

affected child. If this were true we would expect that the incidence of jaundice in babies born after the index cases would not differ from that observed in the G.-6-P.D.-deficient babies in general. As our figures show, the incidence was much higher (four out of eight).

Since a common environmental factor operating in these families or bias in the selection of the material can be excluded, we consider that the high incidence of severe neonatal jaundice in certain families with G.-6-P.D. deficiency must be also genetically determined. In the present material we have not done any quantitative estimation of enzyme activity, and therefore we cannot exclude the possibility that in these families this activity is particularly low. Assuming that the enzyme level is of importance in the development of haemolysis in the neonatal period and that this level is genetically determined, an accumulation of jaundiced babies in certain families can be explained. The fact that some female heterozygotes displaying almost normal enzyme activity develop severe neonatal jaundice seems to be against a close relationship between enzyme level and haemolysis. However, the recent theory that in heterozygous females the red-cell population can be a mosaic for G.-6-P.D. activity invalidates this objection (*Lancet*, 1962).

Another explanation of the accumulation of cases of neonatal jaundice in some families may be the presence of another genetic factor transmitted independently of the G.-6-P.D. deficiency. Since for the development of neonatal hyperbilirubinaemia a multitude of factors may be responsible, this assumed additional genetic factor need not necessarily influence the degree of haemolysis.

An indication for the existence of such an additional genetic factor transmitted independently of the G.-6-P.D. deficiency is our finding that 11 out of 43 male siblings in the families with maternal transmission had severe neonatal jaundice—a ratio of 1 to 4. This is the expected ratio when two independently transmitted factors are needed for the clinical manifestation of a hereditary disorder.

The need of an additional genetic factor for the development of neonatal jaundice may explain the absence of such a clinical manifestation in some racial groups with a high incidence of G.-6-P.D. deficiency.

Summary

Out of 786 Greek male neonates randomly selected 23 showed G.-6-P.D. deficiency, an incidence of 2.92%.

Only one of the 21 deficient babies who had no other cause for neonatal jaundice developed severe degrees of hyperbilirubinaemia. In contrast, among 43 male siblings of index cases—that is, infants with G.-6-P.D. deficiency and severe neonatal jaundice—there were 11 cases of severe hyperbilirubinaemia.

The accumulation of the cases of neonatal jaundice in certain G.-6-P.D.-deficient families is discussed. The suggestion is made that the additional factors necessary for the development of severe neonatal jaundice in the G.-6-P.D.-deficient babies are genetically determined.

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DIURETIC ACTION OF TRIAMTERENE IN MAN

BY

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The introduction of a new diuretic (Laragh *et al.*, 1961; Wiebelhaus *et al.*, 1961; Crosley *et al.*, 1962) compound differing from currently available diuretics in its capacity to increase sodium and chloride excretion with little or no increase in potassium output merits further investigation. Furthermore, if it is able alone or in combination with other agents to produce an effective diuresis when other regimes have failed, its place in diuretic therapy demands serious consideration.

The diuretic effect of the administration of triamterene (2,4,7-triamino-6-phenylpteridine; S.K.F. 8542) by mouth to normal individuals and to 10 selected patients with chronic oedema has been studied. In addition, further investigation of the potassium-sparing action of this drug has been made, and its effect on the excretion of uric acid has been studied.

Methods

The nature of the renal action of triamterene was investigated in four normal subjects maintained on a normal diet with constant fluid, sodium, and potassium intake. The subjects continued moderate activity and no drugs other than those on trial were administered. Urine samples were collected from 8 a.m. to 8 p.m. at two-hourly intervals and a pooled collection was made for the subsequent 12 hours. All the specimens were collected under paraffin and preserved with thymol. After the 24-hour control collection period each individual was given 100 mg. of triamterene by mouth and urine collections were obtained at similar intervals over a further 24 hours.

Clinical trials of triamterene were conducted on 10 selected patients with chronic oedema of varied aetiology. The clinical details are summarized in Table I. Fluid consumption was maintained at 1.5 litres daily and sodium intake was restricted to 25 mEq a day (1.5-g. NaCl diet). All patients were weighed daily, and 24-hour collections of urine were made throughout the period of study. If treatment other than diuretics was

being given prior to the trial this was kept constant during the study period. Potassium supplements were not given. Urine volume and electrolyte excretion were measured daily, and the serum electrolyte and blood-urea concentrations were estimated twice weekly.

