Brit. J. Pharmacol. (1966), **26**, 412–420.

BIOCHEMICAL EFFECTS OF SHORT-TERM TREATMENT WITH CARBENOXOLONE DISODIUM

BY

W. HAUSMANN AND A. L. TÁRNOKY

From the Departments of Medicine and Pathology, Royal Berkshire Hospital, Reading

(*Received October* 22, 1965)

Carbenoxolone disodium (Biogastrone), a triterpene derivative, was first synthesized by Turner & Wotton (1959, unpublished). It shows a superficial resemblance to steroid structures and was first tested as an anti-inflammatory agent in rats and in cats (Finney & Tárnoky, 1960). More recently it has come into use in the treatment of gastric ulcer in man and has been described as the first therapeutically active compound in this field (Doll, Hill, Hutton & Underwood, 1962). A number of clinical trials have been carried out (Doll, Hill & Hutton, 1965; Middleton, Cooke, Stephen & Skyring, 1965; Horwich & Galloway, 1965; Turpie & Thomson, 1965). Doll *et al.* (1962) observed oedema in ten of their first fifty-eight patients, amounting to cardiac failure in two, and this finding has recurred in their second series (Doll *et al.*, 1965), as well as in the cases studied by Horwich & Galloway (1965) and by Turpie & Thomson (1965). All authors attribute their findings to salt and water retention, though none gives biochemical data to support this view. The assumption is reasonable enough, since several workers (Molhuysen, Gerbrandy, De Vries, De Jong, Lenstra, Turner & Borst, 1950; De Vries, Holt, Daatselaar, Mulder & Borst, 1960; Drosdowski, Robel & Sebaoun, 1961; Minvielle, Cristol & Badach, 1963) have reported fluid retention, oedema, hypokalaemia and hypertension as side-effects of glycyrrhizin and glycyrrhetic acid, to which carbenoxolone is related, and Finney & Tárnoky (1960) have suggested that this compound may have a mineralocorticoid-like effect. But no biochemical study of these side-effects in man has been reported and, since the drug has come into general use, such an assessment has become necessary. In the present work, which was not part of a therapeutic trial, we have followed patients by means of common laboratory procedures, and we now suggest four tests for the routine control of patients under treatment.

METHODS

Patients

Fifteen patients (eight men and seven women, 17 to 76 years old) with various gastro-intestinal disorders were investigated. Their clinical details are given in Table 1. All were in-patients treated with bed rest. They were observed for 17 days and given carbenoxolone disodium for 14 days, from the evening of the 2nd to that of the 16th day; one patient (case 3) was treated for 20 days and observed for 23 days. Patients under 60 years received 100 mg three times daily, those over 60 were given 100 mg twice daily, since it had been found that patients over 60 were more liable to

TABLE 1

SUMMARY OF CASES

1, Diagnosis on admission; 2, final diagnosis; 3, carbenoxolone for 14 days; 4, carbenoxolone for 20 days; 5, blood transfusion (on day shown in parentheses, or on minus days before day 1); 6, oral iron; 7, intramuscular iron; 8, antacids; 9, nitrofurantoin; 10, salicylazosulphapyridine; 11, prednisolone; 12, prednisolone enemata

Patient				
Case no.	Age	Sex	Diagnosis	Treatment
1	76	F	1. Anaemia, ? G.I. bleeding. 2. Hiatus hernia, iron-deficiency anaemia	3, 5(3), 6
2	53	F	Crohn's disease, anaemia due to G.I. bleeding, history of prepyloric ulcer	3, 7
3	58	M	G.U., anaemia due to G.I. blood loss	4
4	43	F	Iron-deficiency anaemia, thought to be due to steatorrhea	3, 6, 7
5	71	M	History of G.U., admitted after a stroke	3
6	22	M	1. Diarrhoea, faecal blood loss. 2. Proctitis, psychoneurosis	3
7	52	F	Acute G.I. blood loss from peptic ulceration with negative barium findings; urinary infection	3, 5(1), 8, 9
8	17	F	1. Diarrhoea, loss of weight. 2. Crohn's colitis	3, 6, 10, 11, 12
9	20	M	Haemorrhage from D.U.	3, 5(-2), 8
10	53	M	D.U., hiatus hernia	3, 8
11	43	M	Haemorrhage from acute peptic ulcer, site unknown, after taking salicylate	3, 5(-3), 6
12	42	M	D.U.	3, 6, 8
13	73	F	D.U.; gravitational ulcers	3
14	58	M	D.U.	3, 5(-1), 8
15	52	F	1. Iron-deficiency anaemia. 2. Hiatus hernia	3, 5(4), 6, 7

