pared to those of rats, rabbits and guinea pigs, have an extremely low capacity for esterifying cholesterol can be accounted for by the fact that esterification was studied in the particulate fraction (corresponding to our Pellet II), which we have shown possesses low esterifying and high hydrolyzing activity. In addition, the enzymatic assay in this earlier work(11) was carried out at a pH that favored hydrolysis of cholesterol esters rather than their synthesis.

It is interesting that cell sap prepared from bovine adrenals does not appear to require an exogenous source of ATP, CoA or $Mg^{++}$ for incorporation of labeled free cholesterol into esters. In this respect this tissue resembles rat(12) and hog pancreas(13) and rat small intestine.‡

*Summary.* The presence of enzymes capable of both synthesizing and hydrolyzing cholesterol esters has been demonstrated in bovine adrenal gland homogenates. Most of the esterifying activity was associated with the cell sap, whereas the bulk of the hydrolytic activity seemed to reside in Pellet I and Pellet II of the homogenate. The optimum pH for esterification of cholesterol by the cell sap was 5.0; that for hydrolysis of cholesterol oleate by the combined particulate fraction was 7.5. Dialysis of the cell sap did not significantly alter its capacity to esterify labeled cholesterol, nor did the addition of ATP, CoA and $Mg^{++}$ enhance the esterification reaction in this fraction.

‡ S. N. Shah, unpublished observations.

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## Absorption of Fructose in Man. (29780)

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The mechanism of fructose absorption is unknown. Active transport has not been demonstrated in any species either *in vivo* or *in vitro* but conversion of the fructose to glucose within the intestinal mucosa has been demonstrated in the dog(1), guinea pig(2), and hamster(3). Glucose, which appears to be formed from fructose by a fructokinase pathway similar to that found in liver(4,5) may then be actively transported(3).

In rat intestine, on the other hand, very little conversion of fructose to glucose occurs (6), possibly due to absence of glucose-6-phosphatase. Instead, a considerable proportion of absorbed fructose appears in the portal vein as lactic acid. No observations on this subject in man have been reported. Ginsberg and Hers(5) speculated that in man little conversion of fructose to glucose would occur, as they did not detect microsomal glu-

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cose-6-phosphatase in the single specimen of human small bowel they examined, although more recently glucose-6-phosphatase was found by Öckermann(7) to be present in whole homogenates of human jejunal mucosa. We have therefore studied in man the form in which absorbed fructose appears in the portal vein, and also the efficiency of fructose absorption as compared with that of other hexose sugars.

*Methods.* The absorption rate of fructose in the human jejunum was compared with that of sorbose and mannose using a perfusion technique based on that of Schedl and Clifton(8) and described by the authors elsewhere(9), which uses the non-absorbable marker polyethylene glycol M.W. 4,000 to correct for net water absorption. Portal vein blood during the absorption of fructose was obtained by sampling portal collateral venous channels on the abdominal wall of a patient with portal hypertension, their identity having been previously verified by finding in these veins consistently higher glucose levels than in peripheral blood after ingestion of glucose(10). Portal venous blood in mesenteric veins draining loops of jejunum was also obtained from 5 anaesthetized subjects at laparotomy, before and after injecting sterile fructose solutions into the small bowel lumen. In all experiments, peripheral blood was sampled simultaneously with portal blood, either from an antecubital vein (in the patient with portal hypertension) or the brachial artery (anaesthetized subjects).

Blood glucose was estimated by a glucose oxidase method based on that of Hugget and Nixon(11) and blood lactate was estimated enzymatically(12), in both cases using materials in pack form (C. F. Boehringer & Soehne, Mannheim, Germany). Blood fructose was measured by a modification of the Seliwanoff reaction(13). In the first experiment on the subject with portal hypertension, blood fructose was estimated indirectly by subtracting the glucose concentration determined by glucose oxidase from total blood reducing sugar as determined by reduction of potassium ferricyanide(14). This is indicated by 'Fructose' in parentheses.

