human blood groups, we would certainly have suggested that the small differences of blood-group frequency among different sorts of smoker and between smokers and non-smokers were most probably the effect of sampling variation. As it is, our results are not in conflict with those of Cohen and Thomas (1962), and it is still possible, therefore, that an association between blood group B and smoking may exist generally. Most encouraging is the fact that this association may be of the relatively simple form of a contrast between those who have never smoked and those who have, the former showing an excess of group B. Such an excess is present in both negro and white males in Cohen and Thomas's series and in the present series. It is to be hoped that further data will be accumulated by other workers; the fact that the apparent association is with the relatively rare blood group B means that large numbers will be required before chance can be ruled out as its source.

The importance of showing the existence of any differences in blood-group frequency in relation to smoking, as was pointed out in the *British Medical Journal* (1962), is clear. Any such differences could reflect a genetic element in the adoption of different smoking habits or heterogeneity of the population in this respect for other reasons. In either case light might be thrown on the relation of smoking both to lung cancer and to chronic bronchitis by a search for corresponding variations in the apparent risks of these conditions. To date no particular blood group has been found to be associated with the development of lung cancer, and our findings (Higgins *et al.*, 1963) suggest that in miners, at least, neither blood group nor secretor status is related to the respiratory

symptoms on which a diagnosis of chronic bronchitis is usually based, but further observations are desirable.

Summary

ABO and rhesus blood groups, secretor status, and smoking habits have been determined in 85% of a random sample of miners and ex-miners aged 35-64 from the Rhondda Fach. Neither blood group nor secretor status was significantly related to smoking habits. Our findings and those of Cohen and Thomas in respect of the ABO system and smoking do not, however, differ significantly, and further studies are needed to increase the accuracy of the pooled estimate, which at present suggests that the small number of men who have never smoked is half as large again in group B as in other groups.

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DIURETIC ACTION OF ETHACRYNIC ACID IN CONGESTIVE HEART FAILURE

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The introduction of the thiazide group of diuretics was a major advance in the oral treatment of patients with heart failure. Subsequent derivatives and other chemically unrelated compounds have not shown any major therapeutic advantage over the parent drug. Ethacrynic acid (MK-595) is a new diuretic agent. Its diuretic action was first assessed in five patients with congestive heart failure. Its efficacy in an oral dosage of 150 mg. was then compared with 2 ml. of mersalyl given intramuscularly in 10 patients.

Ethacrynic acid is an unsaturated ketone derivative of aryloxyacetic acid. It is different in structure from the thiazides and it does not contain sulphur, nitrogen, or a heavy metal. The first observations of its diuretic action were made in dogs (Schultz *et al.*, 1962; Baer *et al.*, 1962, 1963). Clinical trials in man (Foltz, 1963) showed that ethacrynic acid was a potent oral diuretic with powerful chloruretic and natriuretic effects. Dose-response studies during this early investigation indicated that the maximum response occurred with 200 mg. of the drug, but above this dosage no increase in the diuretic or saluretic effects were noted. Since a sudden and large diuresis is potentially dangerous it was decided, in this present study, to use a dose of 150 mg.

Assessment of Diuretic Action

Methods

Five in-patients with heart failure (Table I) and associated peripheral oedema were studied. They were treated with

bed rest and a diet very low in sodium (25 mEq/24 hours). Fluids were restricted to 800 ml./day and digitalis was given in optimum dosage. The patients were weighed at the same time each day, and when their weights remained steady 24-hour urinary volumes were measured and the 24-hour excretions of sodium, chloride, and potassium were estimated. These observations were continued for three days to establish basal levels. Ethacrynic acid was then given in a single morning dose of 150 mg. orally for five consecutive days and all the above estimations were continued. The serum levels of sodium, chloride, and potassium and the blood urea were measured on the day before ethacrynic acid was started and on the day after the course had been completed. In two patients the duration of the diuretic action was measured. On the first day of treatment the volume of hourly specimens of urine was measured, starting three hours before the drug was given, and this was continued throughout the day.

