USE OF SPIRONOLACTONE AND HYDROCHLOROTHIAZIDE IN TREATMENT OF OEDEMA

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Over the last few years it has become increasingly apparent that excessive aldosterone secretion plays some part in the genesis and maintenance of oedema, whether this be due to congestive cardiac failure, the nephrotic syndrome, or hepatic cirrhosis (Luetscher and Johnson, 1954; Axelrad *et al.*, 1955; Duncan *et al.*, 1956; Dyrenfurth *et al.*, 1957). Considerable interest therefore is attached to the diuretic action of the 17-spirolactone steroids developed by Kagawa *et al.* (1957). Most investigators are agreed that these compounds act as specific aldosterone antagonists (Wolff *et al.*, 1957; Liddle, 1957, 1958; Salassa *et al.*, 1958; Ross and Bethune, 1959).

Two early spirolactone derivatives, SC.5233 and SC.8109, showed promise in the treatment of oedematous patients (Liddle, 1957, 1958; Bolté *et al.*, 1958) and of cases of hepatic cirrhosis with ascites (Kerr *et al.*, 1958). The former compound, however, was not active by mouth; the second was, but only in large doses. A new derivative, spironolactone (SC.9420), which is more potent, has recently been developed (Gantt and Dyniewicz, 1959), and the purpose of this study was to investigate its clinical value.

Aldosterone secretion is low in normal subjects on a high-sodium intake, and in oedematous patients who have achieved a "steady state" and therefore are not actively retaining sodium. It is not surprising that spironolactone has little diuretic effect on normal people (Liddle, 1957). This study of the effect of spironolactone was therefore carried out under conditions in which aldosterone secretion would be expected to be greatly increased—namely, in patients with active sodium retention, on a low-sodium diet and normal potassium intake.

The diminishing response to diuretics which occurs within a few days is of clinical importance, because a new steady state may be achieved in which the patient still has oedema. This effect may well be mediated by aldosterone, and it is the response of such "resistant" patients to aldosterone antagonists that is the subject of this investigation.

Methods

There are manifest difficulties in assessing the relative merits of two diuretic regimes. Not the least are the spontaneous diuresis which may occur when a patient is first rested in bed and the fact that the initial diuresis is usually better than that obtained by later therapy.

The diuretic effects in this study were compared in units of four days; this time was chosen because it was felt that in any shorter period random variations might obscure the picture, and that if longer periods were used patients might lose their oedema before the trial had finished.

The seven patients were therefore admitted to a metabolic unit, kept at bed rest on a diet constant with respect to sodium (22 mEq/day), potassium (78 or 65 mEq/day), and fluid (1,600 ml./day). The investigation of each patient was divided into four periods, each of four days.

First period (days 1–4), diet and bed rest.

Second period (days 5–8), diet, and hydrochlorothiazide 200 mg. daily in equal six-hourly doses.

Third period (days 9–12), diet, hydrochlorothiazide 200 mg. daily, and spironolactone 800 mg. daily in equal six-hourly doses.

Fourth period (days 13–16), as for period 2.

In two of the seven cases period 2 was lengthened to 5–9 days to ensure that apparent trends were continued if spironolactone was withheld.

A daily record was kept of weight, blood-pressure, volume of urine, and degree of oedema. Biochemical investigations included daily urinary output of sodium and potassium (flame photometer), chloride (Van Slyke and Hiller, 1947), ammonia (Conway, 1950), and titratable acidity (Henderson and Palmer, 1914). Blood was taken by venepuncture thrice weekly for estimation of serum concentration of sodium and potassium (flame photometer), chloride (Van Slyke and Hiller, 1947), carbon-dioxide content (Van Slyke and Cullen, 1917), creatinine (Bonsnes and Taussky, 1945), and urea by a method using urease and Nessler's reagent.