develop side-effects in the course of treatment. One patient (case 8) received the drug while on full doses of prednisolone (60 mg/day). None of the patients was given diuretics or potassium supplements, and there were no restrictions on salt intake.

Patients were weighed daily, their fluid balance was charted from day 3 to day 16, and their blood pressures were recorded about weekly. Urinalysis (with *p*H measurement, bilirubin and urobilinogen tests) was carried out on days 1, 6, 12 and 16. Blood urea, sodium, potassium, bicarbonate, chloride, protein, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, 24-hr urinary sodium, potassium and chloride outputs, and 24-hr urea clearance were measured on days 1, 9 and 16. Bromsulphthalein tests (5 mg/kg) were carried out on days 2 and 17, and other tests on days 1 and 16. These were gastric analysis (basal 1-hr secretion), serum calcium, alkaline phosphatase, bilirubin, cholesterol, protein tests (electrophoresis, thymol, zinc and ammonium sulphate turbidities, C-reactive protein), urinary 17-oxosteroid and 17-oxycorticosteroid outputs, and paper-chromatographic amino-acid pattern. Haematocrit values and [^{131}I]-triiodothyronine uptake of the red cells were measured in nine patients on days 1 and 16.

Investigations

Triiodothyronine uptakes were measured by a modification of the Hamolsky procedure (Goolden, Gartside, Jackson & Osorio, 1962). Total protein, urea, bicarbonate and alkaline phosphatase were measured in a Technicon Autoanalyser. The methods for both steroid estimations were those of Norymberski (Norymberski, Stubbs & West, 1953; Appleby, Gibson, Norymberski & Stubbs, 1955), transaminases those of Mohun & Cook (1957), albumin and globulin those of Lestas (1963), C-reactive protein by a precipitin method (Baxter-Hyland Laboratories), cellulose acetate electrophoresis and amino-acid chromatography as given by Smith (1960), and other tests by Tárnoky (1958).

RESULTS

The only clinical side-effect was an increase in arterial blood pressure in three patients. It was most pronounced in case 1, a patient with defective renal function, who showed a gradual rise amounting to 60/30 mm Hg in all. Two patients showed transient rises, case 4 an increase of 45/20 mm Hg on day 12, and case 15 30/30 mm Hg on day 8. There

was no evidence of developing renal damage as judged by urine volumes, urinalysis, blood urea, serum albumin and urea clearance values. Case 1 had an initially high blood urea level (50 mg/100 ml.) and low 24-hr urea clearance (44% of average normal); these showed a temporary improvement during treatment with carbenoxolone (days 9 to 10: 30 mg/100 ml. and 55%; days 16 to 17: 25 mg/100 ml. and 63%; day "21" (now untreated): 25 mg/100 ml.; day "55" when seen in the out-patients' clinic: 55 mg/100 ml.).

Blood electrolytes showed changes in the bicarbonate and potassium levels, with no great variation in sodium and total protein and minimal variation in chloride. Plasma bicarbonate levels rose in eight patients, markedly in three: case 3 (Fig. 1), on a 3 weeks' course, rose from 26.5 to 28.5 mequiv/l. during the first 2 weeks and to 32.5 mequiv/l. after 3 weeks' treatment; case 11 had 22.5, 30.5 and 31.0 mequiv/l. on days 1, 9 and 16; and case 8 (Fig. 2), who had concurrent steroid treatment, changed from 27.0 to 31.0 and finally to 38.0 mequiv/l.; she returned to 24.5 mequiv/l. 10 days later, when still on prednisolone but taking no carbenoxolone. Twelve patients showed decreased serum potassium levels, mostly within normal limits, but greater in case 1 (from 5.2 to 3.0 mequiv/l. by day 16, rising to 3.4 mequiv/l. a week later and to 5.2 mequiv/l. after a month), and even more pronounced in case 8 (Fig. 2), whose level fell from 5.2 to 2.2 mequiv/l. and rose to 3.8 mequiv/l. in the 10 days after combined therapy ceased.

