provide enough evidence on which to base any useful estimate of the quantity of aldosterone present in urine.

Many complicating substances might have been present in the early crude extracts, and preliminary purification by paper chromatography often led to better bioassay results of the sodium-retaining factor. But this was not always so, and Dyrenfurth and Venning (1959) have recently published their own circumstantial evidence for the existence of an interfering and sodium-excreting factor. They found that extracts freed of most of their cortisol, cortisone, and corticosterone sometimes showed less aldosterone when assayed at a high dose-level than at a lower, and suspected, therefore, that an antagonizing substance was present which could be diluted out. Indeed, they found some urine extracts which actually increased sodium output.

There is good reason to believe, therefore, in the existence of a sodium-excreting factor in man and to believe that this occurs at least sometimes in the urine. Search for such a sodium-excreting factor (S.E.F.) is being pursued vigorously in several research centres.

One such search has been carried out by a Ciba group in Basle (Neher *et al.*, 1958). These workers were able to isolate from hog adrenals a fraction which appeared to have sodium-excreting properties. This they identified as $3\beta,16\alpha$ -dihydroxy-allopregnan-20-one, and this compound has been synthesized by the same group. They believe that this steroid has sodium-excreting properties (S.E.F.), though they admit that its activity is inhibited or enhanced by conditions which have not yet been fully elucidated.

Since a naturally occurring steroid with sodium-excreting properties would clearly be of the highest physiological and therapeutic importance, we have tested this steroid for possible sodium-excreting activity in man under favourable clinical conditions.

Five patients have been used for the tests, all representing, so far as possible, the same clinical state of convalescence from moderate congestive failure with recent oedema. None had received any diuretic during the preceding 10 days or more, and they might therefore have been expected to be very responsive to a sodium diuretic. This particular clinical situation was chosen for the tests because it was one in which a sodium diuretic might prove useful, and one, moreover, likely to be favourable to the revelation of any sodium-excreting activity possessed by the compound.

The first subject was on a normal salt intake, the remaining four being on a low-sodium intake of 22 mEq daily. Baseline urinary excretions of sodium and potassium were measured for four to seven days. The steroid was then given as a daily intravenous injection for three successive days. After two or three further days, in which any effect of the steroid could subside, a single dose of 1 g. of chlorothiazide was given to four of the subjects. The results obtained are summarized in the Table.

Mean Daily Urinary Excretion mEq

Case No.	Daily Dose Steroid (mg.)	4 Days Control		3 Days Steroid		1 g. Chlorothiazide	
		Na	K	Na	K	Na	K
1	40	71	70	68	67	—	—
2	60	10	75	8.6	70	87	79
3	80	6.5	42	10	40	131	65
4	100	7	102	12	87	80	75
5	100	8	37	7	28	58	50
Mean	..	20	65	21	58	89	67

From these experiments it is clear that, under the clinical conditions chosen, the steroid (S.E.F.) caused no significant change in urinary sodium excretion, though chlorothiazide provoked a sharp sodium diuresis. The mean effect in the five cases is an increase of only 5% in sodium excretion, and this may be compared with the mean increase of 330% produced by a single dose of chlorothiazide.

No conclusions can safely be drawn about any effects on potassium excretion because the intake was not fully controlled, but it cannot be large.

Whether this steroid will prove to have sodium-excreting properties under other clinical conditions remains to be seen. This seems unlikely, because the steroid possesses a saturated ring A, and this is not usually associated with physiological activity.

Summary

Evidence suggesting the existence of a sodium-excreting factor in the human subject is briefly reviewed.

A new steroid, $3\beta,16\alpha$ -dihydroxy-allopregnan-20-one, said to have sodium-excreting properties, has failed to show any such activity in a clinical situation in which it could have provided useful therapy.

We are greatly indebted to Dr. Neher and to Dr. Gross, of Basle, for a generous sample of this steroid in a form suitable for intravenous injection.

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Phenethyldiguanide: A Dangerous Side-effect

Phenethyldiguanide (D.B.I.) is the most recent of the hypoglycaemic drugs to become available to clinics in this country. Early work has suggested that D.B.I. has a place in the treatment of adult diabetics, in whom it has an advantage over the arylsulphonylureas by reason of the absence of secondary failures and a wider spectrum of action (Williams *et al.*, 1958; Krall and Camerini-Davalos, 1958; Walker, 1959). In addition, it may in conjunction with insulin improve the control of unstable diabetics (Pomerance, 1957; Odell *et al.*, 1958; Krall and Bradley, 1959).

