The calculated ratios of titres of serum A to B and A to C for each laboratory are also given in Table I, and it is interesting to note that they closely approximated to the theoretical values of 1:5 and 1:25.

The test dose of virus varied between the different laboratories from 30 to 350 TCID₅₀, but there was no evidence that the variation was in any way related to the variation in serum titres.

Potency of Sera in Relation to the Standard

Each of the three standards was assigned a potency of 10 units per ampoule of dry preparation. For each laboratory the potencies of the 15 positive test sera were calculated in terms of the appropriate standard (by dividing the mean titre of each serum by the mean titre of the standard and multiplying by 10) and expressed in units per millilitre. These potencies are given in the Chart and in Table II. It is evident that in general the agreement between the five laboratories was extremely close; with four of the 15 positive sera the variation in potency was less than twofold, and with all but two sera (D-2 and E-3) was within fourfold. It is also evident that the agreement was greater than that obtained when the potencies were expressed in terms of titre-dilutions.

Additional Tests With the Standard Preparations

A number of additional tests were made in the Biological Standards Control Laboratory, the results of which are given in Table III. These results indicate that there was little variation in antibody titre from ampoule to ampoule with each of the three standard preparations. The results also give an indication of the degree of stability of both the dry and reconstituted standards.

The weight of total solids per ampoule was determined for each of the three standard preparations (Table IV). Since each ampoule contains 10 units of antiserum, it is calculated that: 1 unit is contained in 0.01078 g. of the type 1 preparation; 1 unit is contained in 0.01046 g. of the type 2 preparation; and 1 unit is contained in 0.01048 g. of the type 3 preparation.

Conclusions

A collaborative study in which five laboratories took part showed that close agreement was obtained between the different laboratories when the type 1, 2, or 3 neutralizing potencies of poliomyelitis antisera were determined with reference to freeze-dried preparations of antisera. It was therefore decided, with the agreement of those who participated in the study, to establish the three freeze-dried preparations of antisera as British Standard Poliomyelitis Antisera types 1, 2, and 3, and to assign to each a value of 10 units per ampoule. It will now be possible to express the neutralizing potency of sera in terms of units and to abandon the unsatisfactory method of using titre-dilutions.

The standard antisera will be held by the Department of Biological Standards, National Institute for Medical Research, Mill Hill, London, and may be obtained on request by manufacturing and research laboratories.

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ACTION OF CHLOROTHIAZIDE AND "ORADON," ALONE AND IN COMBINATION

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It has been claimed by many that chlorothiazide is superior to other diuretics, that it is effective in all forms of oedema, and that it has no significant side-effects (Ford *et al.*, 1957, 1958; Laragh *et al.*, 1958; Watson *et al.*, 1958; Goodkind *et al.*, 1958; Wener *et al.*, 1958). Later communications, however, have not always been able to substantiate these claims, and caution in the indiscriminate use of the drug has been suggested (*Brit. med. J.*, 1957). Hypokalaemia (Laragh *et al.*, 1958; *Brit. med. J.*, 1958; Slater and Nabarro, 1958), failure to respond after prolonged administration (Slater and Nabarro, 1958; Read *et al.*, 1958), and the production of hepatic coma in cirrhotic patients (Read *et al.*, 1958) have all been reported, and as a result of these studies it would seem wise to carry out routine plasma electrolyte determinations during treatment. In this way oral supplements of potassium can be given if necessary or therapy curtailed if it proves impossible to maintain normal plasma levels.

Laragh *et al.* (1958), Bayliss (1958, personal communication), and Bayliss *et al.* (1958) noticed that the addition of mercurial injections to oral chlorothiazide significantly augmented the sodium and water diuresis. This observation prompted us to reassess the value of combined mercurial and chlorothiazide therapy, not only with injected mercurials but also with an oral form. Such a combination might give a therapeutic response with lower dosages and a lower incidence of side-effects, particularly hypokalaemia, which would be of advantage under the conditions of general practice. During the trial we were also able to evaluate the oral mercurial and to make some interesting observations on the potassium excretion pattern of subjects taking chlorothiazide with and without potassium supplements.

