

Effect of Selected Hexoses, of Epinephrine and of Glucagon on Insulin Secretion in Man

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SUMMARY

Immunochemical methods of measuring serum insulin have implemented studies in man confirming *in vitro* data which suggest that metabolizable sugars such as mannose and glucose cause insulin secretion, whereas galactose, a nonutilizable sugar, does not. Infusions of 2-deoxy-D-glucose are associated with greatly increased epinephrine secretion and sustained hyperglycemia, but no rise in serum insulin levels. Epinephrine infusions induce and prolong hyperglycemia without raising serum insulin levels and effectively inhibit insulin secretion during glucose administration. These findings agree with *in vitro* evidence that epinephrine directly inhibits pancreatic secretion of insulin. Glucagon, on the other hand, sharply stimulates insulin secretion, either alone or after glucose infusions. Data are presented which suggest that this may be a direct effect of glucagon on the release of insulin by the pancreatic beta cell. *DIABETES* 15:571-78, August, 1966.

Knowledge of the factors influencing insulin secretion has been increased by the development of immunochemical assays of insulin and by the availability of *in vitro* preparations such as the perfused rat pancreas¹ and pancreatic segments from various animals.²⁻⁴

Experiments in which insulinogenesis is completely inhibited suggest that the promotion of insulin secretion by glucose from mammalian islets affects the release mechanism directly.⁵ This effect seems related to the metabolism of the glucose molecule, since mannose also promotes insulin secretion *in vitro*, whereas nonmetabolizable sugars such as galactose and xylose do not.¹⁻³ *In vitro*, growth hormone¹⁻³ and thyroxine³ in physiologic doses had no effect on insulin secretion, whereas epinephrine seemed to inhibit islet cell response to glucose.³

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Conflicting results have been reported with glucagon.^{3,4}

Some *in vivo* findings which are at variance with the *in vitro* data were reported by Sheps et al.⁶ who infused mannose in normal human subjects; whereas glucose elicited a marked rise in circulating insulin-like activity, the slight rise after the mannose infusion was not considered significant.

In order to study *in vivo* insulin secretion in man we have used the immunochemical assay of Grodsky and Forsham⁷ to measure serum insulin levels after administration of glucose and other hexoses, as well as after inducing hyperglycemia with glucagon and epinephrine. The effects of these hormones on the pattern of insulin release after prolonged glucose administration were also investigated. In some of the experiments we used obese subjects, whose exaggerated serum insulin response to glucose⁸ made them convenient models.

Preliminary studies on the effects of various hexoses and of epinephrine on *in vivo* insulin secretion have been previously reported by us.^{9,10} Porte et al. gave an early account of epinephrine reducing insulin secretion in response to glucose, which has since appeared in a final paper.¹¹ The effect of glucagon on insulin secretion was mentioned first by Porte et al., and subsequently by Samols et al.¹²

Experimental subjects

1. Eight obese subjects (two male, six female) with no personal or family history of diabetes, previously found to have an excessive serum insulin response after glucose administration,⁸ comprised the experimental group. All were 20 per cent or more above ideal weight (determined by Life Extension Examiner Tables¹³), with a mean of 93 per cent and a range of 25 to 139 per cent. Their ages ranged from twenty-five to forty-four years.

2. Five healthy normal volunteers with no family history of diabetes were used as control subjects. All were within 5 per cent of ideal weight; ages ranged from twenty-one to thirty-six years.

MATERIAL AND METHODS

All subjects were given adequate diets, including at least 200 gm. carbohydrate daily for three days or more, then tested after an overnight fast.

To determine their influence on serum insulin levels, solutions of 20 per cent glucose, D-mannose, or D-galactose were infused at a rate of 10 gm. hexose per minute for six minutes. When 2-deoxy-D-glucose (2-DG) was used, a dose equivalent to 50 mg. per kg. body weight was infused in 100 ml. normal saline within a thirty-minute period. Endogenous hyperglycemia was induced by infusions of aqueous epinephrine in saline, at a rate of 5 to 6 γ per minute for one and one-half hours, or by 2 mg. glucagon dissolved in 500 ml. saline and given for two hours at 16 γ per minute. The crystalline glucagon* employed in these studies contained no more than 0.02 per cent insulin when assayed immunochemically in our laboratory.