TABLE I.—Clinical Data and Response to Treatment of 10 Patients with Chronic Oedema

Case No.	Diagnosis	Period of Study	Serum Albumin (g./100 ml.)	Response to Treatment
1	Hepatic cirrhosis	35 days	3.6	See Fig. 2
2	"	14 "	4.0	" " 3
3	"	25 "	4.2	" " 4
4	Hepatic cirrhosis and rheumatic heart disease	28 "	3.8	Triamterene alone more effective than spironolactone alone. No significant difference in diuretic response of each of these drugs in combination with hydrochlorothiazide
5	Nephrotic syndrome	12 "	3.3	No response to 7 days' treatment with hydrochlorothiazide. Addition of triamterene associated with marked sodium diuresis and clinical improvement
6	Hepatic cirrhosis	12 "	3.3	No clinical improvement. Urinary sodium excretion on spironolactone 1 mEq daily and after addition of triamterene 38 mEq daily
7	Rheumatic heart disease	30 "	—	No clinical improvement. Mean daily urinary sodium and potassium excretion on hydrochlorothiazide was 5 and 80 mEq and after addition of triamterene 40 and 38 mEq respectively
8	"	14 "	—	Good response to triamterene alone. Serum potassium rose from 4.1 to 4.9 mEq l.
9	Ischaemic heart disease	7 "	—	Good clinical response to triamterene. Serum potassium rose from 3.4 to 5.2 mEq l.
10	"	16 "	—	Good response to hydrochlorothiazide and to triamterene

To investigate the mechanism of the action of triamterene on the renal handling of potassium, urinary electrolyte excretion following its administration was compared with that following spironolactone when each drug was given to normal individuals on (1) a rice diet (less than 5 mEq sodium daily), (2) a high-sodium diet (240 mEq sodium daily), or (3) a very-high-sodium diet (370 mEq sodium daily).

In each instance the individual was maintained on the diet until the urinary electrolyte excretion became constant. Twenty-four-hourly urine collections were obtained on two control days before either drug was administered. Fluid and potassium intakes were maintained constant throughout each experiment.

The effect of triamterene on the renal excretion of uric acid was investigated in seven patients without evidence of cardiac or renal disease. Uric-acid excretion was measured in 24-hourly collections of urine obtained for control periods of two to four days and during triamterene therapy (50 mg. q.d.s.) lasting two to four days.

Biochemical Methods.—Sodium and potassium were estimated by flame photometry; chlorides by potentiometric titration using a silver electrode; and carbon dioxide by a manometric method. Titratable acidity was determined by back titration to pH 7.4 with N/50

NaOH using a glass electrode pH meter; urine pH by a glass electrode pH meter; and urine bicarbonate from the carbonic-acid/bicarbonate curve according to pH (Peters and Van Slyke, 1932). Glomerular filtration rate was determined by endogenous creatinine clearance, creatinine levels being estimated by the method of Edwards and Whyte (1959). Urinary uric acid was measured by the method of Folin and Trimble (1924).

Results

Normal Subjects on Normal Sodium Intake

The results obtained from the administration of 100 mg. of triamterene to four normal subjects are presented in Table II and Fig. 1. Each individual responded with a sodium diuresis: the increase in loss of urinary sodium varied between 39 and 151% of the control values. This natriuresis was evident within two hours of taking the drug and coincided with the appear-