Material and Method

The five patients studied in detail had all been suffering from persistent oedema with only fair or poor response to injected mercurials; four of these had congestive heart failure from different causes and one had the nephrotic syndrome.

The usual dose of chlorothiazide, given alone or in combination, was 0.5 g. twice daily, although one patient (Case 5) required 2 g. daily.

The oral mercurial chosen for this study was 3-hydroxy-mercuri-2-methoxy-1-succinimidopropane, theophylline hydrate (known as "oradon"), which has been reported (Hvidberg and Nielsen, 1957) as having an absorption of up to 54% of ingested mercury as judged by urinary recovery and therefore comparing favourably with chlormerodrin, which is reported as

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having an absorption in ingested mercury up to 10% (Greiner and Gold, 1953; Moyer *et al.*, 1953; Doherty *et al.*, 1954; Lawrence *et al.*, 1954). Animal studies also demonstrated increased absorption, as Lund (1958) found that the amount of mercury absorbed with oradon was 60–67% higher than that with chlormerodrin, despite considerable species variation. The daily dose of oradon used was the equivalent of 30 to 60 mg. of mercury (3 to 6 tablets), and was given after meals in all cases.

Precedence was given alternately to the diuretics in different patients to avoid bias in favour of either medication, and a stable state with normal plasma electrolyte levels was obtained before and after each period of treatment whenever the clinical condition of the patient allowed.

The routine treatment necessitated by the respective conditions, including digitalis, antibiotics, prednisone, etc., was continued throughout the study, being modified only by clinical necessities.

Sodium intake was restricted to approximately 25 mEq daily, except in one case (No. 3), where 50 mEq daily was allowed. Additional potassium chloride was given orally as dictated by plasma levels or clinical findings. Ammonium chloride (60 gr. (4 g.) daily) was given when the plasma chloride fell below 90 mEq/litre, preventing hypochloraemia.

Daily urinary excretion of sodium and potassium was estimated by E.E.L. flame photometer, and the accuracy of the total daily volumes of urine was checked by frequent urinary creatinine estimations. The daily excretion of mercury was estimated by the method of Rolfe *et al.* (1955), oxidation being followed by extraction with dithiazone and measurement of colour. Chlorothiazide excretion was determined by measurement of colour of the azo dye produced by diazotization and coupling after cleavage of the heterocyclic portion.

Case 1

Prior to admission this patient, a man aged 60, had increasing oedema and dyspnoea despite daily digitalis and twice-weekly mercaptomerin sodium. On admission he was found to have bronchopneumonia with purulent sputum and cardiac failure with marked oedema, elevated pulsatile jugular venous pressure, and an enlarged pulsatile liver.

TABLE I.—Results of Treatment

Case No.	Daily Dosage of Diuretics	Average Urinary Excretion in mEq/24 Hours			Daily Intake of Potassium in mEq
		Cl	Na	K	
1	No treatment		16	53	
	Mercurial, 60 mg.	56	58	71	
	Chlorothiazide, 1 g.	40	49	90	
	Mercurial, 40 mg.				
	Chlorothiazide, 1 g. } combined	102	83	160	90
2	No treatment		25	38	
	Mercurial, 60 mg.	51	62	30	
	Chlorothiazide, 1 g.	81	110	120	
	Mercurial, 30 mg.				
	Chlorothiazide, 1 g. } combined	108	130	110	80
3	No treatment		46	95	
	Mercurial, 40 mg.	46	62	103	
	Chlorothiazide, 1 g.	109	190	124	
	Mercurial, 30 mg.				
	Chlorothiazide, 1 g. } combined	117	221	180	120
4	No treatment		30	30	
	Mercurial, 60 mg.	176	170	39	
	Chlorothiazide, 1 g.	168	207	122	
	Mercurial, 30 mg.				
	Chlorothiazide, 1 g. } combined	288	253	68	70
5	No treatment		12	60	
	Mercurial, 60 mg.	39	38	54	
	Chlorothiazide, 2 g.	58	88	76	
	Mercurial, 60 mg.				
	Chlorothiazide, 2 g. } combined	243	176	186	110

Treatment with chlorothiazide, antibiotics, and digitalis brought rapid improvement with loss of oedema fluid, although there was a marked drop in plasma potassium despite oral supplements (Fig. 1).