To study the effect of hormones on a sustained state of glucose-induced insulin release by the pancreatic islets, 20 per cent dextrose in water was continuously infused at constant, monitored rates of 13, 26 or 52 gm. glucose per hour for periods of two to four hours. A rate of 26 gm. glucose per hour was employed in most experiments to study either stimulation or inhibition of insulin secretion by added agents. In these experiments, either epinephrine or glucagon was added to the glucose solution during the third and fourth hours of the infusion at concentrations that provided hormone infusion rates of 2.2 γ and 6.0 γ per minute, respectively.

Total reducing sugars were measured by the Nelson-Somogyi method.¹⁴ In patients receiving mannose and galactose infusions, values for these sugars in the blood were calculated after subtracting glucose content, determined by the glucose oxidase method,¹⁵ from the total reducing sugars determined with the use of mannose and galactose standard solutions. Levels of 2-DG were measured by the specific method of DeMoss and Happel.¹⁶ Blood for insulin assay was centrifuged as soon as clotting was complete; serum was extracted with acid alcohol and the crude insulin was precipitated with alcohol-ether;¹⁷ insulin was assayed by the immunochemical method of Grodsky and Forsham employed in previous studies.⁷ Urinary epinephrine was measured by a modification of the fluorometric method described by von Euler and Floding.^{18,19}

*Supplied by Eli Lilly and Co. as the hydrochloride, Lot No. 9118-832897.

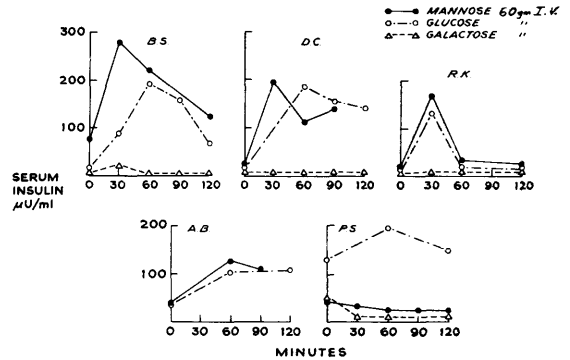


FIG. 1. Serum insulin levels in five obese nondiabetic subjects after rapid infusion (6 min.) of 300 ml. mannose, glucose or galactose as a 20 per cent solution in water.

RESULTS

Effect of selected hexoses on insulin release (figure 1)

Of five obese nondiabetic subjects who manifested an excessive serum insulin response to the rapid intravenous administration of 60 gm. glucose, a comparable elevation of serum insulin levels occurred in four when mannose was administered. The blood glucose levels fell progressively after administration of mannose from a mean fasting level of 81 mg. per 100 ml. to a mean of 48 mg. per 100 ml. at two hours. Galactose did not elevate serum insulin levels when given to four of these subjects, nor was there a fall in blood glucose when this carbohydrate was administered.

Effect of endogenously induced hyperglycemia on serum insulin response (figure 2)

Effect of 2-deoxyglucose. Administration of 2-DG in four obese subjects produced sustained elevation of blood glucose, yet there were no insulin levels above 80 μ U. per ml. despite the prolonged hyperglycemia; whereas in the same subjects, a standard oral glucose tolerance test sustained levels of insulin in the serum above 100 μ U. per ml. Urinary epinephrine excretion levels during a six-hour period after 2-DG administration rose in all subjects from a mean (\pm 2 S.E.) of 0.6 \pm 0.46 to a mean of 32.8 \pm 18.8 μ g. per six hours.