At least once for each subject during the trial, a duplicate day's diet was prepared and analysed for sodium and potassium (by wet-ashing an aliquot of the homogenized diet, the final estimation being done on a flame photometer). At the end of the study, a creatinine-clearance test and a specific gravity concentration test were performed on each subject.

Results

Congestive Heart Failure

Clinical Aspects.—Details of the five patients (Cases 1–5) are set out in Table I. In three, ischaemic heart disease without recent myocardial infarction was responsible for the congestive heart failure, and chronic valvular disease in the other two. Oedema had been present for 1 to 36 months, but was gross in only two patients. Each had received routine diuretic therapy outside this unit before the trial was started. In all but one case every trace of oedema disappeared under the combined regime of hydrochlorothiazide, spironolactone, and a low-sodium intake. Blood-pressures fell during the 16-day trial in most patients, but in general the changes were not clinically significant. No patient had hypertension, and the blood-pressure seemed more dependent on the state of hydration than on the diuretic being used. Four of the five patients responded well to the treatment described, weight losses of between 3.2 and 12 kg. being obtained over the trial period. Case 5 did not respond.

Loss of Weight.—Fig. 1 shows that hydrochlorothiazide, which was the first drug given, was responsible for the greater part of the fall in weight in most

patients. The addition of spironolactone did not significantly affect the rate of fall, except in Case 4 (see Figs. 1 and 3).

Urine Excretion.—A summary of the results of the urine analysis is shown in Fig. 2, in which the average daily excretions of sodium, potassium, chloride, total acidity (ammonia plus titratable acidity), and urinary volume are plotted. Hydrochlorothiazide caused a significant increase in urine volume, sodium, potassium, and chloride, which was diminishing rapidly by the fourth day. When spironolactone was added there was little increase in urine volume, but in most patients the sodium excretion rose, and in all patients the potassium excretion fell markedly to levels below daily intake. When spironolactone was withdrawn, sodium excretion fell and potassium excretion rose

slowly to the high levels obtaining at the end of period 2. All patients were in a state of negative potassium balance while receiving hydrochlorothiazide, but in positive balance when spironolactone was added. Total acid excretion showed no significant changes, except in period 3, when there was a minor reduction.

Serum Levels.—The changes in urinary excretion were accurately reflected in serum concentrations: thus serum sodium levels slowly fell over the period of the trial, some patients becoming very hyponatraemic; this presumably was a result of marked sodium excretion without an accompanying increase in urine volume. Serum potassium levels also fell considerably when hydrochlorothiazide alone was being given (the lowest level was 2.6 mEq/l.) but rose again during the period of combined therapy. As might be expected from the urinary excretion of titratable acidity the carbon-dioxide content of the serum did not change significantly during the trial in any patient.

FIG. 1.—Individual curves of change in weight during the course of the trial.

CASE
NO.

Nephrotic Syndrome

Clinical Aspects.—The cause of the nephrotic syndrome was, in Case 7, combined membranous and proliferative glomerulonephritis; in this patient renal function was greatly impaired, the blood urea remaining between 50 and 70 mg./100 ml. In Case 6 renal amyloid disease was responsible for the nephrotic syndrome. The diagnoses were made by renal biopsy.

Loss of Weight.—In both cases there was a significant loss of weight; the rate of fall in weight was not altered by spironolactone administration.

Urinary Excretion.—In both cases hydrochlorothiazide administration was followed by an increase in urinary volume, sodium, and potassium. The addition of spironolactone to the regime caused, in one subject only, further increase in sodium excretion and a reduction in potassium; Case 7 responded minimally to spironolactone. In both, the proteinuria persisted unchanged.

Side-effects.—No side-effects were observed during treatment with spironolactone, except for one patient who complained of muscular cramps. This may not have been related to therapy.

Discussion

The dynamic equilibrium between intravascular and extravascular fluids is dependent on venous pressure, colloid osmotic pressure, capillary permeability, and tissue turgor. However, it has been apparent for many years that generalized oedema is difficult to explain on this basis alone, and that some other factor or factors are involved.