From March 16 he had no demonstrable oedema, and a more accurate comparison of the diuretics alone and in combination could be made. He lost weight steadily throughout the period of trial, and there was no significant change in daily diuresis, which was maintained at about 1.5 litres daily.

As can be seen from Fig. 1, there was a significant increase in excretion of sodium and chloride when he was on combined therapy as compared with that achieved by either diuretic alone. The increase in potassium excretion was, however, even more striking, as shown in Table I. The average daily excretion of potassium caused by the equivalent of 60 mg. of mercury daily was 71 mEq, with 1 g. of chlorothiazide daily it was 90 mEq, but with 1 g. of chlorothiazide combined with the equivalent of 40 mg. of mercury the daily excretion was 160 mEq. Despite this effect, which is greater than additive, the plasma potassium fell to a lower level when chlorothiazide was given alone than when combined therapy was used.

Since his discharge he has been maintained on digitalis and the equivalent of 30 mg. of mercury daily by mouth without return to his oedematous state after three months.

Case 2

A hypertensive arteriosclerotic woman aged 68 was admitted to hospital with a respiratory infection and congestive cardiac failure. She had fibrillation, and previous response to parenteral mercurials had been very poor or absent. Treatment on admission consisted of mercurial diuretics by injection, antibiotics, and digitalis, and this therapy in hospital produced a rapid response. After this initial improvement there was minimal oedema, providing a more stable basis for comparing the diuretic regimes, and she was treated with the two diuretics alone and in combination, as shown in Fig. 2. All three methods employed produced a slight decrease in weight, a diuresis, and an increase in the urinary excretion of sodium, potassium, and chloride (Table I). The maximum excretion of water and electrolytes occurred with the combined therapy.

As in Case 1, there was a marked drop in plasma potassium when chlorothiazide was given, despite oral supplements, and this was greater when chlorothiazide was used alone than with the combined therapy.

The patient was discharged on digitalis and the equivalent of 30 mg. of mercury orally daily, and has been well controlled on this regime.

Case 3

A man aged 50 with rheumatoid arthritis and nephrotic syndrome had been maintained for many months on prednisone 15 mg. and potassium chloride 3 g. daily. He had developed mild Cushing's syndrome, due to the steroid therapy, and was admitted to hospital with increasing oedema and diminishing response to injected mercurials and exchange resins.

During his stay in hospital he was kept on prednisone and potassium chloride and was allowed 50 mEq of sodium daily. As can be seen from Fig. 3, he was treated for short periods with the oral mercurial, with chlorothiazide, and with both drugs in combination. No significant change in weight occurred, and this was reflected by his state on discharge, which still showed residual oedema despite diuretic therapy. Increased excretion of water and electrolytes was seen with chlorothiazide, and the addition of a mercurial caused only a slight potentiation. As can be seen from Fig. 4, however, there was a diminishing response to the action of chlorothiazide with each repeated administration.

Despite additional potassium, a marked fall in plasma potassium was seen on each occasion that chlorothiazide was given.

FIG. 1.—Chart of Case 1.

FIG. 2.—Chart of Case 2.

Case 4

This patient, a woman aged 82, had a past history of partial colectomy for carcinoma of the colon in 1946, and of left mastectomy for carcinoma in 1953. On admission to hospital, after the occurrence of paroxysmal nocturnal dyspnoea, she was found to be in congestive cardiac failure with marked pulmonary oedema, but she had shown no response to parenteral mercurials prior to admission.

After an initial injection of mercaptomerin sodium, she had three periods of diuretic therapy, which consisted of oral mercurial alone, chlorothiazide alone, and the two drugs in combination (Fig. 5). Each type of treatment produced a significant diuresis and loss of weight, but, whereas the mercurial caused a marked increase in sodium and chloride excretion, chlorothiazide produced a large increase in potassium excretion as well. The combined therapy gave some potentiation of the diuresis, and the pattern of electrolyte excretion was intermediate between that of the two individual drugs.