The action of D.B.I. has not yet been elucidated—it produces hypoglycaemia in the absence of endogenous insulin, thereby differing from the arylsulphonylureas. It has been suggested that it acts by promoting anaerobic glycolysis, which is less efficient than normal aerobic metabolism in that more glucose is required per unit of energy produced (Williams *et al.*, 1958). The

end-product of this process is lactic acid. It has further been said to inhibit enzyme systems in the tricarboxylic acid cycle (Steiner and Williams, 1958; Wick *et al.*, 1958; Krall and Bradley, 1959). The present communication concerns a dangerous side-effect of the drug and measures which may be used to combat it.

Side-effects of D.B.I. fall into two groups—gastro-intestinal and metabolic. The gastro-intestinal upsets, while troublesome in earlier studies, can be reduced in frequency by slow increase of dosage (Pomeranze, 1958; Walker, 1959). Metabolic upset has been indicated by the occurrence of acidosis and ketonuria in the presence of normoglycaemia or mild hyperglycaemia (Hall *et al.*, 1958; Steiner and Williams, 1959). In our experience with over 100 cases of all types of diabetes treated with D.B.I. over two years, it has been a worrying and indeed dangerous complication. Ketonuria with or without acidosis has occurred in about one-third of all cases, always without notable rise in blood-sugar levels. Frank reduction of alkali reserve was present in 11 cases (8 juvenile, 2 adult unstable, and 1 adult stable), usually after months of good control with D.B.I. alone. In two of these the alkali reserve fell to 7 vols.% (3.1 mEq) and 11 vols.% (4.9 mEq) with blood-sugar levels of 208 and 280 mg./100 ml.—this happened suddenly and without any obvious cause. One of these patients died a few hours after admission, though he had been having supplementary insulin in addition to D.B.I. for some months. No lesion was found at necropsy to account for his death.

Clinical observation suggested that ketonuria with acidosis was almost confined to juvenile or unstable diabetics, but ketonuria alone occurred in all types. In no case was any simple cause found to explain the upset, with the possible exception of some adult diabetics when ketonuria accompanied hypoglycaemia and may have been of "starvation" type. It was further seen that ketonuria and acidosis occurred very frequently in patients who had recently undertaken increased physical exercise of any kind.

Because of the lack of any definite knowledge of causation, the measures used to combat ketosis were of necessity empirical; they were (a) increased dietary carbohydrate, (b) reduction in D.B.I. dosage, and (c) use of supplementary insulin.

The two severe cases of acidosis mentioned were treated with insulin, glucose, and alkali intravenously. While these measures are sometimes successful, the drug is now only used alone in a minority of juvenile cases, on account of acidosis or recurrent ketonuria.

It is felt that the place of D.B.I. in diabetic therapy is not yet properly assessed, and that it must depend on elucidation of its hypoglycaemic action and the mechanism of production of acidosis and ketosis.

In an attempt to clarify this problem, a selection of diabetic patients have been given an exercise test with measurement of blood-sugar, alkali reserve, total blood hydrazones, and lactate before and after. The results will be reported on in full later, but confirm that the patients controlled on D.B.I. have raised blood lactate and plasma hydrazone levels at rest (Williams *et al.*, 1957), and that exercise exaggerates this abnormality. The alkali reserve also falls markedly with exercise, the fall being many times as great as may be observed in normal people.

These facts suggest that while D.B.I. lowers blood-sugar, probably by promoting anaerobic glycolysis, there is a defect in carbohydrate metabolism in the intermediate stage, resulting in an accumulation of lactate. The urine of patients controlled by D.B.I. has been found invariably to be extremely acid, providing further indirect evidence. Presumably there is increased lactate formation from anaerobic glycolysis and possibly impaired utilization of this due to interference with the tricarboxylic-acid cycle. In addition, D.B.I. does not promote formation of liver glycogen, and this has been found to be greatly reduced in D.B.I. therapy (Steiner and Williams, 1959). It seems likely, then, that the result of this is increased breakdown of fat in the liver, giving rise to ketonaemia.

These two defects would be complementary, giving rise to acidosis and ketonuria.

It would appear that while D.B.I. may control diabetes in that reduction of blood-sugar is obtained, the means of obtaining this effect are less physiologically correct than when insulin is used. The use of D.B.I., therefore, particularly in diabetes of the unstable type, must be accompanied by close observation and biochemical control. The rapidity of onset of severe acidosis in juvenile cases without premonitory warning is emphasized.

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