TABLE I.—Clinical Details of Patients

Case No.	Age and Sex	Diagnosis	Oedema			Treatment Month Prior to Trial			
			Duration	Initial Severity	Final Severity	Bed Rest	Low-salt Diet	Mersalyl	Chlorothiazide
1	56 M	Ischaemic heart disease	8 months	Mild	Nil	Yes	Yes	Yes	Yes
2	51 F	" " " "	3 years	"	"	No	No	No	"
3	51 M	" " " "	intermittent	Moderate	"	Yes	"	Yes	No
4	72 F	Rheumatic valvular disease	8 months	Gross	"	"	"	"	Yes
5	63 F	" " " "	2 years	"	Gross	"	Yes	"	No
6	53 M	Nephrotic syndrome.	1 month	"	"	"	"	"	"
		Amyloid disease	4 months	"	Nil	"	"	No	"
7	77 F	Nephrotic syndrome.	"	"	"	"	"	"	"
		Membranous glomerulonephritis	4 "	Moderate	Mild	"	No	"	"

TABLE II.—Detailed Biochemical Results

Case No.	Period 1 Days				Period 2 Days				Period 3 Days				Period 4 Days			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
SODIUM mEq./day	14	25	34	32	161	107	51	22	61	64	75	69	36	23	21	17
	42	40	28	71*	208	106	90	24	47	49	51	33	30	10	8	8
	8	10	19	16	104	79	55	30	75	90	94	108	46	56	7	25
	34	41	18	—	—	—	62	26	226	181	146	144	105	44	49	15
	2.4	4.4	4.4	10.5	29	35	8.5	45	58	59	65	39	70	9	34	11
	33	24	37	31	186	198	91	89	73	110	159	†	†	†	†	†
	20	26	31	33	124	105	126	120	94	132	124	105	100	94	60	42
Mean	22	24	24	32	135	105	69	51	91	98	102	83	65	39	30	20
POTASSIUM mEq./day	45	35	34	41	108	97	103	113	73	53	46	33	49	73	88	130
	35	31	47	48*	122	117	98	88	79	48	41	38	41	53	58	66
	30	28	70	72	63	—	52	46	22	15	26	58	66	75	53	57
	30	33	56	—	—	—	47	67	26	29	29	29	45	35	41	34
	6.8	12	10	32	37	35	13	46	42	25	38	21	52	8	62	11
	32	32	34	32	50	59	56	60	46	36	37	†	†	†	†	†
	47	58	53	53	71	90	55	63	33	45	46	51	47	64	69	69
Mean	32	32	43	46	75	76	71	69	46	36	38	38	50	51	62	61
VOLUME ml./day	1,300	1,560	1,490	1,710	2,520	2,180	1,640	1,480	1,690	1,570	1,750	1,630	1,390	1,770	1,970	1,720
	1,810	1,920	1,320	1,960*	2,640	2,080	2,000	1,870	1,630	1,540	1,650	1,310	1,420	1,280	1,380	1,250
	820	910	1,670	1,560	1,900	1,580	1,640	1,310	1,560	1,100	1,700	1,830	1,350	1,450	900	1,130
	1,230	1,000	1,000	1,560	—	—	1,380	1,420	2,430	2,070	1,900	1,750	1,640	1,000	1,230	810
	260	390	280	—	620	470	170	860	710	540	640	420	890	135	1,230	160
	650	670	970	670	1,840	2,340	1,260	1,350	1,020	1,110	1,830	†	†	†	†	†
	1,300	1,470	1,600	1,720	2,150	1,750	1,920	2,000	1,570	2,100	1,880	1,960	1,810	1,840	1,550	1,500
Mean	1,050	1,130	1,220	1,370	1,940	1,730	1,430	1,470	1,520	1,430	1,620	1,480	1,420	1,250	1,380	1,100

* Collections were unsatisfactory in Case 4, days 4–6, owing to nocturnal incontinence. † Patient received 50 mg. hydrochlorothiazide 6 hours before end of collection period. ‡ Patient withdrawn from trial owing to acute abdominal condition.