As with other patients, the administration of chlorothiazide, but not of a mercurial, rapidly lowered the plasma potassium despite oral supplements.

Case 5

A woman aged 55 had a very long history of rheumatic heart disease with congestive cardiac failure, cardiac cirrhosis, and gross ascites due to tricuspid incompetence. In addition, she had lately been shown to have mild diabetes mellitus, which had been controlled by diet alone. Although she had required admission to hospital many times in the past, she had been fairly well controlled as an out-patient for some months on a low-salt diet, exchange resins, twice-weekly mercurial by injection, thrice-daily oral aminometradine, digitalis, and potassium supplements.

Investigation of her case is divided into two periods: the first until April 22, as an out-patient (Fig. 6), and later as an in-patient (Fig. 7). She was admitted because investigation of her coincident mild diabetes proved difficult when she was an out-patient.

As can be seen from Fig. 6, she initially responded well to the combined diuretics but not to either drug alone. She soon, however, became resistant to their combined action, as shown by the increase in weight and decrease in excretion of water and sodium. This loss of response is also borne out in Fig. 4. It is noticeable that there was still a

FIG. 4.—Chart of Case 3. Showing diminishing response to chlorothiazide.

considerable potassium excretion with chlorothiazide even when a diuresis no longer occurred, demonstrating the danger of increasing the dose of chlorothiazide in resistant patients.

After admission recourse was made to the use of mercurials by injection, but the sodium excretion continued to decrease while the weight and ascitic fluid increased. Because of increasing discomfort and because the ascites might play a part in the resistance to the diuretics, it was decided to remove a quantity of the fluid. Abdominal paracentesis was performed on two occasions, 2.9 and 2.0 litres respectively being withdrawn. After the first paracentesis a mercurial was given by injection with no response; after the second paracentesis chlorothiazide was given without response, and yet on each occasion combined therapy gave a dramatic result with marked diuresis, increased sodium excretion, and weight loss (Fig. 7). In

FIG. 3.—Chart of Case 3.

this patient the plasma potassium was lowered by the combined diuretics to a greater degree than by chlorothiazide alone.

It is clear that the accumulation of ascitic fluid was an important factor in the resistance to diuretic agents, but the mechanism is still unknown. The reason for the efficacy of the combined diuretics is also not clear, but it underlines the fact that these drugs have different mechanisms of action and that in some situations a synergism is produced by their combined use.

The patient was discharged home with a greatly diminished weight and ascitic volume but with slight persistent oedema of the ankles.

Potassium Excretion Study

Read *et al.* (1958) and Slater and Nabarro (1958) observed that hypokalaemia was induced with chlorothiazide administration despite large potassium supplements. Our findings were similar, and it therefore

seemed probable that, whatever additional potassium was given, chlorothiazide caused a proportional increase in the excretion of the electrolyte, preventing attempts to maintain a normal plasma level.

In order to study this feature, one of us (W.J.P.) took a series of carefully controlled potassium diets and measured potassium excretion both in the normal state and when taking chlorothiazide 1 g. daily. The excretion values, when taking no diuretics, fell in line with the observations of Tarail and Elkinton (1949), while the results obtained when taking chlorothiazide were also linear but set at a higher potassium excretion rate (Fig. 8). This confirms that the potassium excretion follows the potassium intake and that one cannot expect to prevent hypokalaemia by merely giving potassium supplements simultaneously with chlorothiazide. In fact, such supplements are achieving no purpose, and a more logical course would be to give chlorothiazide intermittently and extra potassium between the periods of diuretic treatment instead of during them.

FIG. 5.—Chart of Case 4.

FIG. 6.—Chart of Case 5 as an out-patient.

Discussion

As with all investigations of this type, the subjects are not static test objects but patients undergoing treatment with a constantly changing clinical state. This changing state was usually most pronounced at the beginning of treatment when bed rest, antibiotics, and hospital regime were having their effects, and at this initial stage diuresis was often produced in oedematous patients without the specific action of diuretics. We have therefore tried to omit this early response and to limit the comparison of diuretic regimes to a more stable period.