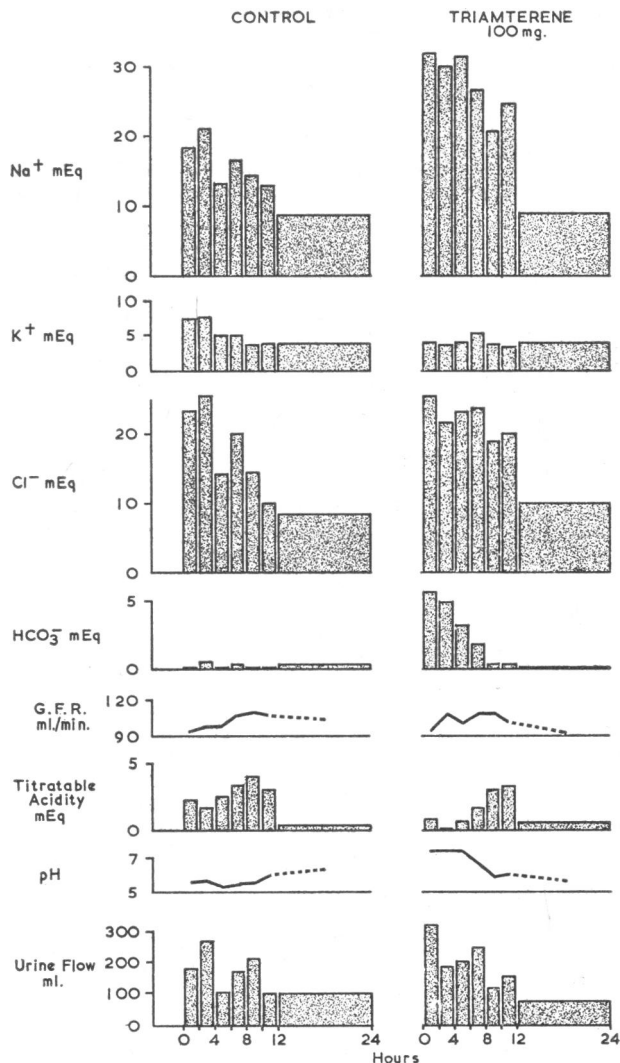


FIG. 1.—Mean effect of triamterene (100 mg.) on urine volume and composition in four normal individuals.

TABLE II.—Ten-hour Urinary Excretion of Water and Electrolytes on Control Day and after 100 mg. Triamterene in Four Normal Subjects

	Sodium (mEq)					Potassium (mEq)					Chloride (mEq)					Bicarbonate (mEq)					Water (ml.)				
	1	2	3	4	M	1	2	3	4	M	1	2	3	4	M	1	2	3	4	M	1	2	3	4	M
Control	106	86	101	92	96	38	31	26	32	32	119	102	111	104	109	3	1	0	0	1	1,545	824	983	1,067	1,105
Triamterene	162	204	140	141	162	22	20	21	40	25	124	171	117	119	133	20	11	17	20	17	1,558	1,384	1,266	1,204	1,353

ance of fluorescence in the urine. Increase in urine flow (1-68% of control values) occurred but was less marked. In three of the four individuals the urinary excretion of potassium was reduced to between 58 and 81% of the control values. An increase in the urinary excretion of chloride also occurred but was not of the same order as the sodium loss. The rise in urine pH and bicarbonate excretion was associated with a fall in titratable acidity. No significant change was found in the glomerular filtration rate.

Direct comparison of the urinary electrolyte excretion after administration of triamterene and chlorothiazide was not made. However, it is of interest to compare the mean pattern of urinary electrolyte excretion previously obtained in two normal individuals given chlorothiazide (1 g.) with the present data (Table III). A greater urinary sodium loss followed the administration of chlorothiazide (1 g.), but this was achieved at the expense of considerable urinary potassium excretion. Triamterene administration, while associated with less sodium diuresis, showed the striking quality of potassium conservation.

TABLE III.—Mean Increase in 24-hourly Water and Electrolyte Excretion of Two Normal Subjects Given 1 g. Chlorothiazide and Four Normal Patients Given 100 mg. Triamterene Expressed as a Percentage Change from the Control Values

	Percentage of Control Values	
	Chlorothiazide	Triamterene
Sodium	282	169
Potassium	147	78
Chloride	187	122
Urine volume .. .	178	122

