the 36 deaths 19 (76% mortality for the group) occurred after the fifth day of perforation though there were survivors from cases presumed to have been perforated for two weeks. It would be instructive to determine whether these cases would do better on the conservative regimen.

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Preliminary Communications

Insulin and Corticoid Response to Intravenous Fructose in Relation to Glucose Tolerance

British Medical Journal, 1969, **3**, 276–277

Summary: In 12 subjects with normal glucose tolerance fructose infusion was associated with a rise in plasma insulin and plasma corticoid levels. Similar but lesser changes were seen in seven maturity onset diabetics in whom there was also a considerable rise in blood glucose. It is suggested that a catabolite of fructose is responsible for these changes.

INTRODUCTION

While investigating the disturbance of carbohydrate metabolism associated with myocardial infarction it was found that fructose infusion caused significant rises in plasma insulin and blood glucose. It has been stated that fructose does not stimulate insulin secretion in man (Samols and Dormandy, 1963; Swan *et al.*, 1966) or animals (Grodsky *et al.*, 1963; Coore and Randle, 1964; Goetz *et al.*, 1967). This communication describes the changes in plasma insulin, plasma corticoid, and blood glucose in subjects with normal and abnormal glucose tolerance after fructose infusion. The effects of fructose on plasma levels of these hormones have not been previously described in such subjects.

MATERIALS AND METHODS

Twelve convalescent men (aged 43–70 years) with normal glucose tolerance who were in a general medical ward comprised the control group. The diabetic group comprised two male and five female maturity onset diabetics (aged 28–68 years) treated by diet alone. All patients readily agreed to participate in this study.

Infusions were made via a catheter introduced into the superior vena cava; blood samples were also obtained by this route. After the catheter had been in situ for at least half an hour the control subjects were given either 50 ml. of 62·5% fructose or an equivalent quantity of 50% glucose over five minutes. The diabetics received only fructose. Ninety minutes after the first sugar had been infused the other sugar was given in the same way. Half the controls received the fructose infusion first and the glucose second, and in this respect the order was purely random.

Blood was withdrawn for insulin and corticoid assay before and 30 minutes after each infusion. Blood sugar was estimated on blood taken before and 60 minutes after each fructose infusion. Plasma fructose was measured at five-minute intervals after time had been allowed for mixing until one hour after the fructose infusion.

Blood sugar was estimated on a Technicon AutoAnalyzer (Technicon AutoAnalyzer Methodology, 1963). Plasma fructose was estimated by the method of Kulka (1956). Plasma corticoid was measured by Mattingly's (1962) method, and plasma insulin by the method of Hales and Randle (1963). Values for blood glucose were calculated by subtracting 90% of the appropriate fructose level from the concomitant blood sugar level.

RESULTS

The results are summarized in the Table. In the control group plasma insulin levels showed a mean rise of 25·3 μU/ml. 30 minutes after fructose. The diabetic group showed a smaller mean rise of 14·0 μU/ml. The difference between the two groups was not significant. Mean plasma insulin levels rose about twice as much after glucose as after fructose in the control subjects (57·4 μU/ml.), this difference being highly

Changes in Plasma Insulin, Corticoid, and Blood Glucose After Infusions of Fructose and Glucose in Control and Diabetic Subjects

	Plasma insulin Mean ± S.E.M. (μU/ml.)	Plasma corticoid Mean ± S.E.M. (μg./100 ml.)	Blood glucose Mean ± S.E.M. (mg./100 ml.)
Control subjects:			
Before fructose	36·0 ±2·0	21·1 ±2·5	74·8 ± 5·8
Change after fructose	+25·3* ±5·7	+3·8† ±1·9	−1·8‡ ±4·0
Before glucose	35·8 ±2·5	20·0 ±2·4	—
Change after glucose	+57·4* ±8·9	−3·1† ±1·0	—
Diabetic subjects:			
Before fructose	39·9 ±6·8	29·9 ±2·4	168·9 ±25·2
Change after fructose	+14·0 ±5·9	+0·9 ±2·7	+50·6‡ ±5·1

Significant differences: * $P < 0.005$. † $P < 0.0025$. ‡ $P < 0.0001$.

significant (Fig. 1). Blood glucose was not significantly raised 60 minutes after fructose infusion in the controls, though a pronounced rise was detected in the diabetics.