*Results.* The absorption rate of fructose in relation to that of glucose and other monosaccharides is shown in Table I. If fructose were absorbed by simple passive diffusion, its absorption rate should not be greater than that of sorbose or mannose, which have an identical molecular weight. As in animal studies, it is clear that in man the absorption of fructose is relatively efficient. Due to differing kinetics(9) the precise relationship of fructose absorption to that of galactose and glucose varies at different loads, but at high loads its absorption rate approaches that of glucose. With this perfusion technique, however, which in our hands has an error of $\pm 10\%$, absorption of sorbose and mannose cannot be detected.

The concentration of glucose, fructose and lactic acid in simultaneous samples of peripheral and portal collateral blood after the ingestion of 50 g of fructose on 2 separate occasions is shown in Fig. 1 and 2. The consistently higher levels of lactic acid in portal blood would appear to indicate mucosal conversion of fructose to lactic acid. In one of the two experiments some conversion to glucose also appears to be occurring, although in both experiments the fact that portal venous glucose concentration was slightly higher than that in systemic blood even in the fasting state, makes interpretation of this rather difficult. In both experiments a considerable proportion of the fructose was absorbed unchanged.

In 2 similar experiments in which 50 g of glucose was given, there was a slight rise in

TABLE I. Relative Absorptive Rate of Monosaccharides in the Human Jejunum. (Glucose = 100.)

| Load of sugar (g/min/30 cm jejunum) | Galactose | Glucose | Fructose | Xylose | Sorbose | Mannose |
|---|---|---|---|---|---|---|
| 1.0 | 107 | 100 | 89 | — | — | — |
| .5 | 107 | 100 | 65 | — | — | — |
| .2 | 104 | 100 | 65 | 43 | 0 | 0 |

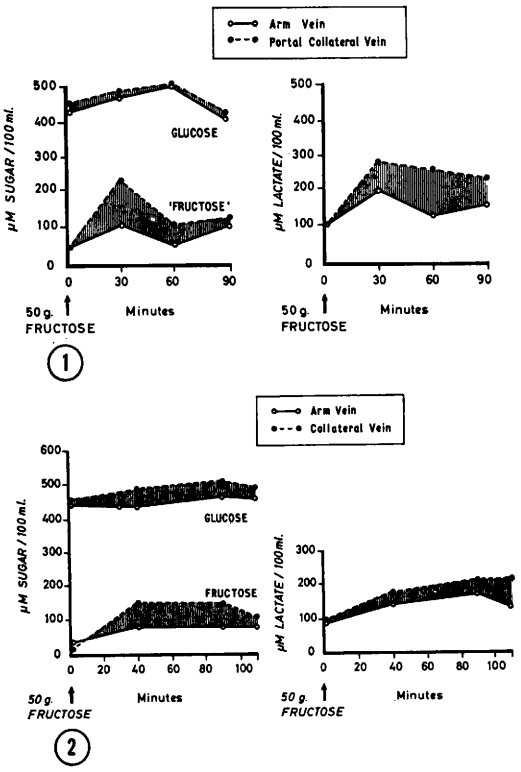


FIG. 1. Concentration of glucose, lactate and 'fructose' in blood taken simultaneously from a portal collateral vein and an arm vein, before and after 50 g of fructose orally.

FIG. 2. Concentration of glucose, lactate and fructose in blood taken simultaneously from a portal collateral vein and an arm vein, before and after 50 g of fructose orally.

blood lactate concentration (maximum rise was 40 μm/100 ml) but this was equal in portal and in systemic blood, indicating no significant conversion of glucose to lactic acid within the mucosa.