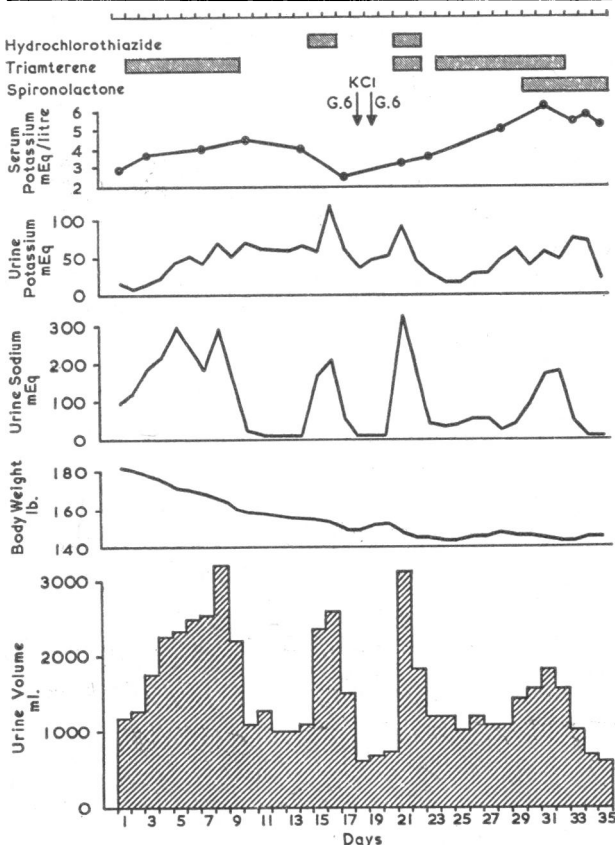


FIG. 2.—Case 1. Urine electrolyte excretion, body weight, and serum potassium concentration during treatment with hydrochlorothiazide (50 mg. b.d.), triamterene (50 mg. q.d.s.) and spironolactone.

Patients with Chronic Oedema

The results obtained after the administration of triamterene (50 mg. q.d.s.) alone and in combination with other diuretics to patients with chronic oedema are summarized in Table I. Triamterene alone is an effective diuretic with the rare quality of potassium conservation. In combination with hydrochlorothiazide it not only enhances the urinary sodium excretion but reduces the potassium loss (Figs. 2 and 4). It also enhances the diuretic action of spironolactone (Fig. 3). In none of these patients was there any significant rise in the blood-urea concentration.

Normal Subjects on Low-sodium Diets

Two subjects were given a rice diet containing less than 5 mEq of sodium daily to stimulate endogenous aldosterone secretion. During the control period Na/K ratios of 0.13 were achieved. The urinary water and electrolyte excretion following the administration of triamterene (50 mg. q.d.s.) and spironolactone (100 mg. q.d.s.) were measured. The dose selected for each

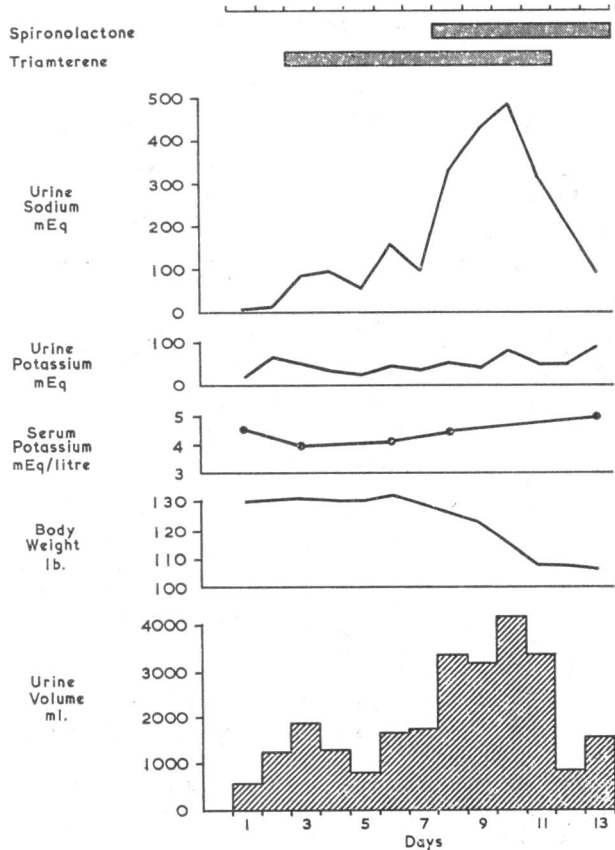


FIG. 3.—Case 2. Urine electrolyte excretion, body weight, and serum potassium concentration during treatment with triamterene (50 mg. q.d.s.) and spironolactone (100 mg. q.d.s.).