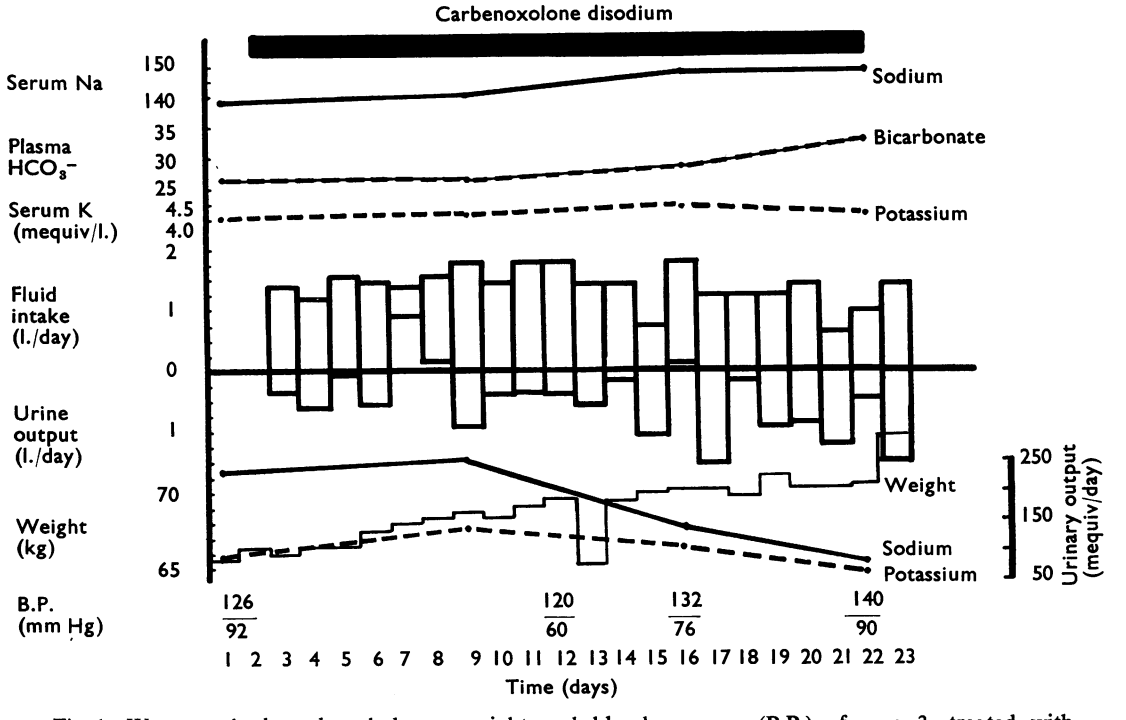

Fig. 1. Water and electrolyte balance, weight and blood pressure (B.P.) of case 3, treated with carbenoxolone disodium. Fluid intake is plotted upwards from the horizontal line, urine output downwards from the top of the fluid intake columns Carbenoxolone disodium was given

downwards from the top of the fluid intake columns. Carbenoxolone disodium was given

