tween the effects upon potassium and sodium excretion is present, 2MeFF having a relatively greater sodium-retaining effect and FF a greater potassium-losing effect. The urinary Na/K ratios may, therefore, be misleading when used as a sole guide of effectiveness. The kaliuretic effects of the steroids used appear to be blunted by prior salt depletion and augmented by salt loading. This might be explained by the variation of endogenous aldosterone excretion caused by salt loading and depletion.

In one subject in whom a paradoxical, sustained increase in sodium excretion occurred following intravenous 2MeFF, significant elevations in GFR and renal plasma flow were present. In this subject, the natriuresis associated with increased filtered loads of sodium predominated over the sodium-retaining effects of this potent electrocorticoid.

Following intravenous administration, the electrolyte effects of both steroids became manifest within one and 2 hours and were still present at the end of 4 hours.

Conclusion. 1. Intravenous administration of 9α-fluorohydrocortisone and 2-methyl-9α-fluorohydrocortisone in doses sufficient to produce profound electrolyte effects in 6 salt-depleted and 6 salt-loaded subjects produced no significant change in glomerular filtration rate, with the exception of one salt-depleted subject, in whom there was an increase in both glomerular filtration rate and effective renal plasma flow following 2MeFF. 2. 2MeFF had a more profound sodium-retaining effect than did FF. Even in salt-depleted subjects, the sodium-retaining effects of both compounds were demonstrable. 3. FF had a more profound potassium-losing effect than did 2 MeFF. Kaliuresis was greater in the salt-loaded than in the salt-depleted subjects. 4. Plasma concentrations of sodium, potassium, and chloride did not change significantly during the 4 hour study after intravenous administration of the steroids.

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Possible Relations of Hypoglycaemia Induced by Mono-amine Oxidase Inhibition and Angina Pectoris.† (27007)

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The initially favorable results of the value of the mono-amine oxidase inhibitors in treatment of angina pectoris have latterly been tempered by further experiences of their use(1), and the response to therapy is probably, at best, unpredictable. However, it is of interest that Weiss et al.(2), using one of these drugs, iproniazid, in treatment of depressive patients, showed that those patients whose appetite, weight and sense of well being improved, demonstrated a definite hypoglycaemic response to the drug. It occurred to us that a similar correlation with hypoglycaemia may also exist in patients who showed improvement in the symptoms of angina pectoris as a result of such treatment. In considering the nature of this hypoglycaemia, the ganglion blocking action of iproniazid(3) may have

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resulted in a type of hypoglycaemic insensitivity due to inhibition of sympathetic discharge to the adrenal medulla and liver, such as follows hexamethonium therapy(4): or secondly, the slight galactose intolerance noted by Weiss et al. may have been a factor in production of hypoglycaemia, since it is known that an increased blood galactose may have some hypoglycaemic action in the normal individual(5). To try to elucidate these points it was decided to compare the response of total blood sugar and blood glucose levels to a mixed oral dose of glucose and galactose under the influence of ganglion blockade from mecamylamine, and mono-amine oxidase inhibition from iproniazid and nialamide respectively. The latter, unlike iproniazid, produces only minimal postural hypotension(6).

Methods. The following carbohydrate tolerance test was performed in all subjects. A fasting venous blood sample was collected, then a mixture of 25 g glucose and 25 g galactose in 250 ml water was given by mouth. Further venous samples were withdrawn 10, 20, 30, and 45 minutes later. Blood glucose levels were estimated by a modification of the glucose oxidase method of Middleton and Griffiths(7), and total blood sugar by a copper-reducing method(8).

Fifteen normal adults were studied initially, followed by 12 patients with angina pectoris, half of whom were to be treated with iproniazid 50mg daily, and the other half with nialamide 100mg daily. Carbohydrate tolerance tests were carried out before and 6 weeks after commencing therapy. These patients were asked to record the number of attacks of angina pectoris occurring each day and to note their severity. Finally 3 hypertensive patients were studied before treatment, and again after a postural fall of blood pressure had been obtained following 5 days therapy with mecamylamine 2.5mg twice daily. The tests were carried out 2 hours after the morning dose of 2.5 mg mecamylamine.