drug was that recommended for routine clinical practice. The increase in urinary sodium loss resulting from treatment with the first drug was replaced by oral sodium chloride before the second drug was given. The results obtained in each patient were similar and the mean values are therefore presented in Table IV. Triamterene (50 mg. q.d.s.) produced a greater sodium and water diuresis than spironolactone (100 mg. q.d.s.). The marked reduction in potassium excretion following triamterene is particularly striking.

Normal Patients on High-sodium Diets

Two normal individuals were given diets containing 240 mEq of sodium daily in order to reduce endogenous aldosterone secretion. The urinary excretion of water and electrolytes was measured during a control period and after the administration of triamterene (50 mg. q.d.s.). The patterns of electrolyte excretion were similar in each patient, and the mean values are presented in Table V. There was a marked increase in the urinary excretion of sodium, chloride, and water following the dose of triamterene and most significantly a decrease in the excretion of potassium. To assess the degree of endogenous aldosterone production under these conditions another normal individual on a similar dietary regime was given spironolactone, 100 mg. q.d.s. This produced a significant increase in the urinary excretion of sodium and water with a slight diminution in

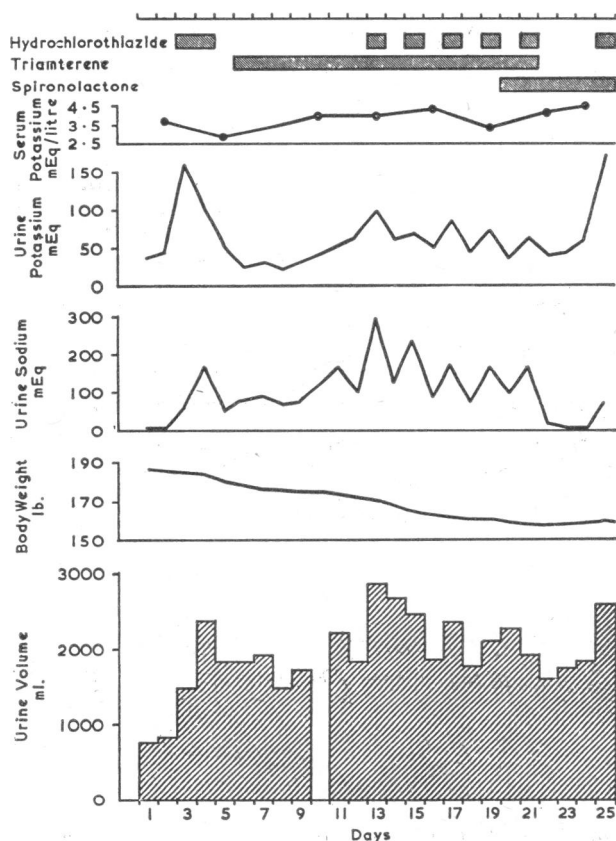


FIG. 4.—Case 3. Urine electrolyte excretion, body weight and serum potassium concentration during treatment with hydrochlorothiazide (50 mg. b.d.), triamterene (50 mg. q.d.s.), and spironolactone.

TABLE IV.—Mean Water and Electrolyte Excretion After Spironolactone (100 mg. q.d.s.) and Triamterene (50 mg. q.d.s.) in Two Normal Individuals on Low-sodium Diets

	Control	Spironolactone	Triamterene
Sodium (mEq/24 hours) ..	4	34	44
Potassium ..	32	31	18
Sodium/potassium ratio ..	0.13	1.1	2.4
Chloride (mEq 24 hours) ..	5	24	24
Urine (volume (ml./24 hours))	1,275	1,365	1,448

the excretion of potassium, demonstrating that endogenous production had not been entirely suppressed.