Effect of epinephrine and glucagon alone on insulin secretion. Three obese subjects, given 5 to 6 γ epinephrine per minute for 120 min., had no elevation of serum insulin above baseline levels despite a sustained elevation of blood glucose. Equivalent or lesser degrees of hyperglycemia, induced by infusions of glucagon in saline (16 γ per minute) were associated with definite elevations of serum insulin levels in two obese subjects, resulting in maximum levels of 106 μ U. per ml. in one subject and 300 μ U. per ml. in the other.

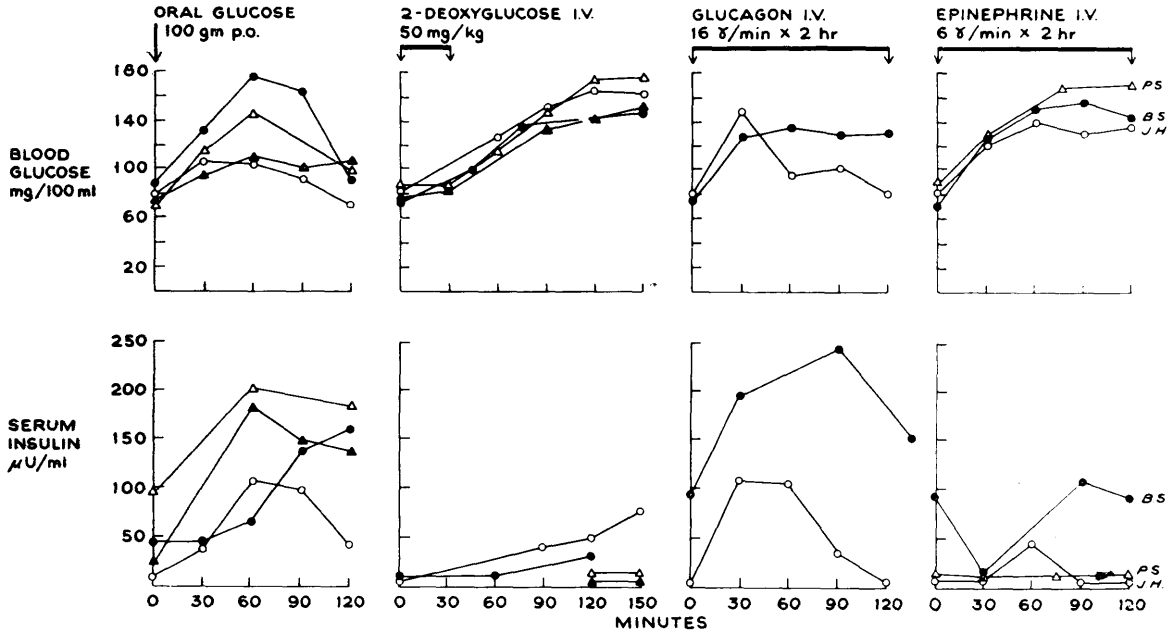


FIG. 2. Comparison of blood glucose and serum insulin levels in obese patients given oral glucose or infusions of 2-DG, glucagon, or epinephrine in physiologic saline solutions.

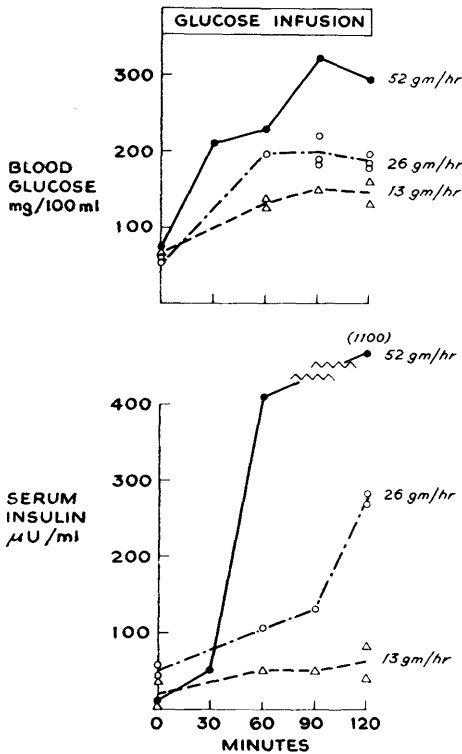


FIG. 3. Comparison of blood glucose and serum insulin levels after 20 per cent dextrose in water was infused at rates of 13, 26 or 52 gm. per hour in an obese subject. Disconnected symbols represent observations during other experiments at the same dose level.