Results. The total blood sugar curve in all patients was within normal limits, both before and during treatment. It is seen from Fig. 1 which compares carbohydrate tolerance in a patient before and during treatment with mecamylamine, that while ganglion blockade does not effect the fasting sugar levels, it produces a temporary fall of blood glucose in the early phase of the test. These changes are best summarised in the form of a glucose index (G.I.) which expresses the ratio between blood glucose and total blood sugar (Fig. 2) as follows: Blood glucose (mg per 100 ml) $\times$ 100/Total blood sugar (mg per 100 ml) = G. I. In the 15 normal adults, the mean G. I. $\pm$ standard deviation was determined. The mean fasting G. I. of the different normal individuals varied from 74.5% to 90.8%, and during the 45 minutes of the test did not change significantly (i.e., blood glucose and total blood sugar levels rose in about the same proportion), although there was an increase in the standard deviation—thus after 45 minutes the normal G. I. range was 66.6-98% (Fig. 2). In some of the angina patients, the amine oxidase inhibitors caused a fall of both fasting blood glucose, and also of glucose levels throughout the period of the test. As total blood sugar remained unaffected, there has evidently been a change in distribution of the blood sugar fractions, which is reflected in a reduced G. I. (Fig. 3 and 4). It is noticeable that the changes resulting from iproniazid are more marked than those from nialamide.

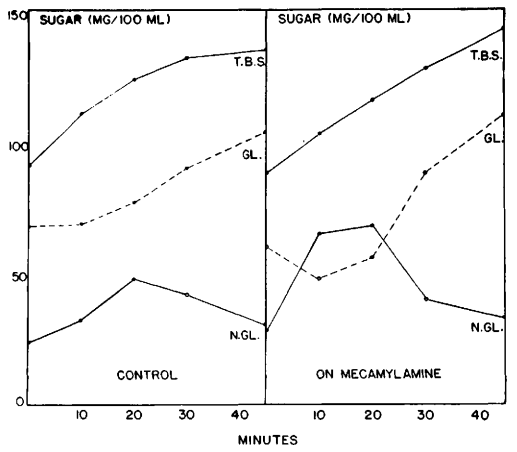

FIG. 1. Effect of mecamylamine on carbohydrate tolerance. T.B.S.—total blood sugar; GL.=glucose; N.GL.=non-glucose sugar by difference.

Eleven of the 12 angina patients claimed some improvement of their symptoms, but analysis of the records showed that the number of attacks per day was halved in only 8 (cases 1-4 on iproniazid, and cases 7-10 on nialamide), (Fig. 3 and 4). All these patients

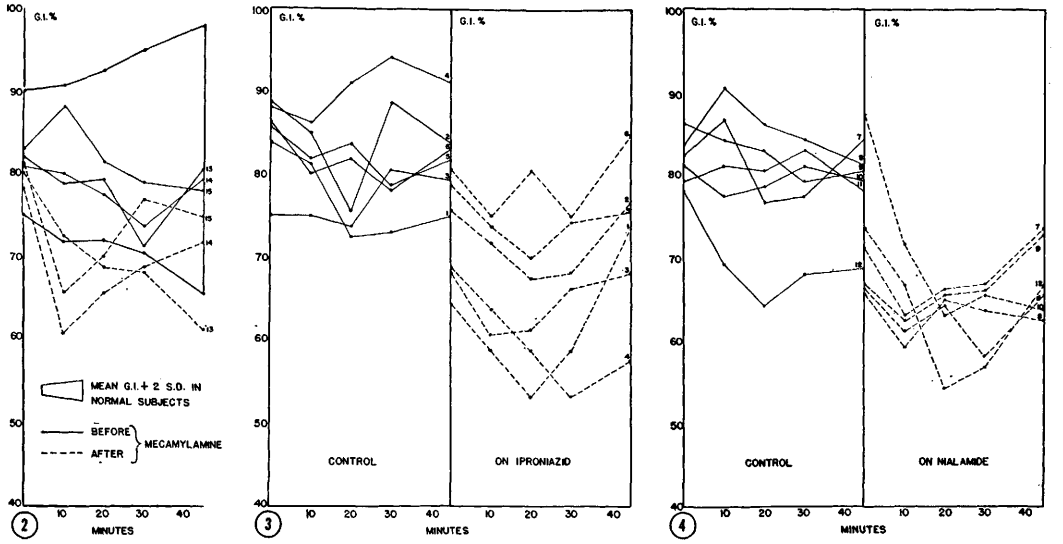

FIG. 2. Mean glucose index + 2 standard deviations in 15 normal individuals, compared with glucose index in 3 hypertensive patients before and while receiving mecamylamine. Numbers indicate individual patients.

FIG. 3. Glucose index on 6 patients before and after receiving iproniazid for 6 weeks. Numbers indicate individual patients.