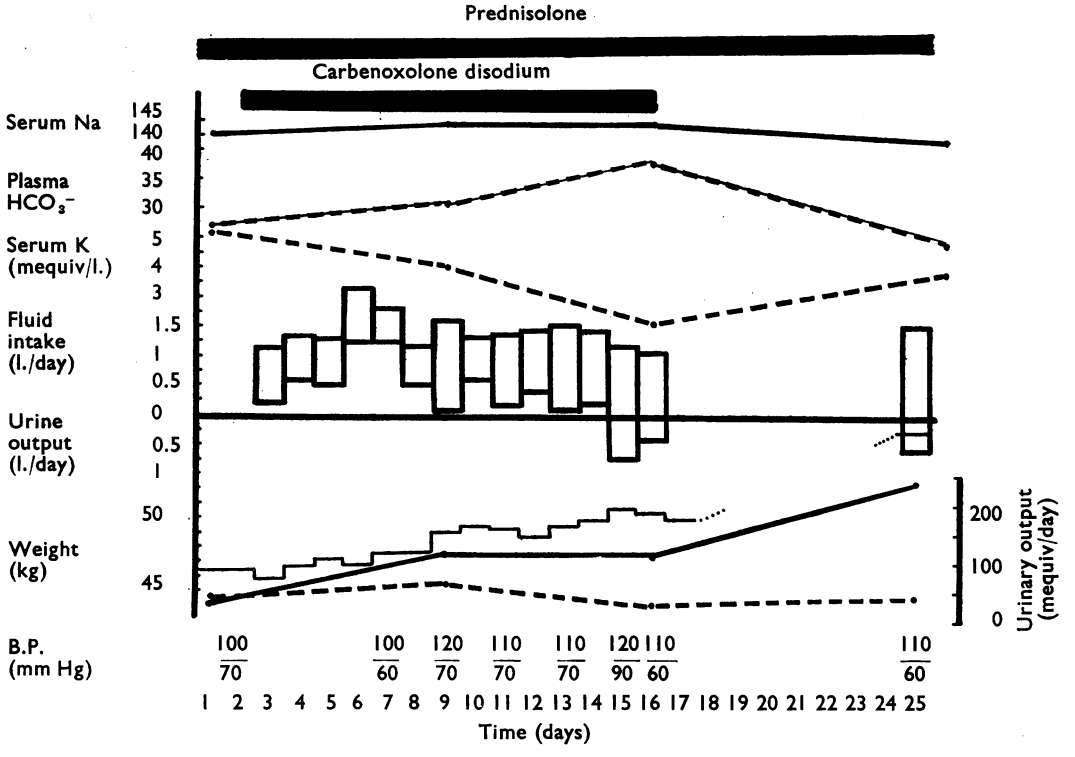

Fig. 2. Water and electrolyte balance, weight and blood pressure of case 8, on treatment with prednisolone (during upper black bar), supplemented by a 14-day course of carbenoxolone disodium (during lower black bar). The notation and presentation is that of Fig. 1.

Although urinary sodium figures showed the expected wide individual differences (they ranged from 19 to 300 mequiv/day), clear trends emerged. Nine patients had a rising sodium output (the others showing a decrease or no change), and the mean increase was 70% of the pretreatment value. Potassium values varied less between patient and patient. Here, too, the output rose in eight cases, but the mean change was only 55% higher than the pretreatment figure. In thirteen patients the trends in sodium and potassium changes were parallel and tended also to follow changes in urine volume. The urinary sodium: potassium ratio, often a sensitive index of excretory changes in steroid therapy (where it exaggerates two opposing effects), proved useful only in case 8. In the other patients, given carbenoxolone without steroids, the ratio tended to follow the urinary sodium figures (ten cases), being no more sensitive when its excretion fell and only half as sensitive when there was a rise in output. Serum and urine figures in this series were not obviously related.

Patients' water balance was assessed on a simple record of their daily fluid intake and urine output (shown in Figs. 1 and 2); conventional correction for food intake and insensible loss gave no additional information. Normal day-to-day variation was seen. Only case 6 showed some shift towards a positive balance, but his weight remained constant. A steady gain in weight was more general. It was pronounced in case 3

(Fig. 1), who gained 3.3 kg/week in the first fortnight, only 0.5 kg in his third week of treatment, but showed a sudden gain on the last day. The remaining patients varied from no change to 2.2 kg/week.

Day: night urine volumes tended to show a small transient rise around day 7, unrelated to the 24-hr volumes. Steroid excretion showed little change and no trend except for case 9 whose 17-oxosteroid output rose from 10.9 to 21.8 mg/day and 17-oxycorticosteroid from 8.1 to 19.3 mg/day. Urinary amino-acid patterns were normal, and there was no glycosuria.