Effect of prolonged infusions of glucose in obese subjects (figure 3)

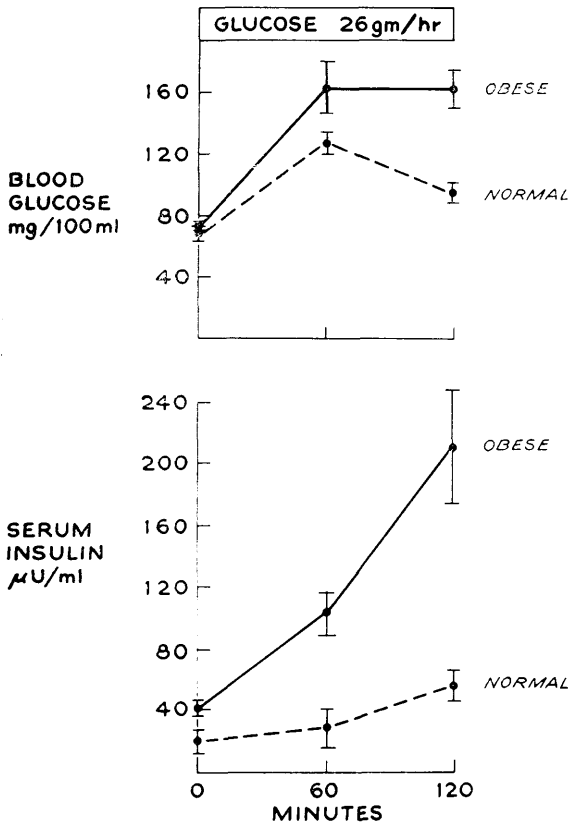
When varying amounts of glucose were administered to an obese subject, the following responses occurred: 13 gm. per hour produced sustained levels of blood glucose between 130 and 160 mg. per 100 ml., yet on two occasions failed to raise serum insulin values above 80 μ U. per ml.

Increasing the rate of infusion to 26 gm. per hour on two occasions resulted in blood glucose levels of 175 to 190 mg. per 100 ml. and serum insulin levels consistently higher than 100 μ U. per ml., values varying between 104 and 280 μ U. per ml. at 60, 90 and 120 min. When glucose was given at 52 gm. per hour to produce blood glucose levels 210 to 320 mg. per 100 ml., serum insulin levels as high as 410 μ U. per ml. at 60 min. and 1,000 μ U. per ml. at 120 min. resulted.

An infusion rate of 26 gm. per hour was arbitrarily selected as a convenient dose for evaluating either facilitation or inhibition of the insulin secretion induced by glucose. The mean response of four normal and four obese subjects to this load is shown in figure 4.

Effect of epinephrine and glucagon on insulin secretion during prolonged glucose infusion (figure 5)

When epinephrine was added at 2.2 γ per minute during the third hour of a sustained glucose infusion at 26 gm. per hour, the levels of blood glucose rose immedi-



ately and progressively in all patients. Despite the elevation in blood sugar, serum insulin levels dropped to values below those observed at the end of the infusion of glucose alone in three of the four subjects. The one patient whose insulin levels were not reduced by the above dose of epinephrine was the most obese of the four, weighing 180 kg.