Figure 1

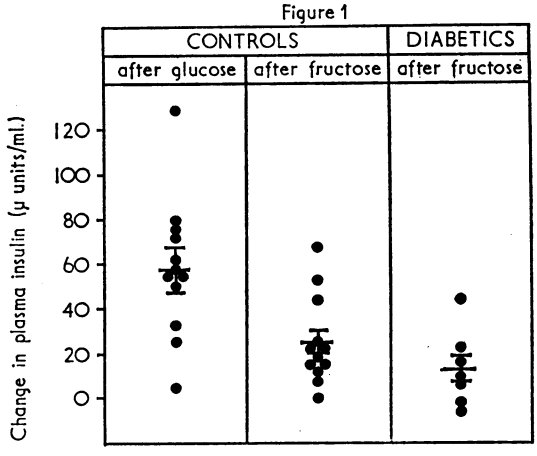

Figure 2

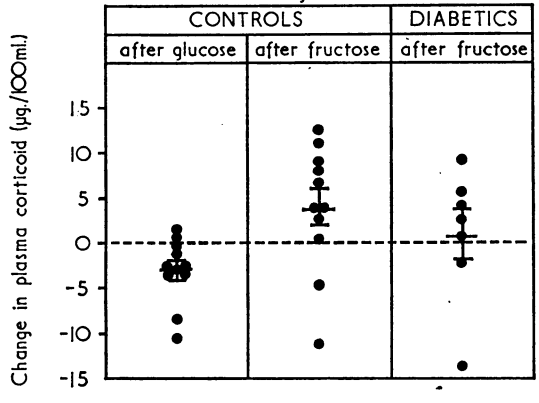

FIG. 1.—Changes in plasma insulin 30 minutes after infusions of fructose and glucose; means ± S.E. are indicated. FIG. 2.—Changes in plasma corticoid 30 minutes after infusions of fructose and glucose; means ± S.E. are indicated.

In the control group plasma corticoid levels showed a small mean rise of 3·8 μg./100 ml. 30 minutes after fructose and a small mean fall of 3·1 μg./100 ml. 30 minutes after glucose infusions (Fig. 2). The difference in the plasma corticoid response to fructose and glucose was highly significant. The diabetics showed a smaller mean rise in plasma corticoid after fructose, though this was not significantly different from the controls.

DISCUSSION

The results show that in subjects with normal glucose tolerance the infusion of fructose is associated with insulin secretion. Coore and Randle (1964) showed that fructose itself did not stimulate insulin secretion in isolated rabbit pancreas at a concentration of 300 mg./100 ml. Grodsky *et al.* (1963) found only slight stimulation of insulin secretion with fructose at a concentration of 500 mg./100 ml. in isolated rat pancreas. In the present study observed plasma fructose concentrations did not exceed 108 mg./100 ml., and it therefore seems unlikely that fructose itself raised the plasma insulin levels by direct stimulation of the pancreatic β-cells.

Several studies (Weinstein and Roe, 1952; Tagnon and Devreux, 1955; Bergstrom and Hultman, 1967) have shown that in normal subjects fructose infusions of the order given in the present investigation produce only slight rises in blood glucose. The maximum rise does not usually exceed 30 mg./100 ml., and this occurs within the first 40 minutes after the infusion, thereafter falling close to fasting levels by about 60 minutes. This agrees with the negligible change in blood glucose found in our control group one hour after fructose infusion. Grodsky *et al.* (1963) showed that a rise in glucose concentration of more than 50 mg./100 ml. was necessary to stimulate insulin release from isolated rat pancreas, and Coore and Randle (1964) obtained similar results with isolated rabbit pancreas. It thus seems improbable that glucose alone was responsible for the rise in plasma insulin after fructose infusion, for even if it be assumed that a maximum rise in blood glucose of 30 mg./100 ml. did occur in these subjects it is an order of magnitude less than after glucose infusion; but in spite of this the rise in plasma insulin after glucose infusion was only twice as great as after fructose infusion.

We would suggest that a catabolite of fructose, either alone or as a potentiator of a small rise in blood glucose, is responsible for the rise in plasma insulin after fructose infusion. To this end further investigations are in progress.

The small but significant rise in plasma corticoid in the control group after fructose contrasts with the small fall after glucose and constitutes a further difference in the metabolic response to these hexoses. The smaller mean rise in the diabetic group was due to a pronounced fall in plasma corticoid in one subject (Fig. 2). The mechanism responsible for this rise must remain speculative. It is well known that large fructose infusions give rise to epigastric discomfort in some subjects (Elliot *et al.*, 1967) and that this might be responsible for the release of corticotrophin, but in this study no correlation was found between the occurrence of pain and the rise in plasma corticoid. It is, however, possible that the rise measured was due solely to a rise in the non-specific fluorogens, which may comprise as much as 30% of plasma corticosteroids, as determined by this method.

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