Calcium and alkaline phosphatase levels showed little variation. Case 8 had the only abnormal calcium level (4.0 mequiv/l.) and the only concurrent change in phosphatase activity (from 14 to 7 King-Armstrong units), but case 15 showed a rise in phosphatase level (from 4 to 13 units). Cholesterol and triiodothyronine uptake figures underwent little change, except for case 10, whose cholesterol, the highest in the series, fell from 305 to 160 mg/100 ml.; his triiodothyronine uptake was not determined. Six patients began the trial with positive C-reactive protein tests, and four were improved. Electrophoretic serum globulin patterns showed only a small rise in the γ-globulin of case 12 and in case 13 a return to normal of an initially raised α_2-globulin fraction.

A change in liver function was noted in case 2, whose bromsulphthalein retention rose from 25%, 2% (at 5 and 45 min) to 51%, 13%, with a change in glutamic-pyruvic transaminase from 20 to 60, then 45 Cabaud units; in case 7, whose glutamic-pyruvic transaminase level rose from 15 to 70, then 60 units; and case 15, whose glutamic-oxaloacetic transaminase level increased from 25 to 40, and glutamic-pyruvic transaminase from 15 to 55 units. There was no appreciable change in urobilinogen excretion, serum bilirubin, protein turbidity tests or the serum albumin level, except that case 1 showed changes in the albumin: globulin ratio which could have been attributed to hepatic causes had they not attended changes in renal function. The levels were 3.5% albumin: 3.1% globulin on day 1, 2.7: 4.2 on day 16, and 4.0: 2.9 on day 21.

Gastric aspirates yielded one significant finding: the appearance of visible mucus or a marked increase in its amount in 7 cases; its disappearance was noted in one case. (The reports were by technicians trained to carry out gastric function tests but not specifically asked to look for mucus.) There was no trend in changes of volume, *p*H, acid content or peptic activity.

DISCUSSION

Carbenoxolone was originally synthesized in the course of a study of its parent compound glycyrrhetic acid (Finney & Somers, 1958), which was thought to be responsible for the anti-inflammatory effect of liquorice. It was expected to be a useful drug with some steroid-like properties (a formal similarity of the molecules and some resemblance in pharmacological effects) but attracted sudden attention through the finding that instead of causing steroid ulcer it was an active therapeutic agent in gastric ulceration. This finding made it important to examine carbenoxolone in three directions, its uses and limitations in clinical practice, its mode of action *per se*, and a comparison of its effects with those of steroids, since this might suggest structural modifications in steroid drugs

to reduce their ulcerogenic effect. Though the present study was in the immediate clinical field, its findings are informative in the other two directions.