Two normal individuals were given a diet containing 370 mEq of sodium daily to ensure more complete suppression of endogenous aldosterone production. This object was not entirely successful, as is seen in

TABLE V.—Mean Urinary Excretion of Water and Electrolytes of Two Normal Patients on a Diet Containing 240 mEq Sodium Daily During a Control Period and After Triamterene (50 mg. q.d.s.)

	Control	Triamterene
Sodium (mEq/24 hours) ..	170	281
Potassium ..	62	42
Sodium/potassium ratio ..	2.7	6.7
Chloride (mEq/24 hours) ..	189	270
Urine volume (ml./24 hours) ..	1,270	2,129

Table VI (subject A), which shows the urinary electrolyte excretion after the administration of 1,200 mg. of spironolactone. An increase in the urinary excretion of sodium and a reduction in the potassium output was still demonstrable. However, when this effect is

TABLE VI.—Urinary Electrolyte and Water Excretion in Two Individuals (A and B) on a Sodium Intake of 370 mEq Daily, During a Control Period and After the Administration of Spironolactone (300 mg. q.d.s.) and Triamterene (50 mg. q.d.s.)

	Sodium mEq/24 hr.	Potassium mEq/24 hr.	Sodium/Potassium Ratio	Chloride mEq/24 hr.	Volume ml./24 hr.
<i>Subject A</i>					
Control ..	354	87	4.1	389	2,289
Spironolactone ..	406	71	5.7	413	2,160
Control ..	316	84	3.8	335	1,483
Triamterene ..	306	45	6.8	360	1,960
<i>Subject B</i>					
Control ..	338	70	4.8	370	2,535
Triamterene ..	420	56	7.5	375	3,220

compared with that following 200 mg. of triamterene in the same individual a much more striking reduction in the urinary excretion of potassium was demonstrated. Little natriuretic effect was observed in this instance. In contrast the response to triamterene in the second individual on a similar high sodium intake showed a natriuretic effect whilst the potassium-sparing effect, though still present, was less marked (Table VI, subject B).

Uric-acid Excretion During Triamterene Therapy

The urinary excretion of uric acid was studied in seven patients in whom there was no evidence of renal or cardiac disease. All patients received a normal ward diet of approximately constant composition. In all instances there was an increase in uric-acid excretion during the period of triamterene (50 mg. q.d.s.) administration (Table VII).

Toxic Effects

We have encountered no toxic effects in the limited number of patients and normal individuals whom we have treated with triamterene in a dose of 200 mg. daily. In particular there was no evidence of bone-marrow damage or impairment of hepatic function

TABLE VII.—Mean Daily Uric Acid Excretion on Control Days and after Triamterene (50 mg. q.d.s.) in Seven Patients Without Evidence of Renal or Cardiac Disease. Figures in Parentheses Indicate the Number of Observations

	Case A	Case B	Case C	Case D	Case E	Case F	Case G	Mean
Control ..	248 (5)	289 (3)	402 (3)	578 (3)	287 (3)	461 (2)	462 (2)	369 (21)
Triamterene ..	345 (2)	555 (5)	468 (3)	590 (2)	611 (4)	639 (2)	730 (2)	535 (20)

attributable to the drug. We did not find any significant change in the glomerular filtration rate in the normal subjects and no rise in the blood-urea concentration in patients receiving treatment. In one patient (Case 1) the reduction in potassium excretion was associated with a rise of the serum potassium to abnormally high levels (6.2 mEq/l.), and this must be recognized as a potential hazard of long-term treatment. Two patients noted slight nausea.

Discussion

Many powerful diuretic agents are currently available for the control of pathological sodium retention. To merit serious consideration any new diuretic must not only be safe and easy to administer but also be either more effective as a natriuretic agent or possess especially advantageous properties.

In this report triamterene has been shown to increase the urinary excretion of sodium, although in this respect it is less powerful than chlorothiazide. It does, however, possess a striking capacity to conserve potassium, a feature which is of great importance to many patients with oedema and of considerable interest in the study of renal tubular transport mechanisms. It is readily absorbed from the gut, producing a natriuretic effect within two hours of oral administration and lasting for 12 hours. Excretion of the drug or its metabolic products in the urine produces a characteristic fluorescence which provides confirmation of ingestion and absorption.

