	21	48	L.H.D.	Aortic aneurysm
18 "	27	48	R.H.D.	Pulmonary embolism
24 "	16	50	R.H.D.	Congestive failure (subclinical)
33 "	11	29	R.H.D.	(1) Endocarditis, acute bacterial, of mitral and tricuspid valves. (2) Subacute and chronic pyelonephritis. (3) Nephrosclerosis, benign

of the left ventricle. He died suddenly, following an episode of severe chest pain. Permission for necropsy was not obtained, but the clinical picture suggested a ruptured aneurysm with haemorrhage. He showed no signs of failure up to the time of death.

Permission for necropsy was obtained in the three other patients who died during the study. Detailed case histories on these patients follow.

Case 27

When first seen in the clinic, this patient, a white woman aged 48 with R.H.D., was classified as having mitral stenosis and insufficiency, and questionable aortic insufficiency with slight hypertrophy of the right and left ventricle, class II. She was maintained in fluid balance with digitalis and a low-salt diet for two years. She then presented evidence of acute rheumatic fever, and her failure increased to class IV. She was hospitalized, improving considerably on symptomatic therapy. She was then followed in the clinic as a class II patient, on chlormerodrin (4 tablets daily; 40 mg. Hg), in addition to maintenance digitalis and a salt-free diet. She remained in fluid balance for 18 months on this regimen. She was later seen by a private physician, who advised her that she did not require digitalis or chlormerodrin. Twelve weeks later she was admitted to the hospital in a moribund condition, with irreversible failure. She did not respond to any therapy, and died suddenly.

Necropsy showed a rheumatic calcified mitral valve and a partially calcified aortic valve with hypertrophy of both right and left ventricles. There was a large haemorrhagic infarct of the right lower lobe. Sections of the kidney

FIG. 1.—Case 27. Renal tissue shows congestion, with moderate glomerulonephritis. (×65.)

FIG. 2.—Case 27. Liver tissue shows only passive congestion and early mild portal cirrhosis. (×65.)

(Fig. 1) showed cloudy swelling in the tubules with some increased cellularity of the glomerulus. There was no evidence of tubular necrosis. Sections of the liver (Fig. 2) showed congestion around the central vein with haemosiderin deposits. There was no disruption of liver architecture.

The patient received chlormerodrin equivalent to 20,160 mg. Hg. Analysis of the internal organs for retention of mercury demonstrated that the kidney contained only 11.48 mg. Hg per 100 g. of dry tissue. Comparable amounts for the other organs are shown in Table VI.

Case 16

This patient, a coloured man aged 50 with R.H.D., had rheumatic aortic stenosis, mitral stenosis, and insufficiency. He was graded class II and was kept in fluid balance with

TABLE VI.—Tissue Analysis for Mercury

	No. with Renal Disease Unrelated to Mercury, Found at Necropsy	Organo-mercurials (Total mg. Hg)	Kidney	Liver	Heart	Spleen	Large Intestine	N.P.N. Studies			
								Patients	No. Uraemic	Range in Non-uraemics (mg./100 ml.)	Average of All Patients (mg./100 ml.)
(mg. Hg per 100 g. Dried Tissue)											
Griffith and others (1954)*											
15 cases	9	None	2.05	0.37	—	0.12	—	4 cases	1	55-115	122
14 „	9	400 or less	2.96	0.34	—	0.04	—	8 „	2	33-88	66
16 „	12	400 or more (av. 4,692)	15.29	1.38	—	0.32	—	6 „	1	36-82	73
Present Study											
Case 27	0	20,160	11.48	0.694	0.0144	—	1.34	{ 40 mg. of N.P.N. per 100 ml.			
„ 16	0	22,160	9.63	0.474	0.0006	—	0.40	42	„	„	„
„ 11	+	22,600	15.68	0.773	None	0.221	7.3	30	„	„	„
								20	„	„	„

* Values for mercury shown are averages for patient groups.

chlormerodrin (equivalent to 30 mg. Hg daily) for two years, along with maintenance digitalis and a salt-free diet. He received 2 ml. of meralluride for six months prior to attending the cardiac clinic.