In reviewing our results the problem was one of selecting those changes that were attributable to carbenoxolone. Likely effects were thought to be ones previously reported as due to carbenoxolone or related drugs, those showing a common trend in the present series and, finally, changes seen in patients of this series who developed side-effects. Apart from its anti-inflammatory and anti-ulcerogenic activity the known effects of this group of drugs in man are the potentiation of minimal doses of adrenocortical hormones in the treatment of Addison's disease (Molhuysen *et al.*, 1950; Borst, Holt, De Vries & Molhuysen, 1953), salt and water retention causing a gain in weight and oedema (Molhuysen *et al.*, 1950), hypokalaemia and hypercapnia (Drosdowski *et al.*, 1961; Minvielle *et al.*, 1963) with a possible potassium loss (Card, Mitchell, Strong, Taylor, Tompsett & Wilson, 1953; Louis & Conn, 1956), cardiac failure, headaches and hypertension (Doll *et al.*, 1965). The only clinical side-effect in our patients treated with bed rest as well as carbenoxolone was a symptomless hypertension. There was no cardiac failure or oedema, even where electrolyte figures were outside normal limits. Weight increases were not clearly related to fluid balance figures or chemical findings and seemed to be part of a general clinical improvement rather than fluid retention. But a number of measurements changed together often enough to support a causal connection, especially when seen in an otherwise heterogeneous group of patients. The decrease in serum potassium and increase in plasma bicarbonate were the most obvious changes; they have also been described by previous authors as effects of the glycyrrhizin group of drugs and form part of the known actions of mineralocorticoids. More unexpected was the raised urinary sodium output, since it differed from the reports of other workers who observed sodium retention together with water retention and oedema, but it was consistent with the fact that our patients did not show these. Taken as a whole the changes in our series are reminiscent of primary aldosteronism in that hypertension and a tendency towards hypokalaemic alkalosis were seen and that oedema was characteristically absent. This picture is not exclusively one due to high aldosterone secretion and could, less typically, be due to deoxycortone, and overproduction of hydrocortisone, or the effect of analdosteronism; furthermore, while it would not be expected to lead to a retention of sodium, it leaves the rise in its output unexplained. Our evidence here is incomplete, and daily sodium measurements might have shown more variation in output; in particular it does not exclude an initial transient sodium retention followed by the sodium diuresis, which, taken by itself, recalls a glucocorticoid effect. The increased loss of both sodium and potassium in our series marks it off from out-patient studies with glycyrrhizin and carbenoxolone (Molhuysen *et al.*, 1950; Doll *et al.*, 1965), when oedema or sodium retention were found, and also from several observations in animals and man of only an equivocal effect on potassium excretion (Card *et al.*, 1953; Hassan, Palumbo & Elmadjian, 1954; Louis & Conn, 1956; Finney, Somers & Wilkinson, 1958; Finney & Tárnoky, 1960; Wang, Lui & Lou, 1965). We do not know whether the recognized diuretic effect of bed rest will explain the difference, but two findings of the Dutch group are worth noting: Molhuysen *et al.* (1950) studied nine patients treated with glycyrrhizin and bed rest; none developed oedema, but several cases treated as out-patients had definite oedema of the legs. De Vries *et al.* (1960) report a case of

rheumatoid arthritis treated with corticotrophin and liquorice whose sodium and potassium excretion was so sensitive to changes in posture and activity that their output rose during the afternoon hour of rest as well as at night. We studied recumbent patients ; the findings that differ from ours are mostly in ambulant cases or in animals, with no postural effect involved.

Whatever the character of these changes, their partial nature should be emphasized. The electrolyte effects were largely trends occurring within normal limits of concentration, and no patient exhibited the full list of changes. Thus case 1 (whom current practice would exclude from treatment both on account of her age and impaired renal function) had a symptomless rise in blood pressure, hypokalaemia and hypercapnia but showed a transient decrease in sodium output, and case 3, treated for the longest period, had hypercapnia but a steady serum potassium level and a decreasing sodium excretion. Case 8 showed the combined effects of steroid and carbenoxolone therapy ; the steroid effect predominates but is much enhanced by carbenoxolone. It seems that such a dosage scheme should be used with caution, especially perhaps in deciding the proportions of the two drugs. This patient had 60 mg of prednisolone and 300 mg of carbenoxolone disodium daily ; De Vries *et al.* (1960) have given 3.2 g of glycyrrhetic acid in support of a small (8 mg) dose of cortisone with no ill effect.

Other biochemical findings are more simply stated. Liver-function changes were limited to the two most sensitive tests, the glutamic-pyruvic transaminase level and bromsulphthalein retention ; but the fact that they occurred at all in short-term treatment suggests that, at the risk of being overcautious, testing should be carried out until wide experience of carbenoxolone has been gained in a variety of conditions. Glutamic-pyruvic transaminase estimations are the simpler of the two tests. The drug has shown no effect on renal function (the temporary improvement seen in case 1 could be due to bed rest rather than carbenoxolone), no obvious effect on thyroid function and, when given without steroids, no effect on bone metabolism. The decrease in urinary 17-keto-steroid output observed by Louis & Conn (1956) was not seen. The C-reactive protein test, used as an index of inflammatory change or tissue breakdown, showed some improvement.