Results

In all the patients a diuresis occurred during treatment with ethacrynic acid. The amount of the diuresis naturally varied with the degree of peripheral oedema that was present. Thus in three patients (Cases 1, 2, and 3) who had gross pitting oedema of the legs and lower trunk an average of 2,229 ml., 1,840 ml., and 1,896 ml. respectively was excreted daily over the five-day period of treatment. In Cases 4 and 5 there was minimal pitting oedema of

the lumbar region only, and in these the comparable figures were 1,154 ml. and 642 ml. respectively. To demonstrate the diuretic effect of the drug the above figures were compared with the average urinary volume excreted per 24 hours during the three days prior to treatment (Table I). Each of the patients lost weight during treatment, the amount being greater in those who were grossly oedematous.

TABLE I.—*Urinary Electrolyte Changes and Diuretic Response in Five Patients Treated with Ethacrynic Acid*

Case No.	Age and Sex	Cause of Heart Failure	Degree of Oedema	Average Urinary Volume (ml./24 Hours)		Average Sodium Excretion (mEq/24 Hours)		Average Chloride Excretion (mEq/24 Hours)		Average Potassium Excretion (mEq/24 Hours)		Weight Loss over 5 Days (kg.)
				B	D	B	D	B	D	B	D	
1	54 F	M.I.	Gross	869	2,229	6.3	151.6	8	170	40	81.6	7
2	53 F	M.S., M.I.	"	482	1,840	25.0	137.6	37.6	180	28	54.6	5
3	58 F	A.S., A.I.	"	940	1,896	33.3	133.4	63.6	140	33.3	51	5.5
4	68 F	Thyrotoxicosis	Minimal	930	1,154	23.5	26.6	34	63.4	39	54	1.5
5	56 F	M.I.	"	347	642	13.5	25.2	29.5	47.4	25	38.4	2

B = Values for the 3-day basal period before treatment. D = Values for the 5-day period during treatment.
M.I. = Mitral incompetence. A.S. = Aortic stenosis. A.I. = Aortic incompetence. M.S. = Mitral stenosis.

In the three patients (Cases 1, 2, and 3) in whom a large diuresis occurred the average amount of sodium and chloride excreted in 24 hours was greatly increased, whereas in Cases 4 and 5, with less oedema, the increase was much smaller (Table I). There was a smaller but definite increase in the potassium excretion in all the patients, even in those with minimal oedema who had a small diuretic response. In none of the patients was there a significant change in the serum sodium, chloride, or potassium levels, which were estimated the day before and the day after treatment (Table II). In one patient (Case 2) who had a large diuresis, the blood urea rose from 20 mg. to 35 mg./100 ml. but there was no significant increase in any of the other patients.

TABLE II.—*Changes in Serum Electrolytes and Blood Urea Before and After Treatment with Ethacrynic Acid*

Case No.	Serum Sodium (mEq litre)		Serum Chloride (mEq litre)		Serum Potassium (mEq litre)		Blood Urea (mg. 100 ml.)	
	B	A	B	A	B	A	B	A
1	144	140	104	100	3.2	3.3	20	20
2	146	148	102	102	4.5	4.3	20	35
3	140	138	112	108	4.9	4.7	55	50
4	148	150	104	105	4.3	4.6	30	36
5	146	148	102	102	4.5	4.3	20	25

B = Values on day before treatment started. A = Values on day after treatment finished.

In the two patients (Cases 2 and 3) in whom the duration of action of ethacrynic acid was estimated the diuresis started one hour after administration, reached a maximum in two hours, and returned to a basal level of urinary output in eight hours (see Chart).

Duration of response to 150 mg. of ethacrynic acid in Cases 2 and 3.

Comparison of Ethacrynic Acid and Mersalyl as Diuretic Agents

Methods

Ten subsequent in-patients with heart failure and peripheral oedema were treated with bed rest and optimum dosage of digitalis. They were given a low-sodium diet (40 mEq/day) and their fluid intake was not restricted.