More recently it has been shown that the urine of patients accumulating oedema contained abnormally large amounts of a "sodium retaining factor" (Deming and Luetscher, 1950; Singer and Wener, 1953). Following the characterization of aldosterone, this steroid was soon shown to be identical with the sodium-retaining factor (Luetscher, *et al.*, 1954, 1956). The evidence that aldosterone plays a significant part in the development and maintenance of oedema is now impressive and is reviewed elsewhere (August *et al.*, 1958).

Of particular interest clinically are those patients who are "resistant" to conventional diuretics such as the mercurial drugs and the more recently developed benzothiadiazine drugs (chlorothiazide and related compounds). It seems a reasonable hypothesis that aldosterone secretion may be in part responsible for the gradually diminishing response to diuretics; eventually a state is reached where sodium excretion equals sodium intake. This steady state may occur when the patient is still oedematous; and if it is indeed fixed by competing effects of aldosterone and a diuretic, then the giving of spironolactone should alter the equilibrium in the direction of a diuresis.

It is also possible that aldosterone may be responsible for the fact that total exchangeable potassium in oedematous patients is low (Birkenfield *et al.*, 1958), and for the further potassium depletion which follows administration of chlorothiazide and related compounds (Bayliss *et al.*, 1958). Oedematous patients who had not responded well to conventional diuretic therapy were therefore investigated by the protocol set out above.

The results obtained in this study (Table II) confirm the potassium-losing properties of hydrochlorothiazide, and also that this undesirable effect can be effectively controlled by spironolactone. The potassium-retaining effects of spironolactone observed under the conditions of this trial are more dramatic than those found by other investigators using earlier aldosterone

FIG. 2.—Mean values for all seven patients included in the trial. For detailed results see Table II.

antagonists under different experimental conditions. The diminishing sodium-losing response to hydrochlorothiazide shown by most patients is in this study a more rapid process than found by other observers, but this may be a result of the high dosage of hydrochlorothiazide. After four days on hydrochlorothiazide, most patients were approaching a plateau of steady excretion of sodium and potassium. On the addition of spironolactone to the regime there was an increase in the sodium excretion and a fall in potassium excretion (see Fig. 2).

By interpolation between period 2 and period 4, it is possible to arrive at a very approximate figure for the sodium loss and potassium retention caused by spironolactone. These derived data show that the ratio of sodium loss to potassium retained varied widely, and could not be correlated satisfactorily with any other clinical or biochemical parameters.

Also there is a great disparity between the effect of spironolactone on electrolyte excretion on one hand and water excretion on the other. If, as seems probable, spironolactone is a potent inhibitor of aldosterone, this would suggest that there is also a separate abnormality in water metabolism. This has been suggested by other workers, and the role of antidiuretic hormone in the aetiology of oedema has been discussed by Buchborn (1959). The experience of Kerr *et al.* (1958) and of

FIG. 3.—Case 4. The only patient with a marked increase in diuresis on combined therapy. Nocturnal incontinence prevented complete collections on four days.

FIG. 4.—Case 1. To indicate the response in a typical patient.

Liddle (1958), that oedematous patients with renal insufficiency do not respond to aldosterone antagonists, parallels our own, and suggests that in such patients aldosterone is relatively unimportant. It is of interest to note that Case 7, who responded least well to spironolactone, was the only patient who did not exhibit a rapidly diminishing response to hydrochlorothiazide. Case 4 was the only patient (see Fig. 3) who showed a marked increase in diuresis during combined treatment. A more typical response is shown in Fig. 4 (Case 1).

Clinically, it appears that aldosterone antagonists are most effective in preventing potassium wastage during orthodox diuretic therapy. This can perhaps more easily be done by potassium chloride supplements, but some patients find this unpleasant, and some excrete so much potassium in the urine that supplementation is difficult. In this trial we have found clear evidence that spironolactone is of help in removing excess sodium from the body, but the effect on the removal of oedema fluid is less convincing.