The increased production of gastric mucus may have some bearing on the mechanism by which carbenoxolone exerts its therapeutic effect. It has been observed by Goodier (1964, personal communication), in stomachs removed from patients with gastric ulcers, after a short preoperative course of carbenoxolone. None of the present cases had gastric ulcers, and the increased secretion seems to have been the response of a healthy stomach wall. The significance of both findings lies in their relation to the work of Menguy & Masters (1963, 1965) and of Robert & Nezamis (1963), who have reported decreased mucus production after giving cortisone or prednisolone. In their view steroid ulcers are due to steroid-induced impairment of gastric mucus secretion.

Though largely subclinical, the biochemical changes of this study mostly confirm previous reports on the effect of carbenoxolone and related drugs. Four tests seem of value in monitoring treatment: the serum potassium, bicarbonate, glutamic-pyruvic transaminase, and the urinary 24-hr sodium output. Their use, interpreted in conjunction with blood pressure figures, is recommended for clinical practice.

SUMMARY

1. Fifteen patients with various gastro-intestinal disorders were treated with carbenoxolone disodium for 2 weeks. Their weight, fluid balance, blood pressure, electrolyte status, gastric, renal and liver functions were studied. Some indication of adrenocortical, thyroid and bone metabolism and anti-inflammatory activity was obtained.

2. Most results remained within normal limits, but three patients developed symptomless hypertension, which was transient in two. Two cases had low serum potassium, and two high bicarbonate levels; there were no cases of oedema. There was a subclinical tendency towards lowered serum potassium and increased bicarbonate levels. The effect of carbenoxolone given to hospital in-patients suggests a limited similarity to primary aldosteronism and differs from its effect in ambulant patients; this postural effect is discussed.

3. A raised mucus content in the gastric aspirate of some patients after treatment with carbenoxolone may be connected with its mode of action in gastric ulcer.

4. The following tests are suggested as guides to clinical management: serum potassium, bicarbonate, glutamic-pyruvic transaminase, and the urinary 24-hr sodium output.

We should like to thank Professor J. M. Robson for suggesting this investigation, Dr E. V. Cox for referring two patients, Dr D. V. Mabbs for the [^{131}I]-triiodothyronine uptake tests, the house physicians, nursing and laboratory staff for their help, and Dr S. Gottfried (Biorex Laboratories) for a gift of carbenoxolone disodium tablets.

REFERENCES

APPLEBY, J. I., GIBSON, G., NORYMBERSKI, J. K. & STUBBS, R. D. (1955). Indirect analysis of corticosteroids. 1. The determination of 17-hydroxycorticosteroids. *Biochem. J.*, **60**, 453–460.

BORST, J. G. G., HOLT, S. P. TEN, DE VRIES, L. A. & MOLHUYSEN, J. A. (1953). Synergistic action of liquorice and cortisone in Addison's and Simmonds's disease. *Lancet*, **i**, 657–663.

CARD, W. I., MITCHELL, W., STRONG, J. A., TAYLOR, N. R. W., TOMPSETT, S. L. & WILSON, J. M. G. (1953). Effects of liquorice and its derivatives on salt and water metabolism. *Lancet*, **i**, 663–668.

DE VRIES, L. A., HOLT, S. P. TEN, DAATSELAAR, J. J. VAN, MULDER, A. & BORST, J. G. G. (1960). Characteristic renal excretion patterns in response to physiological, pathological and pharmacological stimuli. *Clin. chim. Acta*, **5**, 915–937.

DOLL, R., HILL, I. D. & HUTTON, C. F. (1965). Treatment of gastric ulcer with carbenoxolone sodium and oestrogens. *Gut*, **6**, 19–24.

DOLL, R., HILL, I. D., HUTTON, C. & UNDERWOOD, D. J. (1962). Clinical trial of a triterpenoid liquorice compound in gastric and duodenal ulcer. *Lancet*, **ii**, 793–796.

DROSDOWSKI, M., ROBEL, P. & SEBAOUN, J. (1961). Syndrome de déplétion potassique simulant une maladie de Conn, provoqué par la glycyrrhizine. *Presse méd.*, **69**, 294–295.

FINNEY, R. S. H. & SOMERS, G. F. (1958). The anti-inflammatory activity of glycyrrhetinic acid and derivatives. *J. Pharm. Pharmacol.*, **10**, 613–620.

