

given atropine. A dose of 1.2 mg. was injected intravenously to produce a tachycardia comparable to that at which the ST-T changes occurred. No ST-T changes were produced, though if a sudden severe fright was administered they then occurred. This suggests that both anxiety and exercise were producing similar E.C.G. changes, and that the rate increase itself was not responsible (Fig. 3).

In competitive motor-racing three healthy, experienced racing drivers had an increase in the heart rate to between 190 and 205. The rate was recorded at 150-180 in the 15 minutes before the start (Fig. 4), and at the signal indicating two minutes before the start a rate in excess of 180 was usual. This increased up to 200 to 205 by the time of the start (Fig. 5), and in some cases was maintained at this level continuously throughout the event. In the meantime the driver was unaware

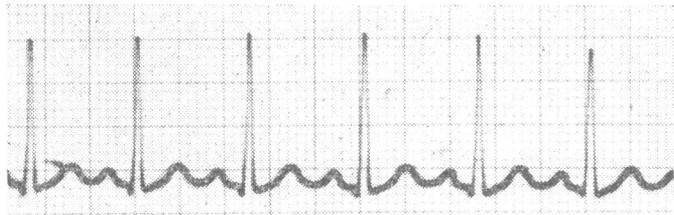


FIG. 3.—Subject A. B. Comparable tachycardia produced by atropine.

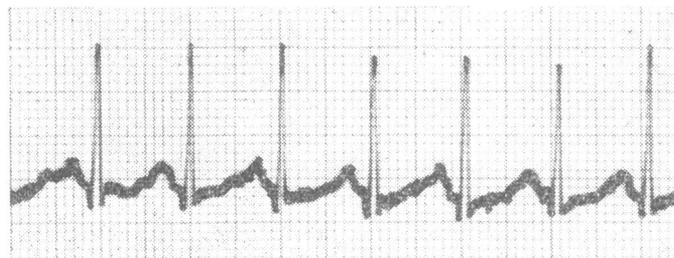


FIG. 4.—Subject C. D. Five minutes before the start of a motor race.

of palpitation or any other symptoms except for the natural nervousness experienced before any competitive event. The heart rhythm in all these observations was sinus tachycardia.

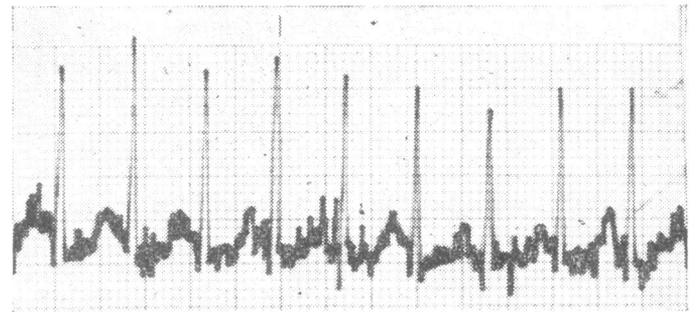


FIG. 5.—Subject C. D. One minute after the start, approaching a sharp bend at approximately 115 m.p.h. (185 km.p.h.).

SUMMARY

Motor-car driving in London traffic may be associated with an increased heart rate, which is very rapid in certain persons with normal cardiovascular systems. ST-T changes in the electrocardiograms occurring at the same time seem to be related to anxiety rather than the tachycardia. Even more rapid heart rates may develop in certain drivers before and during competitive motor-racing.

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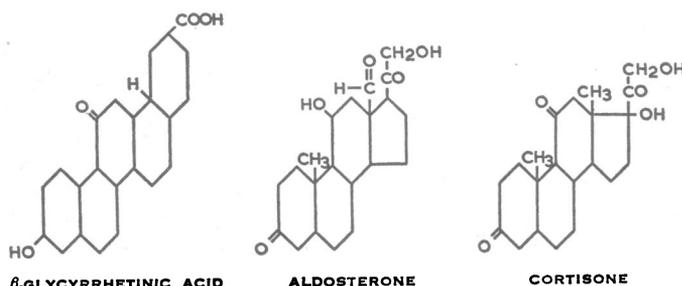
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Medical Memoranda

Assessment of Possible Glucocorticoid Activity of Carbenoxolone Sodium

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Carbenoxolone sodium (Biogastrone), which is the disodium salt of β -glycyrrhetic acid, has recently been used in the treatment of gastric ulcer (Doll *et al.*, 1962; Turpie and Thompson, 1965; Middleton *et al.*, 1965). The chemical



Structural similarity between β -glycyrrhetic acid and adrenal steroids.

similarity to cortisone and aldosterone is shown in the Formulae. Like the glucocorticoid group of adrenal steroids, it possesses an oxygen atom at position eleven. It would not be surprising if carbenoxolone possessed glucocorticoid activity, and it is an investigation of this property which is the subject of this paper.