When evaluating diuresis there are many factors to be

considered in addition to simple weight changes and water loss. This is particularly so in the nephrotic syndrome (Case 3), where osmotic factors are important, and in this case there was minimal water diuresis, although marked changes in electrolyte excretion occurred. In this and other cases it might have been possible to interpret changes of plasma and urinary electrolyte concentrations by estimating changes in the total readily exchangeable body electrolytes, but this was beyond the scope of the present study.

Chlorothiazide

The introduction of chlorothiazide is probably the major advance in therapeutics since the advent of penicillin, and it is clearly an extremely potent oral diuretic which is effective in most oedematous states. There are, however, certain dangers which should be clear to those using the agent, particularly in general practice, where constant supervision of patients is not always practicable.

Hypokalaemia can occur despite potassium supplements. Severe degrees of hypokalaemia will cause muscular weakness and coma, but even moderate lowering of plasma potassium will cause potentiation of digitalis and thereby overdosage in patients being treated with digitalis.

Resistance to the diuretic action of chlorothiazide can occur after repeated administration (Fig. 4), and, despite this loss of diuretic effect, increased potassium excretion still takes place (Fig. 7).

There is therefore a very real danger of hypokalaemia in these resistant cases, where the dose of chlorothiazide might well be increased in an attempt to regain a diuresis.

Marked potentiation of ganglionic-blocking agents has been demonstrated which prevents intermittent treatment with chlorothiazide in patients who have been stabilized on antihypertensive treatment.

Oral Mercurial (Oradon)

Previous clinical experience with oral mercurials has been disappointing. The main reason for this was the poor absorption of the organic mercury and the gastro-intestinal irritation produced by high oral dosages. Excretion studies with chloromerodrin (Moyer *et al.*, 1953) showed that 5 to 10% of the ingested mercury could be recovered in the urine. The same study stated that the equivalent of 40 to 60 mg. of mercury had to be taken to get an effective dose and yet 60 to 80 mg. of mercury tended to cause gastro-intestinal upsets. With the dose limited to 40 mg. daily, the maximum absorption was 4 mg. of mercury, which is one-tenth of that contained in 1 ml. of mersalyl. Because of this poor absorption, the dose had to be pushed beyond the level of tolerance in many cases to get a therapeutic effect, and, also, it was impossible to give only intermittent therapy, with the consequent dangers of chronic mercurialism.

In this study oradon was used and excretion studies were performed. These showed that, when the excretion

FIG. 7.—Chart of Case 5 as an in-patient.

FIG. 8.—x=Values obtained in normal subjects (quoted from Tarail and Elkinton, 1949). ●=Values obtained in normal subject (W. J. P.). O=Values obtained in normal subject (W. J. P.) taking chlorothiazide 0.5 g. twice daily.

during the days of treatment and for 24 hours after treatment were estimated, the average mercury reclaimed was 36.6% of the ingested dose (range 24.9 to 47.2%) (Table II). As with chloromerodrin, each tablet contained the equivalent of 10 mg. of mercury, and therefore it was possible to absorb more organic mercury than that contained in 1 ml. of mersalyl by giving one tablet three times a day for four days. When we consider the rapid excretion of injected mercurials, it is possible that the oral therapy is actually a more efficient regime. In addition, the gastro-intestinal irritation is a measure of the ingested and not the absorbed dose, so that equal amounts of this new oral mercurial can be given before side-effects occur, but that dose will be three to four times as effective.

The cases studied here show that oradon is an effective oral diuretic with minimum electrolytic disturbance when given alone. Case 5 had slight looseness of the motions when taking six tablets daily, but this tendency

decreased with treatment and there were no side-effects in the other patients.

The efficacy of this oral mercurial in chronic studies has also been demonstrated by Flatmark and Mathisen (1958), who obtained a satisfactory result, without side-effects, in most cases on two tablets daily (after breakfast) for five days in each week.