FINNEY, R. S. H., SOMERS, G. F. & WILKINSON, J. H. (1958). The pharmacological properties of glycyrrhetinic acid—a new anti-inflammatory drug. *J. Pharm. Pharmacol.*, **10**, 687–695.

FINNEY, R. S. H. & TÁRNOKY, A. L. (1960). The pharmacological properties of glycyrrhetinic acid hydrogen succinate (disodium salt). *J. Pharm. Pharmacol.*, **12**, 49–58.

GOOLDEN, A. W. G., GARTSIDE, J. M., JACKSON, D. J. & OSORIO, C. (1962). Uptake of ^{131}I-triiodothyronine by red cells. *Lancet*, **ii**, 218–220.

HASSAN, W. E., PALUMBO, J. F. & ELMADJIAN, F. (1954). The electrolyte effects of licorice preparations in the adrenalectomized rat. *J. Amer. pharm. Ass. sci. Ed.*, **43**, 551–554.

HORWICH, L. & GALLOWAY, R. (1965). Treatment of gastric ulceration with carbenoxolone sodium: a clinical and radiological evaluation. *Brit. med. J.*, **ii**, 1274–1277.

LESTAS, A. N. (1963). Rapid estimation of albumin and globulin in serum by elution after micro-electrophoresis. *Proc. Ass. clin. Biochem.*, **2**, 104–106.

LOUIS, L. H. & CONN, J. W. (1956). Preparation of glycyrrhizinic acid, the electrolyte-active principle of licorice: its effect upon metabolism and upon pituitary-adrenal function in man. *J. Lab. clin. Med.*, **47**, 20–28.

MENGUY, R. & MASTERS, Y. F. (1963). Effect of cortisone on mucoprotein secretion by gastric antrum of dogs; pathogenesis of steroid ulcer. *Surgery*, **54**, 19–28.

MENGUY, R. & MASTERS, Y. F. (1965). Influence of parathyroid extract on gastric mucosal content of mucus. *Gastroenterology*, **48**, 342–349.

MIDDLETON, W. R. J., COOKE, A. R., STEPHEN, D. & SKYRING, A. P. (1965). Biogastrone in in-patient treatment of gastric ulcer. *Lancet*, **i**, 1030–1032.

MINVIELLE, J., CRISTOL, P. & BADACH, L. (1963). L'abus de réglisse (glycyrrhizine). Expression clinique: paralysies avec hypokalémie (2 observations). Hypertension artérielle (25 observations). Discussion physiopathologique. *Presse méd.*, **71**, 2021–2024.

MOHUN, A. F. & COOK, I. J. Y. (1957). Simple methods for measuring serum levels of the glutamic-oxalacetic and glutamic-pyruvic transaminases in routine laboratories. *J. clin. Path.*, **10**, 394–399.

MOLHUYSEN, J. A., GERBRANDY, J., DE VRIES, L. A., DE JONG, J. C., LENSTRA, J. B., TURNER, K. P. & BORST, J. G. G. (1950). A liquorice extract with deoxycortone-like action. *Lancet*, **ii**, 381–386.

NORYMBERSKI, J. K., STUBBS, R. D. & WEST, H. F. (1953). Assessment of adrenocortical activity by assay of 17-ketogenic steroids in urine. *Lancet*, **i**, 1276–1281.

ROBERT, A. & NEZAMIS, J. E. (1963). Effect of prednisolone on gastric mucus content and on ulcer formation. *Proc. Soc. exp. Biol. (N.Y.)*, **114**, 545–550.

SMITH, I. (1960). Ed. of *Chromatographic and Electrophoretic Techniques*, 2nd ed. London: Heinemann.

TÁRNOKY, A. L. (1958). *Clinical Biochemical Methods*. London: Hilger.

TURPIE, A. G. G. & THOMPSON, T. J. (1965). Carbenoxolone sodium in the treatment of gastric ulcer with special reference to side-effects. Gut, **5**, 591–594.

WANG, P. C., LUI, K. T. & LOU, H. Y. (1965). Studies of the desoxycorticosterone (DOC)-like actions of glycyrrhetinic acid in the rat. *Acta pharm. sin.*, **12**, 50–53.