MATERIALS AND METHODS

Five men and five women (age range 35-72) receiving carbenoxolone for the treatment of gastric ulcer were studied. The dose given was 50 mg. thrice daily and treatment was continued for 16 to 37 days. Prior to the institution of therapy a 25-g. intravenous glucose-tolerance test was carried out (Boyd *et al.*, 1962) and repeated at the termination of the course of treatment.

Blood-sugar estimations were determined by enzymatic methods as "true glucose" (Huggett and Nixon, 1957), and the results of the glucose-tolerance test expressed as the glucose increment index (I.I.) (Amatuzio *et al.*, 1953).

Throughout the course of treatment body-weight, blood-pressure, and serum electrolytes were checked at frequent intervals.

RESULTS

The results are summarized in the Table. Boyd *et al.* (1962), using the same methods, report the normal range for the I.I. to be 2.52–5.13. Five patients in the present series had values above the lower limit of normal before treatment and six after treatment. Two had normal values both before and after treatment, and three who had previously had abnormal results had normal levels after therapy.

Summary of the Clinical and Biochemical Data for the Ten Patients Studied

Case No.	Days of Treatment	I.I. Before	I.I. After	Weight Change (Kg.)	Serum K ⁺ (mEq/l)	B.P. (mm.Hg)	Oedema
1	22	2.86	2.64	+4.5	-0.9	140/80-200/100	-
2	30	2.60	2.02	+6.2	-1.3	150/80-190/90	+
3	28	2.92	2.82	+2.75	-0.3	115/70-140/95	-
4	25	2.86	2.33	+2.1	-1.3	No change	-
5	26	2.15	2.74	+2.1	-0.9	140/75-160/85	-
6	16	2.10	2.19	+3.5	-0.9	No change	-
7	27	2.07	3.04	+6.5	-0.9	No change	-
8	27	2.16	3.14	-1.3	0	130/80-155/100	-
9	33	1.56	1.51	0	-0.9	No change	+
10	37	3.90	6.04	+0.3	-0.6	No change	-
Mean		2.52	2.85				
S.D.		±0.61	±1.16				

t=0.46

Only two patients gave values below normal both before and after treatment, and in one of these (Case 9) the presence of hepatic cirrhosis could account for the very low increment index.

Two patients who had normal pretreatment values gave abnormal results when the course of therapy was completed.

The range of increment index before treatment was 1.56–3.90, with a mean of 2.52 (S.D.±0.61). After the course of treatment the range was 1.51–6.04, with a mean of 2.85 (S.D.±1.16). Analysis of pretreatment and post-treatment figures shows no statistical difference (t=0.46).

Eight of the 10 patients studied showed a gain in weight ranging from 0.3 to 6.5 kg. Only two of these (Cases 1 and 2) gave a history of weight loss before the beginning of therapy.

All but one patient showed a fall in the serum potassium level during the course of treatment. This fall ranged from 0.3 to 1.3 mEq/l.

Five patients showed distinct elevation of the blood-pressure, but only two developed clinical oedema. As one of these two (Case 9) also had liver disease with a low serum albumin, it is unlikely that carbenoxolone was the primary factor.

DISCUSSION

The literature contains many reports regarding the mineralocorticoid properties of liquorice derivatives. Revers (1948), using crude liquorice in the treatment of gastric ulceration, noted oedema in approximately one patient out of five. The salt-and-water retaining properties of liquorice were further studied by Borst *et al.* (1953) and by Card *et al.* (1953).

More recently Doll *et al.* (1962), using carbenoxolone in the treatment of gastric ulcer, reported the development of oedema in 11 out of 58 patients. No studies on glucose metabolism were mentioned.

Brown *et al.* (1959) studied the effects of glycyrrhetic acid hydrogen succinate in animals. The blood-glucose levels of rabbits showed no change when 20 mg. of the substance was given intravenously to fasting animals or injected 10 minutes before a glucose-tolerance test. This lack of alteration in carbohydrate tolerance in animals is in keeping with the results of the present study.

The failure to influence glucose tolerance adversely could be due to the use of too small a dose of carbenoxolone, but this is unlikely in view of the clinical and biochemical evidence of mineralocorticoid effect in a large proportion of patients. It would appear, therefore, that carbenoxolone sodium in therapeutic doses has no effect on glucose tolerance.

One of the explanations for the healing properties of carbenoxolone in gastric ulceration is that it has an anti-inflammatory effect similar to that of the adrenal steroids. As this action is a function of the glucocorticoids rather than the mineralocorticoids, it is surprising that carbenoxolone would appear to have only mineralocorticoid effects. Alternatively, its reputed healing action may be totally unrelated to its steroid-like properties.

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