FIG. 4. Glucose index in 6 patients before and after receiving nialamide for 6 weeks. Numbers indicate individual patients.

had a fairly consistent fall of the glucose index, both fasting and throughout the test. It is interesting to note that case 4, who showed the greatest clinical improvement (no further chest pain on exertion, and a return to work after 7 years absence on account of chest pain) had the most marked fall of glucose index. By contrast, case 12, who gained no improvement from treatment, and claimed the tablets made him worse, showed an unusually low G. I., before treatment which was unaffected by therapy.

Discussion. The different response to the carbohydrate tolerance test of subjects receiving iproniazid or nialamide on the one hand, and mecamylamine on the other, makes it unlikely that these drugs have a common action on carbohydrate metabolism. Ganglion blockade appears temporarily to enhance the hypoglycaemic action of galactose, probably by a mechanism of decreased hypoglycaemic sensitivity. However, in the case of the mono-amine oxidase inhibitors, the reduced fasting blood glucose, and the lower glucose index throughout the test suggest some other explanation, for example, an interference with hepatic glycogenolysis.

The mode of action of the mono-amine oxidase inhibitors in alleviating the symptoms of angina pectoris is ill-understood. Several alternative hypotheses have been suggested and have recently been reviewed(9). However, in view of this change in carbohydrate tolerance, which appears to coincide roughly with an improvement in symptoms, it seems pertinent to refer to the recently reported improvement in anginal symptoms during treatment with tolbutamide(10, 11). By their action on carbohydrate metabolism both mono-amine oxidase inhibitors and tolbutamide may alter the primary sources of energy utilized by the heart muscle, and thereby modify the symptoms of angina pectoris.

Summary. Twenty-five grams of glucose and 25 g of galactose was given by mouth to 15 normal subjects and to 15 patients. Total blood sugar and blood glucose was estimated on each subject and the glucose index calculated. The test was repeated in the 15 patients after treatment with mecamylamine, iproniazid, and nialamide. The difference in response to ganglion blockade and inhibition of mono-amine oxidase is discussed. The reduction of the glucose index, in this pre-

liminary study, correlated approximately with an improvement in the symptoms of angina pectoris. The possible significance of this is discussed.

Addendum. Since completing these carbohydrate tolerance studies, we have tested the purity of several samples of the standard preparations of glucose and galactose, such as are routinely used in oral glucose and galactose tolerance tests. The galactose preparations had a non-galactose content of 4-14% (w/w), of which about half was copper reducing, and a small fraction glucose oxidase reducing: the glucose preparations had a non-glucose content of 2-10%, most of which was copper reducing, but not glucose oxidase reducing. However, since we used glucose and galactose from the same stock bottles throughout the tests, we believe that the changes of carbohydrate tolerance are genuine.

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Urinary Metabolites of Mevalonic Acid: Evidence That Mevalonic Acid is not a Precursor of Isovalthine.* (27008)

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The discovery(1, 2), isolation(1, 2), identification(2), and synthesis(2) of a new amino acid, S-(isopropyl-carboxymethyl)-cysteine, termed isovalthine has been recently described by Japanese investigators. This amino acid was observed in the urine of hypercholesterolemic individuals. The structure of the amino acid is such as to suggest that it arises biogenetically by addition of cysteine to $\triangle^1$-isopentenyl pyrophosphate followed by or simultaneously with loss of pyrophosphate and oxidation of the primary alcohol to an acid. $\triangle^1$-Isopentenyl pyrophosphate may be visualized as a compound in equilibrium with $\triangle^2$-isopentenyl pyrophosphate which, in turn, is in equilibrium with $\triangle^3$-isopentenyl pyrophosphate. The latter 2 compounds are known intermediates in utilization of mevalonic acid (MVA) and are interconvertible by the enzyme isopentenyl pyrophosphate isomerase(3). If this or a related mechanism has any merit, it would suggest that isovalthine may be a significant "detoxification" product of intermediates in sterol biosynthesis whereby these intermediates are diverted from sterol biosynthesis and appear in the urine as an innocuous metabolite. The experiments described here involving recovery of added carrier isovalthine from the urine of hypercholesterolemic individuals that had received MVA-2-C^{14} demonstrate that either (a) MVA is not a precursor of isovalthine, or (b) MVA may be a precursor of isovalthine but the metabolite is not encountered in all cases of hypercholesterolemia. Evidence is also presented that MVA is the precursor of an amphoteric metabolite possibly related to

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