He developed a bradycardia of 40 with A-V block, and had several episodes of Stokes-Adams syndrome. During these attacks he did not show any clinical signs of failure. The last episode of syncope, for which he was hospitalized, showed electrocardiographic evidence of complete dissociation with a ventricular rate of 34. In the ensuing ten days he slowly developed irreversible myocardial failure in spite of all therapy and died on the twelfth hospital day.

Necropsy showed aortic and mitral stenosis with hypertrophy of the right and left ventricles. Sections of the kidney showed no tubular necrosis (Fig. 3). The basement membrane of the tubules appeared sharp, without any disruption of its normal architecture. Sections of the liver showed congestion about the central vein with deposits of haemosiderin (Fig. 4). There was no damage to the liver cells.

This patient received chlormerodrin and meralluride equivalent to 22,160 mg. Hg. Analysis of tissues for mercury, however, showed a concentration of only 9.63 mg. per 100 g. of dry tissue, and correspondingly small amounts in other organs. Note that the amount detected in cardiac tissue was negligible (Table VI).

Case 11

This patient, a white woman aged 29 with R.H.D., was a class II cardiac case with mitral stenosis and insufficiency, and aortic insufficiency. She had received weekly parenteral organomercurial therapy (meralluride, 2 ml.) for two and a

FIG. 3.—Case 16. Renal tissue shows congestion, without tubular necrosis. ($\times 110$.)

FIG. 4.—Liver of Case 16. No damage to cells. Congestion surrounding central vein, with deposits of haemosiderin. ($\times 140$.)

FIG. 5.—Case 11. Thickening of glomerular capsule and of tubular basement membrane, without tubular inflammation or necrosis. ($\times 110$.)

FIG. 6.—Liver of Case 11. No evidence of necrosis. Section shows congestion and oedema, with deposits of haemosiderin. ($\times 140$.)

half years prior to attending the clinic. She was then placed on chlormerodrin, three tablets equivalent to 30 mg. Hg a day, for six months. At the end of that period she required only 10 mg. a day, which she continued for two years and three months. She also received prophylactic oral penicillin. She then developed symptoms and signs of bacterial endocarditis proved by blood cultures, but did not respond to treatment in spite of massive combined antibiotic therapy. The terminal clinical picture was myocardial failure.

Necropsy revealed acute and chronic endocarditis of the mitral and tricuspid valves; hypertrophy of the right and left ventricles; subacute and chronic pyelonephritis; nephrosclerosis, benign; and chronic passive congestion of the liver. Sections of the kidney showed some thickening of the capsule of the glomerulus and thickening of the basement membranes of the tubules (Fig. 5). There was no inflammation or necrosis of the tubules. Some sections showed thickening of the smaller arterioles. Sections of the liver showed congestion, oedema, and deposits of haemosiderin (Fig. 6). There was no evidence of necrosis. The patient received the equivalent of 22,600 mg. Hg as organomercurial diuretics. Her kidneys contained less than 16 mg. Hg per 100 g. of dry tissue.

It is notable in Case 11—which has the greatest concentrations among our three patients in the kidneys, liver, and large intestine (Table VI)—that no mercury was detected in the cardiac tissue. In all three cases the mercury content of the heart muscle was infinitesimal. This analysis stands in strong evidence against the direct action of mercury from organomercurial diuretics upon the heart muscle.

Thus none of our patients who came to necropsy showed evidence of any glomerular, renal tubular, hepatic, or cardiac pathology attributable to mercury.

Discussion

The lack of any renal toxicity ascribable to the diuretic in our patients corroborates early experimental results with chlormerodrin in laboratory animals. Handley, Chapman, and Moyer (1951) found that no diarrhoea, stomatitis, or other evidences of severe reaction to mercurials were sustained by dogs given chlormerodrin or meralluride, at doses several times the therapeutic level, over a period of four months. Similarly, histological studies of renal tissue from rats and guinea-pigs given massive doses of chlormerodrin revealed no significant structural changes (Fig. 7).