Combined Diuretics

As shown in Figs. 1-6, there was a potentiation of effect in every case where the two drugs were used together. This was demonstrated in all patients, not only in the diuresis but also in the excretion of the three electrolytes studied, with the exception of one patient (Case 4) who excreted less potassium on combined therapy than when on chlorothiazide alone.

There were, however, one or two aspects that were not clearly potentiated by the combined therapy. In the first place, there tended to be a less marked drop in plasma potassium in most cases when combined therapy, as opposed to simple chlorothiazide, was given, and in the second place there was no observed change in pH of urine or of plasma bicarbonate, although these were seen when chlorothiazide alone was given.

As suggested earlier, this potentiation supports the evidence that the drugs work by different mechanisms (Laragh *et al.*, 1958). This was confirmed by a study of the sodium/water ratio, which showed that more water per unit of sodium is excreted with chlorothiazide than with mercurials or with the combined therapy.

The potentiation of the electrolyte excretion probably precludes the use of the combined diuretics except in cases resistant to the individual agents.

Selection of Diuretics

The foregoing observations give considerable guidance in selection of the ideal oral treatment for a patient with oedema.

Chlorothiazide is recommended for the initial control of moderate cases or for maintenance of severe cases, but it should be given in short courses of two to four days with potassium supplements administered between courses. Particular care should be taken if the patient is on digitalis or antihypertensive therapy, and the dose should not be increased without careful electrolyte studies if resistance to the diuretic action occurs.

TABLE II.—Urinary Recovery of Ingested Mercury

Case 1			Case 2			Case 3			Case 4			Case 5		
Date	Equi- valent of Hg Ingested in mg./day	Urinary Excretion of Hg in mg./ 24 Hours	Date	Equi- valent of Hg Ingested in mg./day	Urinary Excretion of Hg in mg./ 24 Hours	Date	Equi- valent of Hg Ingested in mg./day	Urinary Excretion of Hg in mg./ 24 Hours	Date	Equi- valent of Hg Ingested in mg./day	Urinary Excretion of Hg in mg./ 24 Hours	Date	Equi- valent of Hg Ingested in mg./day	Urinary Excretion of Hg in mg./ 24 Hours
Feb. 18	60	21.55	Feb. 24	60	1.03	Apr. 26	40	8.31	May 16	60	3.86	Apr. 2	60	2.17
" 19	60	20.35	" 25	60	10.89	" 27	40	11.48	" 17	60	14.08	" 3	60	15.88
" 20	60	16.28	" 26	60	8.77	" 28	40	14.78	" 18	60	23.06	" 4	60	13.96
" 21	60	15.15	" 27	60	25.69	" 29	40	15.56	" 19	60	19.43	" 5	60	18.86
" 22	—	7.92	" 28	60	15.60	" 30	40	13.33	" 20	60	25.14	" 6	60	19.14
" 26	40	6.77	Mar. 1	—	5.33	May 1	—	7.95	" 21	60	30.64	" 7	60	28.27
" 27	40	20.47	" 15	30	7.05	" 10	30	10.99	" 22	—	8.18	" 8	—	13.18
" 28	40	13.83	" 16	30	10.90	" 17	30	13.98	June 5	30	6.13	" 11	60	21.07
Mar. 1	40	18.15	" 17	30	11.05	" 18	30	22.32	" 6	30	28.10	" 12	60	21.25
" 2	40	10.62	" 18	30	9.05	" 19	30	18.00	" 7	30	15.60	" 13	60	11.96
" 3	—	1.75	" 19	30	4.45	" 20	30	25.30	" 8	30	11.90	" 14	60	49.49
			" 20	—	2.45	" 21	—	5.41	" 9	—	7.21	" 15	—	8.01
Totals ..	440	153.84 (35.0%)		450	112.26 (24.9%)		350	165.31 (47.2%)		480	193.33 (40.3%)		600	225.4 (37.5%)

Total equivalent mercury ingested, 2,320 mg. Total urinary mercury recovered, 1,849.98 mg. Average percentage excreted in urine, 36.6%.

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.

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CLINICAL EVALUATION OF HYDROCHLOROTHIAZIDE

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Chlorothiazide ("chlortide," "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

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.