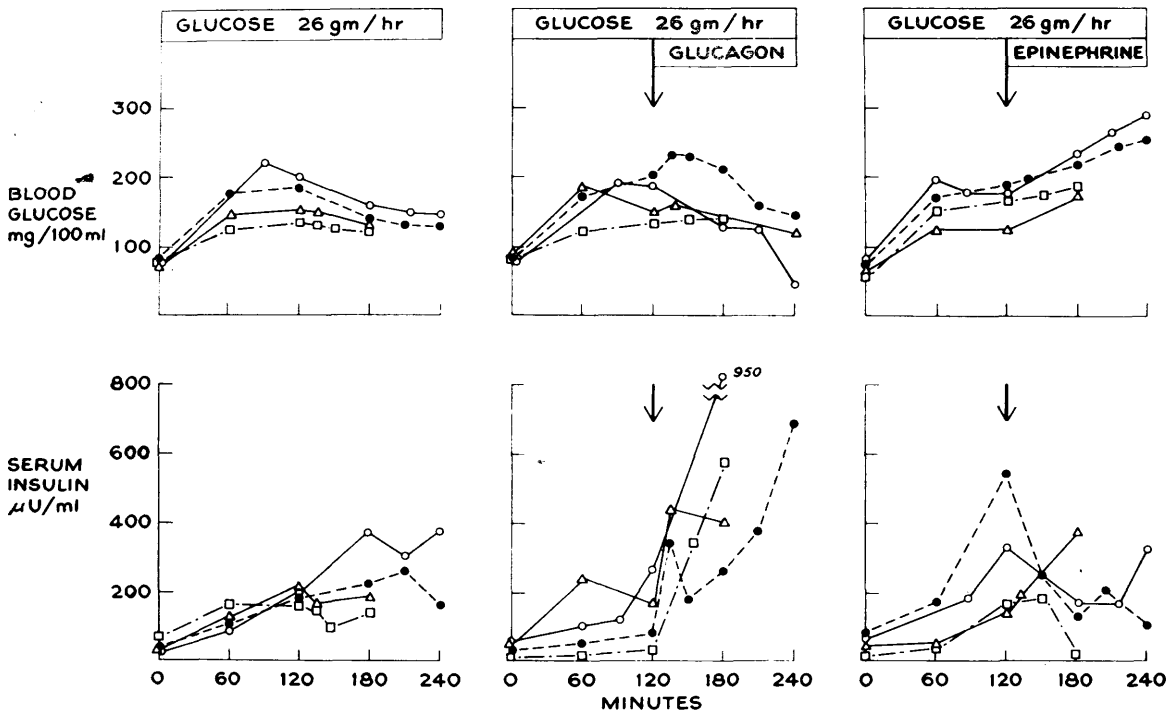
When added at 6.0 γ per minute during the third hour of a glucose infusion, glucagon produced a slight initial rise followed by a progressive decline in blood glucose. These changes were accompanied by a marked and sustained rise of serum insulin levels in all subjects.

Insulin stimulation in normal subjects

Glucose administration (figure 6). Infusion of 26 gm. glucose per hour for three hours did not sustain blood glucose levels above 110 mg. per 100 ml. in three normal subjects, nor did insulin values rise above 60 μ U. per ml. at this dose. It was only after very high doses of glucose (78 gm. per hour) accompanied by blood glu-

FIG. 4. Levels of blood glucose and serum insulin in normal and obese subjects during infusions of glucose. Each bracketed point represents the mean \pm SE of four patients who were tested on three separate occasions.

FIG. 5. Effect of glucose alone and glucose plus glucagon or epinephrine in each of four obese subjects.



DISCUSSION

The immunochemical measurement of serum insulin levels in man after administration of hexoses and various hormones correlates well with observations of the direct effects of these substances on isolated pancreatic systems in vitro.

The exaggerated insulin response of the obese subjects was found to be produced by mannose as well as glucose, while galactose, a hexose not utilized by peripheral tissues, did not provoke insulin release. This response in vivo to mannose but not to galactose differs from a report by Sheps et al.⁶ but correlates with in vitro findings¹⁻³ and suggests that a glucose metabolite initiates insulin release rather than the glucose molecule itself.