When given to patients with oedema triamterene alone has an undoubted natriuretic effect associated with potassium conservation and an increase in urine volume (Figs. 2 and 3). The urinary sodium loss is not as great as that following hydrochlorothiazide (Figs. 2 and 4), but in combination with the latter triamterene not only enhances the urinary sodium excretion but reduces the kaliuresis caused by the hydrochlorothiazide (Figs. 2 and 4) and results in a rise in serum potassium concentration without the use of potassium supplements.

The reduction in urinary excretion of potassium after the administration of triamterene, with an increase in sodium and chloride and a reduction in hydrogen-ion excretion and titratable acidity, is reminiscent of the effect of aldosterone antagonists of the spironolactone type and would suggest a similar mode of action. Triamterene (50 mg. q.d.s.) was given to sodium-depleted subjects and its renal action compared with that of spironolactone (100 mg. q.d.s.). It was shown to have a similar natriuretic effect but a much more pronounced potassium-sparing action than spironolactone. When endogenous aldosterone secretion was suppressed by increasing the sodium intake to very high levels the potassium-sparing effect of the drug was not diminished, suggesting that this action of triamterene is not mediated through the antagonism of aldosterone.

The suggestion that the action of triamterene on the renal tubule differs from that of spironolactone is supported by the finding in patients with oedema of a greater diuretic effect of the drugs in combination than either drug produces individually (Figs. 3 and 4). In view of the therapeutic dose of spironolactone used (100 mg. q.d.s.), enhancement of an anti-aldosterone effect cannot definitely be excluded in these patients.

Drug-induced hyperuricaemia following the administration of thiazide diuretics is now well recognized (Oren *et al.*, 1958; Healey *et al.*, 1959; Aronoff, 1960). By contrast we have found that triamterene increases the

excretion of uric acid over the short period of our investigation. More prolonged study with serial serum uric-acid estimations is required to confirm this observation.

The properties of triamterene make it a particularly useful diuretic in those patients in whom hypokalaemia and hyperuricaemia are troublesome features. It is probably the diuretic of choice in patients with gout.

Summary

The diuretic action of triamterene has been investigated in normal subjects and in patients with oedema. It has been shown to have a moderate natriuretic effect, with a striking capacity to reduce the excretion of potassium. It potentiates the diuretic action of hydrochlorothiazide while reducing its kaliuretic effect and obviating the need for potassium supplements. Its action has been compared with that of spironolactone in normal subjects on low and high sodium intakes, and reasons are given for suggesting that its effect on potassium excretion is not the result of aldosterone antagonism. Over short periods of study it increases uric-acid excretion.

We thank Dr. A. W. Spence and Mr. A. H. Hunt for allowing us to study patients under their care; Mrs. Eileen Akers for the electrolyte determinations; Mr. Peter Cull for the figures; Miss Knapman, Miss Bale, and their nursing staff for their willing co-operation; and Smith Kline & French for supply of triamterene.

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"In all the countries of the Western World, Britain spends the least on drugs at 16s. per head per annum; Holland 22s. 2d., Sweden 25s. 8d., Western Germany 26s. 1d., U.S.A. 33s., Italy 47s. 5d., and Belgium 55s. 4d. Gross excess elsewhere, however, does not justify over-prescribing [in Great Britain], and there is a lot of unnecessary prescribing. There are many causes for this: the desire to take medicine seems to be the chief thing which differentiates man from the lower animals, and patients sometimes demand drugs with threats that, unless they get them, they will remove their cards from the doctor's list. My profession must bear its full share of responsibility. Another factor, however is the immensely skilful advertising pressures in the pharmaceutical houses, some of whose promotion of new and untried remedies is subject to justifiable criticism. Your products are known, almost plaintively, as 'ethicals' to distinguish them from medicines advertised direct to the public. The word 'ethical' should, however, imply more than this. Your advertising through the post, the medical press, and through representatives has a profound influence on medical practice—much more potent than the bleatings of professors of therapeutics. It is essential to bear in mind that great influence carries with it great 'ethical' responsibilities..." (Sir Derrick Dunlop, opening London Medical Exhibition, November 12.)