It is interesting to compare our analysis of human tissues for mercury with a study by Griffith *et al.* (1954). These investigators analysed the organs of 45 patients with congestive heart failure. Of the group studied, 15 had no record of having received mercury. Amounts of mercury found in their tissues are shown in the top line of Table VI. Since both young and old individuals were included in this group, it could be assumed that a trace of mercury may be found in the tissues at all ages. Therapeutically, 14 persons received less than 400 mg. of organomercurial, and 16 received 400 mg. or more. The latter group averaged 4,692 mg. The mercury content of their livers, spleens, and kidneys are shown in Table VI. Griffith *et al.* concluded that the N.P.N. values, available in 18 of the 45 patients, could not be interpreted as indicating that the amounts of mercury in the tissues of these patients were harmful. It should be noted that two-thirds of their cases involved renal disease—not of the type caused by mercurial damage or toxicity. The high N.P.N. values were consistent with the type of renal pathology.

In our own patients the amounts of organomercurial received were all in a narrow range, just above 20,000 mg. This range is roughly five times as great as the highest average of Griffiths *et al.*, and about 50 times greater than the average for their patients who received less than 400 mg. of mercury. N.P.N. values were lower in our patients than the average in their patients.

Despite the much larger amounts of organomercurial taken by our patients, the mercury content of the kidneys was less in two cases and about the same in one. For some reason, in spite of the much greater total dosage,

the mercury content of the kidney of our patients was *not* proportionately higher than that of the patients of Griffiths *et al.*

Part of the difference between our results and theirs may be related to the large number of cases with renal disease, unrelated to organomercurials, in their study (Table VII). Our patient with highest kidney mercury

TABLE VII.—*Kidney Disease in 45 Cases (Griffiths et al., 1954)*

	15 Cases No Hg	14 Cases 400 mg. Hg or Less	16 Cases 400 mg. Hg or More
Nephrosis	2	2	2
Renal infarct	1	0	2
Pyelonephritis	0	1	2
Nephrosclerosis	6	6	5
Hydronephrosis	0	0	1
No disease	6	5	4

content (Case 11) had pyelonephritis and benign nephrosclerosis. Our other two cases, both with low kidney mercury content, had no renal disease. Apparently, relatively little mercury is accumulated in the "normal" kidney of the patient with congestive heart failure. On the other hand, even where there is advanced kidney damage from other causes, as in their patients and our Case 11, only a slight increase in mercury content can be noted. The latter findings support the clinical thesis that organomercurials can be used in the presence of kidney damage so long as diuresis is constant.

Conclusions

In our opinion, this clinical and laboratory investigation disproves the fear of an "inorganic mercury" effect from the retention of massive cumulative doses of parenteral and oral organomercurials. If there was a splitting off of inorganic mercury ions from the large amounts of organomercurials used in this series the effect upon the kidney should have been evident clinically, histologically, and in the tissue analysis. There was no renal damage from mercury in any of these areas.

Our clinical experience with the organomercurials—meralluride and chlormerodrin—supports the concept of a "specific organic molecule" as being responsible for the diuretic action, rather than a mercury action *per se*. This concept was stressed by Saxl and Heilig (1920) in their original description of the modern use of organomercurials as diuretics. More recent authorities (Smith, 1951; Strawn *et al.*, 1956) agree that mercurials are excreted as organic compounds, and that the mercury is not split off. Goodman and Gilman

FIG. 7.—Typical sections of renal tissue from experimental animals given chlormerodrin twice weekly. No pathological changes are seen. (A) Guinea-pig, 4 mg. Hg/kg. subcutaneously, 35 doses. (B) Guinea-pig, 6 mg. Hg/kg. orally, 35 doses. (C) Rat, 9.6 mg. Hg/kg. subcutaneously, 64 doses. (D) Rat, 20 mg. Hg/kg. orally, 72 doses. (Pathological evaluations by Francis D. Speer, Professor of Pathology, New York Medical College.) ($\times 103$.)