The cellular inhibitor of glucose metabolism, 2-DG, has been shown to block the stimulation of insulin release by glucose in vitro.²⁰ When 2-DG was infused in obese subjects at rates sufficient to produce sustained levels of hyperglycemia, an associated rise in serum insulin levels did not occur as it would with a comparable hyperglycemia caused by either a standard oral glucose tolerance test or an infusion of glucagon. The mechanism of 2-DG induced hyperglycemia seems to depend on an intact sympathetico-adrenal medullary axis²¹ and is associated with a large output of urinary epinephrine.^{19,21} Although 2-DG in vitro can directly inhibit the effect of glucose on the release of insulin by the pancreatic islets, the inhibition in vivo could in addition be caused by the released epinephrine, also a known inhibitor of insulin secretion in vitro.³ That this effect of epinephrine could occur in man was shown by the absence of increased insulin secretion above the baseline levels in obese subjects infused with enough epinephrine to produce prolonged hyperglycemia. Moreover, epinephrine reduced the insulin levels stimulated by continuous infusion of glucose in three of four obese subjects, again despite an associated increase in blood glucose levels. These findings are in agreement with those of Kosaka et al.,²² who recently reported that serum insulin-like activity does not rise after epinephrine-induced hyperglycemia in dogs. Porte et al.¹¹ have also noted that epinephrine inhibits all the common stimuli to insulin secretion in normal subjects.

Epinephrine has long been known to be a diabetogenic hormone. The presence of pheochromocytoma leads to hyperglycemia, as do acute stress and emotional upsets. The latter contribute to the problem of control in diabetic patients. Attempts have been made to explain this physiologic mechanism on the basis of the glyco-

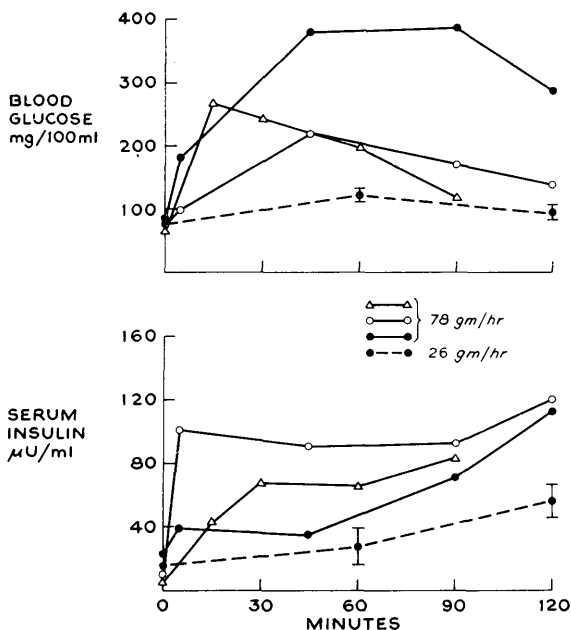


FIG. 6. Effect of sustained glucose infusions on blood glucose and serum insulin levels in three normal subjects. Broken lines and brackets represent mean levels \pm SE during infusion of glucose at a rate of 26 gm. per hour. Solid lines represent individual values during glucose infusions at a rate of 78 gm. per hour.

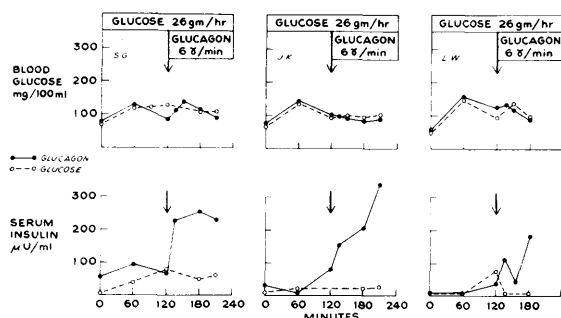


FIG. 7. Effect on serum insulin response of glucagon added during third and fourth hours of a constant infusion of glucose in each of three normal subjects is represented by solid lines. Broken lines indicate values during control infusion with glucose alone.

cos levels over 350 mg. per 100 ml. that serum insulin levels as high as 120 μ U. per ml. were obtained.