Summary

A new steroidal spironolactone, spironolactone (SC.9420), was used in conjunction with hydrochlorothiazide in seven patients with oedema, five with congestive cardiac failure, two with the nephrotic syndrome.

In six of the seven patients the addition of spironolactone caused a significant increase in the sodium excretion and a marked reduction in the potassium excretion induced by hydrochlorothiazide in all patients.

These preliminary results suggest that spironolactone is of limited value in the treatment of cases of refractory

oedema, but that it will protect the patient against the known hazard of hypokalaemia associated with the use of hydrochlorothiazide.

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"At the North London [Miss Buss's school], in addition to regular drill and gymnastics, there were special remedial exercises for girls with crooked spines or other disabilities. An annual medical inspection by a woman doctor was started in 1882, possibly at the instigation of Elizabeth Garrett Anderson, who had become a Governor a few years earlier. . . . The first medical inspection at the North London revealed the alarming facts that only one girl in five measured had a straight spine and three out of eleven normal sight. To take a single example, a girl of 14 'has had rickets and now has attacks of momentary stupor, especially when at all pressed to work. Will gain much from the gymnasium, but must be treated . . . as a child of eleven or twelve.' . . . There was no medical inspection at Cheltenham [Ladies' College] in Miss Beale's lifetime. . . . If a girl showed signs of strain or illness a doctor was immediately called in; but Miss Beale felt that the responsibility belonged to parents and not teachers, and she did not favour the idea of a regular medical inspection." (*How Different from Us—Miss Buss and Miss Beale*, by Josephine Kamm, Bodley Head, 1958.)

MULTIPLE SCLEROSIS

A NOTE ON SOCIAL INCIDENCE

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It is an impression commonly held among neurologists that patients with multiple sclerosis tend to be above the average in attractiveness and intelligence, and that there is a relative preponderance of sufferers in the higher-income groups of the population.

One of us (H.M.) must admit to a long-standing suspicion that the condition was proportionately commoner in private than in hospital practice, and was surprised at the result of subjecting this impression to numerical analysis. Amongst 2,193 consecutive new out-patients referred to this department between 1956 and mid-1959 there were 198 cases of multiple sclerosis (9%); 2,203 approximately contemporaneous private consultations yielded only 116 cases (5%). The fallacies of interpreting these figures in terms of social-class prevalence are obvious, and they do little more than confirm the notorious unreliability of "clinical impression."

A survey of multiple sclerosis in Northumberland and Durham furnished material for a more direct assessment of the social incidence of the disease. All 519 general practices in Northumberland and Durham were approached for information about the total number of patients registered in each practice and the number of established cases of multiple sclerosis among them. Information was obtained from 352 practices, covering a total of approximately 1,400,000 patients of all ages; 700 cases were reported in which a diagnosis of multiple sclerosis had been made, almost invariably after consultant reference. Personal neurological examination of these patients reduced the number of authenticated cases to 662, which gives a prevalence rate of 47 per 100,000 of the total population at risk. However, figures drawn from a population of 466,714 under the care of practitioners personally known to us for the scrupulousness with which they keep their medical records and the readiness with which they refer patients for specialist opinion yield a prevalence rate of 59 per 100,000. Any such figure is certain to be an underestimate, if only because of the delay which ensues between the appearance of the initial symptoms and the making of a firm diagnosis; but we believe that the higher figure represents a closer approximation to the true prevalence, and that there are probably no fewer than 1,100 established cases in the whole region, which has a total population of 2,262,292 (1951 census).

The patients yielded by the survey comprised 390 females and 272 males, giving a sex-distribution of 58.9% female and 41.1% male—figures closely comparable with those reported from Northern Ireland by Allison and Millar (1954), whose 644 cases comprised 56.1% females and 43.9% males.