They were weighed at the same time each day. When the weight had remained steady ethacrynic acid, 150 mg. orally in a single dose (A), and mersalyl, 2 ml. intramuscularly (B), were administered, using the patterns A B B A, A B B A and B A A B, B A A B in alternate patients and omitting treatment for one day between each dose. The daily weighings were continued during the trial period of 16 days. Thus each patient provided two paired comparisons of the diuretic effect of the two drugs.

The weight losses over 24 hours after the administration of each drug were recorded. The sum of these is the total weight loss (Table III). Calculating the sum of the weight losses after four doses of both mersalyl and ethacrynic acid, an average weight loss per dose for each drug was obtained. The efficiency of ethacrynic acid as compared with mersalyl was then calculated from the ratio of the average weight loss per dose of ethacrynic acid to that of mersalyl, the result being expressed as a percentage. In each paired comparison the total weight loss after the two doses of each drug was obtained, and the drug producing the greater weight loss was considered the better. The sign test (Gold *et al.*, 1960) was then applied. The plus sign (+) was given to those patients in which ethacrynic acid was the better drug in both paired comparisons, the minus sign (-) to those in which mersalyl was better. If ethacrynic acid was better in one of a pair of comparisons and mersalyl in the other, the sign 0 was used (Table III).

Results

It can be seen (Table III) that the diuretic effect of ethacrynic acid was very variable as compared with mersalyl. Assuming the efficiency of mersalyl to be 100%, that of ethacrynic acid varied from 0% in Case 12 to 680% in Case 10. This great variation did not seem to depend on the total amount of oedema fluid lost, since in Cases 9 and 10 ethacrynic acid was clearly the better drug, yet Case 9 lost 14.32 kg. during the period of the trial while Case 10 lost only 1.7 kg. The data were more fully analysed using the signs (+, -, or 0) which had been accorded to each patient. All patients with the sign 0 were disregarded. The number with + (3) or - (2) was noted.

The formula $\frac{(X - Y - 1)^2}{X + Y}$ was then applied where X is the greater of these numbers and Y the lesser. Thus in the present series $\frac{(3 - 2 - 1)^2}{3 + 2} = 0$. This indicates that the results obtained have no statistical significance and are probably due to chance (Gold *et al.*, 1960). If it is assumed that

TABLE III.—Comparison of Mersalyl 2 ml. and Ethacrynic Acid 150 mg.

Case No.	Sex and Age	Cause of Heart Failure	Pattern	Total Weight Loss (kg.)	Average Weight Loss (kg.) per Dose Mersalyl (S)	Average Weight Loss (kg.) per Dose Ethacrynic Acid (T)	Efficiency of Ethacrynic Acid T S (%)	No. of Paired Comparisons		Sign
								Mersalyl Better	Ethacrynic Acid Better	
6	F 73	M.I.	ABBA	7.84	0.990	0.966	97.5	1	1	0
7	M 59	M.I.	BAAB	11.36	0.909	1.930	212.3	0	2	+
8	M 23	A.S., A.I., M.I.	ABBA	3.98	0.900	0.133	12.5	2	0	—
9	M 56	C.A.D.	BAAB	14.32	0.800	2.745	343.1	0	2	+
10	F 74	C.A.D.	ABBA	1.70	0.050	0.340	680.0	0	2	+
11	F 63	M.S.	BAAB	3.75	0.680	0.280	41.2	1	1	0
12	F 73	C.A.D.	ABBA	2.61	0.650	0	0	2	0	—
13	M 75	A.S., B.P. +	BAAB	6.36	0.113	1.480	130.9	1	1	0
14	M 71	C.A.D.	ABBA	3.75	0.51	0.48	92.1	1	1	0
15	M 57	A.S., A.I.	BAAB	6.7	0.92	0.71	77.2	1	1	0

M.S. = Mitral stenosis. M.I. = Mitral incompetence. A.S. = Aortic stenosis. A.I. = Aortic incompetence. B.P. + = Hypertension. C.A.D. = Coronary artery disease. Sign: + = Ethacrynic acid better in two paired comparisons. — = Mersalyl better in two paired comparisons. 0 = Mersalyl and ethacrynic acid each better in one of two paired comparisons.

mersalyl has a uniform diuretic action, these results imply that the effect of ethacrynic acid is very variable from patient to patient.