Glucagon administration (figure 7). When 6.0 γ per minute of glucagon was added during the third hour of a 26 gm. per hour glucose infusion in the normal subjects, there was initially a very slight rise in blood glucose which progressively fell during the infusion. However, a rapid and marked rise of serum insulin levels, which was maintained throughout the infusion, occurred in all three subjects.

genolytic action of epinephrine on the liver, which results in elevation of blood glucose. This concept has been based on the demonstration that epinephrine activates phosphorylase in rat liver slices *in vitro*²³ and reduces liver glycogen content after administration to animals *in vivo*.²⁴ Recent studies using physiologic concentrations of epinephrine in perfused rat liver,²⁵ and *in vivo* experiments in dogs²⁶ have not confirmed the earlier findings, indicating that hepatic glycogenolysis may be a less important effect of epinephrine *in vivo*. A peripheral effect of epinephrine in blocking glucose uptake by muscle has been described by Cori and Cori²⁷ and attributed to the accumulation of intracellular glucose-6-phosphate,²⁸ a product of muscle glycogen breakdown that inhibits further phosphorylation of glucose.²⁹ Randle et al.³⁰ demonstrated direct interference with glucose uptake and metabolism in muscle by fatty acids. The direct activation of intracellular lipase with the elevation of free fatty acids could be an additional mechanism of epinephrine-induced hyperglycemia.

In addition to these established mechanisms, the data in this report suggest that, in man, epinephrine also blocks insulin release from the pancreas. The recent finding of Loubatières et al.³¹ of a cytotoxic action of epinephrine on the beta cells, which can be specifically blocked by dihydroergotamine in the dog pancreas perfused *in vivo* affords additional assurance that the insulinopenic action of epinephrine is indeed the result of a direct effect on the beta cell. Therefore, in response to acute hypoglycemia, epinephrine may not only maintain blood glucose levels by hepatic and peripheral effects, but also by inhibiting further insulin release from beta cells. In this fashion, during "fight or flight," epinephrine would conserve blood glucose for use by the central nervous system while fatty acids, also liberated by epinephrine, would provide the major fuel for the exercising muscles, and in addition would further reduce glucose uptake by muscle tissue.

Glucagon was found to produce not only hyperglycemia but a definitely elevated serum-insulin response in obese subjects. A striking enhancement of insulin secretion was also noted when glucagon was added during a prolonged glucose infusion. In this case, only a slight, transient rise in venous blood glucose occurred at the beginning of the glucagon infusion, and a subsequent progressive decline of blood glucose was associated with increasing levels of serum insulin. In all these experiments the very slight amount of contamination of injected glucagon with insulin was insufficient to account for the high levels of circulating insulin.

Glucagon has long been known to increase hepatic glucose output, both *in vivo*³² and *in vitro*.^{33,34} The mechanism of action has been attributed to the glycogenolysis that results from the activation of phosphorylase²³ and possibly to enhancement of hepatic gluconeogenesis.³³ Increased insulin release could be secondary to the early hyperglycemia *in vivo*, but direct stimulation of the beta cell by glucagon appears to be a more likely explanation. Under the experimental conditions reported here, only a minimal effect on hepatic glucose output after glucagon would be expected, for Clancy et al.³⁴ noted after catheterizing the hepatic vein of normal males that, although glucagon increased hepatic glucose output after overnight fasting, it had little or no effect if preceded by a glucose infusion. When glucagon was added during glucose infusions, serum insulin increased without a consistent increase in blood sugar. Finally, in our three normal subjects infused with three times the dose of glucose used in the glucagon experiments, serum insulin did not exceed 125 μ U. per ml. despite blood glucose values as high as 300 mg. per 100 ml.