The results of the studies undertaken in anaesthetized subjects were somewhat different, and are shown in Table II. Systemic blood lactic acid levels were remarkably stable during the study periods, being in the high normal range, and there was only a slightly greater concentration of lactic acid in portal blood than in systemic arterial blood. Systemic blood glucose levels fluctuated considerably during the operations, but there was never a significantly greater concentration of glucose in portal blood than in systemic arterial blood. Considerable amounts of fructose were, however, appearing in the portal venous blood. In one similar study using 0.5% instead of 5% fructose solution, there was a slight rise in mesenteric fructose concentration, but again no rise—indeed a slight fall—in the mesenteric blood concentration of glucose and lactic acid. In a study using 5% glucose solution the concentration of lactic acid was 20 μm/100 ml and 28 μm/100 ml higher in portal venous blood than in systemic blood, at 5 and 15 minutes respectively. This slight rise was comparable to that occurring during fructose absorption. In the same study, the portal venous glucose concentration exceeded the systemic blood glucose level by an amount similar to that of fructose when fructose was being absorbed.

*Discussion.* The absorption of fructose is relatively efficient when compared to that of such monosaccharides as sorbose and mannóse which have an identical molecular weight. When studied *in vivo*, the absorption rate of fructose approaches that of glucose as the intraluminal concentration is increased both in man(9) and in animals(15, 16). Verzár(15) was apparently the first to suggest that this was due to transformation of fructose into glucose during absorption. The glucose, he suggested, was then actively absorbed, while that part which remained as fructose was absorbed by pure diffusion. This

TABLE II. Mesenteric Blood Levels of Fructose, Glucose and Lactic Acid Compared to Simultaneous Arterial Blood Concentrations, Before and After Injection of 5% Fructose Solution into the Jejunal Lumen.

| Time relationship to fructose injection | No. of observations | Mesenteric vein concentrations - arterial blood concentration (μM/100 ml) Mean values | | |
|---|---|---|---|---|
| | | Fructose | Glucose | Lactic acid |
| Before | 2 | 0 | — 9 | + 9 |
| After 5 min | 3 | +240 | +16 | +22 |
| " 15 " | 2 | +276 | —54 | +97 |
| " 30 " | 2 | +141 | —21 | +17 |

theory has more recently been supported by *in vitro* experiments(2).

We have demonstrated that, in man, the efficient absorption of fructose cannot be due to conversion to glucose, as this was minimal *in vivo* both when studied in portal collateral blood in an unanaesthetized subject with portal hypertension, and in anaesthetized subjects studied at laparotomy. Significant conversion of fructose to lactic acid was demonstrated in the patient with portal hypertension, and this could result in some speeding of fructose absorption by a 'trapping reaction'(17). However, conversion to lactic acid only occurred to a slight extent in the anaesthetized subjects. The reason for this difference is not clear but it is obvious that, under the same conditions, considerable amounts of fructose were being absorbed, and appearing as such in the portal venous blood. Experiments *in vitro* appear to indicate that the passive diffusion rate of fructose increases at high intraluminal concentrations, so that the rate of appearance of fructose then approaches that of glucose(2). At low intraluminal fructose concentrations, on the other hand, the rate of appearance of glucose on the serosal surface may greatly exceed that of fructose. For this reason the experiment with 0.5% fructose solution was performed. These *in vitro* findings do not therefore appear to be relevant in the intact animal, at least in man.

It is clear therefore that fructose absorption is not dependent upon conversion to either glucose or lactic acid. The possibility that some other metabolite may be formed was not excluded. However, the considerable amount of fructose that appears unchanged in portal blood, which was comparable with that of glucose during glucose absorption, makes this an unlikely explanation. Diffusion alone cannot be sufficient, and the fact that active transport has not been demonstrated does not exclude a special mechanism. Xylose, a sugar which until recently was usually considered to be a passively absorbed sugar, has recently been shown to be actively transported(18) and to share the glucose absorption mechanism at some point(19). A separate special transport system for fructose is a strong possibility.

*Summary.* Perfusion studies in man show that fructose absorption is relatively efficient. Observations in patients with a portal collateral circulation and at laparotomy have shown that this is not due to its conversion into glucose and lactate in the intestinal mucosa.

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