(1955) state: "Older evidence suggested that the mercurials were active by virtue of their release of mercuric ion (Hg^{++}). However, it is more likely that organic mercury complexes dissociate as such and act in the form of the specific organic molecule, R-Hg^{+} ." The N.N.R. specifications for chlormerodrin explicitly state that there should be "absence of ionizable mercury and other heavy metals, as indicated by the standard sodium sulfide reaction" (Council on Pharmacy and Chemistry, 1953).

Most prejudice against organomercurial diuretics is probably ascribable to the unsupportable assumption that modern organomercurials have the same basic toxicity as such toxic inorganic mercurials as bichloride of mercury and calomel. The few early organomercurials with significant toxicity, such as "novasurol" and "esidrone," have been out of use for many years, but their memory serves to prejudice the minds of many physicians.

Because the organomercurials are the most potent diuretics, and so vital in prolonging the life of the cardiac patient, the unwarranted fear of their prolonged use must be dispelled if we are to help the cardiac patient to more years of comfortable living and employment. The absence of mercurial toxicity in our patients, who took massive total doses of organomercurials over a four-year period, should remove all fear of the use of these important therapeutic agents. It is our opinion that the organomercurial drug is itself harmless provided that the physician is master of his therapy at all times. He must be alert to signs or symptoms of allergy or sensitization to the medication. He must not permit the repeated use of the organomercurials, or any other drug as a matter of fact, when such use elicits continued allergic reaction. Most of the so-called toxic reactions reported to be due to organomercurials might have been avoided if the physician had become aware of the sensitivity symptoms.

Summary

Forty-eight clinic patients in chronic congestive heart failure were maintained in a state of cardiac compensation with the oral organomercurial chlormerodrin (neohydrin) over a four-year period. All patients received maintenance digitalis and were advised to stay on a salt-free diet.

An additional five patients treated during the four-year period had gastro-intestinal disturbances manifested by nausea, vomiting, and diarrhoea. These patients were withdrawn from the study because of their intolerance to the drug.

Of the 48 patients, 39 had previously received parenteral meralluride (mercuhydrin) from six months to ten years prior to initiation of treatment with the oral drug; the other nine had never received parenteral organomercurials prior to treatment with chlormerodrin.

Combined total dosage of oral and parenteral mercury ranged from 6,240 to 78,560 mg. per patient, with no clinical evidence of renal toxicity due to the organomercurials.

Renal function was tested in every patient by means of urinalysis and tests for urea nitrogen, N.P.N., and creatinine. Urea-clearance tests were done in 17 patients. The sole abnormalities detected were occasional albuminuria in seven.

Of the eight deaths in the series, none of which were related to toxicity of the diuretic, three came to necropsy. There was no gross or microscopical evidence of renal damage due to mercury.

Tissue analysis for mercury revealed a small mercurial content in the kidneys, and infinitesimal amounts in heart muscle, liver, spleen, and large bowel.

Chlormerodrin showed no evidence of renal toxicity over a four-year period. Most so-called "toxic reactions" to organomercurial diuretic therapy can be eliminated by proper control of therapy in sensitive patients.

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The *Handbook* of University College Hospital, London, gives information on clinical pathology, preparation of patients for surgery and various types of examination, medico-legal topics, and much else besides. It also includes some tables of normal values. The editors are Dr. T. D. Whittet, Ph.D., chief pharmacist to the hospital, and Professor M. Maizels and colleagues of the department of clinical pathology, and it is obtainable from Dr. Whittet for 10s. 6d. (postage 6d.). In addition, the hospital issues "Therapeutic Notes," which are pamphlets providing in a small compass useful information on groups of drugs. Number 1, for instance, is on haemopoietic substances; number 2 on barbiturates; number 5 on penicillin. Leaflets are also provided which give supplementary formulae to those listed in the *B.P.*, *B.P.C.*, and *B.N.F.* The *Pharmacopoeia* issued by the Hospital for Sick Children, Great Ormond Street, contains instructive therapeutic notes besides a list of 210 prescriptions for children. The notes give information in summary form on the commonly prescribed groups of drugs such as antihistamines, sulphonamides, antibiotics, analgesics, and vitamins. It is obtainable for 10s. 6d. (postage 6d.) from the secretary of the hospital.