Degradation products of glucagon protect insulin from destruction by the hepatic "insulinase" system.³⁵ The presence of increased insulin after administration of glucagon in man or intact animals, therefore, does not distinguish between a stimulatory effect of glucagon on pancreatic insulin release and decreased clearance of insulin by the liver.

However, indications that glucagon has a direct effect *in vivo* on secretion of insulin by the beta cell are supported by *in vitro* findings of R-Candela et al.,⁴ who reported that glucagon stimulated release of insulin-like activity from pieces of duck pancreas. Preliminary data from rat pancreas perfusion studies also reveal stimulation of immunologically measurable insulin by glucagon.³⁶ However, a direct effect was not verified *in vitro* in the studies of Coore and Randle,³ who used a lesser amount of glucagon on segments of rabbit pancreas.

Glucagon, administered systemically to patients with insulinoma, causes profound hypoglycemia.^{36,37} Since many of these tumors respond poorly to glucose administration³⁸ a direct effect on insulin secretion may be responsible. The poor results reported in the treatment of hypoglycemia with glucagon in newborn infants³⁹ may be explained by a direct stimulatory effect on islet cells.

The evidence that glucagon exerts a direct effect on the stimulation of insulin secretion from the pancreas adds a new dimension to its physiologic role. Glucagon

thus may not only provide increased circulating glucose from hepatic stores, but it may also facilitate the provision of carbohydrate to peripheral muscle and adipose tissue through stimulation of insulin secretion. This contrasts with the role of epinephrine which, by inhibiting insulin secretion, interferes with glucose uptake by peripheral tissues, making more glucose available to the nervous system.

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Relationships Between Alcohol, Heart Disease, and Liver Disease

(Continued from page 570)

to ethanol resulted in an increased uptake of fructose, a corresponding rise of formation of polyol (sorbitol and glycerol), and a decreased output of lactate and pyruvate. A corresponding increase in glucose output was observed and the oxidation of ethanol to acetate was almost double that found when ethanol alone was infused. A decreased output of lactate and of pyruvate suggested that the pathway via glycerate was blocked. Reduction of glyceraldehyde to glycerol via the ADH-NADH complex could explain this fructose effect on ethanol metabolism. The NADH formed by dehydrogenation of alcohol could be reoxidized by glyceraldehyde without prior dissociation from the enzyme.

Simultaneous infusion of ethanol and fructose doubled the splanchnic ethanol uptake and acetate output. Splanchnic blood flow increased 30 per cent, and oxygen uptake 60 per cent. The lactate/pyruvate ratio in hepatic venous blood was greatly increased by ethanol with or without fructose. Infusion of ethanol increased splanchnic uptake of fructose. The output of lactate and pyruvate was reduced to one third during ethanol-fructose infusion as compared with fructose alone. The splanchnic output of glucose was three times greater during ethanol-fructose infusion than it was during

fructose infusion alone. These observations suggest that at least some of the uncertainties regarding ethanol metabolism are closer to resolution.

Another clinical effect of alcohol is on the myocardium. Although little is known about the mechanism of this condition, it has been referred to by several previous authors. H. D. Levine, T. E. Piemme, and K. E. Monroe (*Am. Heart J.* 69:140, 1965) described this condition, which apparently arises in persons who use alcohol to excess. They noted in the course of reading electrocardiograms that there was a characteristic abnormality of the T waves, usually an unusual sharpness, and also a suggestion of abbreviation of the QRS complex, a slight elevation of the RS-T segment, and a tendency toward a shortened QT segment. The authors suggested that this overall appearance might be called a "brisk" electrocardiogram.

The evidence seems overwhelming that intemperate use of alcohol is detrimental to the heart; that is unless hepatic cirrhosis ensues. Cirrhosis itself is hardly a condition to be desired. Whether the simultaneous ingestion of fructose would lessen the hazards of drinking is unknown.

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