Discussion

The results obtained in the first five patients demonstrated that ethacrynic acid was a potent diuretic with considerable natriuretic and chloruretic effects. A definite, though smaller, kaluresis also occurred. There was no consistent change in the levels of serum sodium, chloride, or potassium even after five days of continuous treatment. No side-effects were noted in any of the 15 patients.

In Case I there was gross oedema which had not responded previously to treatment with mersalyl, hydrochlorothiazide, triamterene, or spironolactone, both singly and in various combinations. Ethacrynic acid produced a dramatic diuresis (average of 2,229 ml. daily) and 7 kg. in weight were lost during five days. After this she responded well to hydrochlorothiazide and mersalyl. In one patient with advanced cor pulmonale not included in the trial, a single dose of 150 mg. of ethacrynic acid produced an enormous diuresis with a loss of 12.73 kg. in weight during 24 hours. He died suddenly the next morning, and although this might be expected in such a patient, it is possible that the magnitude of the diuresis contributed to his death. In such patients a smaller initial dose of 50 mg. might well be more appropriate.

We chose to compare the effects of mersalyl and ethacrynic acid on the basis of weight loss, since this is the best overall index of their efficiency in removing oedema fluid. When compared in this way with mersalyl, the notable feature was the variability of the response to ethacrynic acid. This may well be due to differing degrees of intestinal absorption, but, whatever its cause, it is a disadvantage in the oral administration of the drug. In this trial 150 mg. of ethacrynic acid was used, but it seems probable that had the maximum effective dose of 200 mg. been given the same variation in response would have occurred. Whereas this trial was purposely designed merely to compare the diuretic effect of 2 ml. of mersalyl and a single oral dose of 150 mg. of ethacrynic acid in patients with heart failure, it must be stressed that it is only one facet in the investigation of a new diuretic, and further observations are necessary regarding its optimum oral dosage (single or multiple), its diuretic effect in combination with other drugs, its effect when given intravenously, and its effect in other conditions where fluid retention is present.

Since the completion of the trial three further patients with heart failure and intractable oedema were given ethacrynic acid in doses of 50 mg. six-hourly. The weight loss and urinary output per 24 hours were in excess of that obtained when using a single morning dose. This observation may

well indicate that using the drug in divided dosage will give better results. This limited study indicates that ethacrynic acid is a potent oral diuretic but variable in its action. Its effect may be dramatic in some patients previously unresponsive to other diuretics, and this alone would make it a most useful drug.

Summary

In five patients the diuretic action of ethacrynic acid (MK-595) was investigated over a period of five days. It is a potent diuretic. Large amounts of urinary sodium and chloride were excreted and lesser amounts of potassium. No significant change occurred in the level of serum electrolytes. In only one patient did the blood urea rise significantly. No side-effects were noted. Maximum diuresis occurred two hours after administration of the drug.

When compared with mersalyl (2 ml. intramuscularly) in 10 subsequent patients, a single oral dose of ethacrynic acid (150 mg.) had a variable effect.

In this limited trial it is concluded that ethacrynic acid is a useful diuretic agent and can have a dramatic effect in some patients.

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"The ever-rising contribution of married women, especially of married women with professional qualifications and training, who work whole-time or part-time, is one of the major economic and social phenomena of our day. This is a change which we cannot resist even if we would. We shall do well to make it welcome, and adapt our methods and ideas to draw the utmost benefit from it. Nursing is not the only activity, nor are hospitals the only organizations, whose character and working are being profoundly influenced and altered by it; but they are among the most important. In the last five years the number of part-time nurses in our hospitals has increased by 50%, and there is every indication of the increase continuing. Already 19% of all nursing time in our hospitals is contributed by part-time staff, whose numbers approach 60,000." (Mr. Enoch Powell, at Broomfield Hospital, Chelmsford, October 15.)