ABSTRACTS

Anonymous: GLUCORECEPTORS, INSULIN RELEASE AND DIABETES (EDITORIAL). Lancet *2*:646-47, October 4, 1975.

Since quantitative studies have shown a sigmoid relationship between extracellular glucose concentration and the rate of insulin release, the concept is proposed that a glucoreceptor, probably in pancreatic beta cells, reacts to external glucose concentration and modifies insulin release through transducer and effector systems. Three glucoreceptor models are suggested. The first is a substrate-site model in which a metabolite of glucose in the beta cell triggers insulin release, and defines the receptor as an enzyme regulating glucose phosphorylation. The second is a regulator site model that involves the interaction of a direct receptor for glucose and leads to conformational changes that activate an insulin-release system. The third is a two-site model combining features of the substrate site and regulator-site schemes. This model was suggested by the observation that sugars that are poorly metabolized or not metabolized can stimulate insulin release provided a substimulatory concentration of a metabolizable sugar is present. Evidence for a direct receptor is provided by showing that the alpha anomer of glucose stimulates insulin release more effectively than the beta anomer, but either anomer is effective as a substrate for islet metabolism. If diabetes in man is a disorder of glucose receptors, insulin secretion to other stimuli, such as amino acids, might not be impaired. Such data are not yet available in man. T.G.S.

Bellman, Otto; and Hartman, Edzard (Dept. of Obstet. and Gynec., Univ. of Bonn, Div. of Physical Chemistry and Information Science of Schering AG Berlin, Germany): INFLUENCE OF PREGNANCY ON THE KINETICS OF INSULIN. Am. J. Obstet. Gynec. *122*:829-33, 1975.

During pregnancy there is an elevation of fasting serum insulin levels, and it is well known that during the course of pregnancy complicated by diabetes the insulin requirements increase considerably as pregnancy advances. To determine whether pregnancy has an influence on insulin kinetics, the disappearance rate of intravenously injected insulin was investigated in 30 women during the third trimester of pregnancy and also six to eight weeks postpartum. Both women with normal glucose tolerance and those with latent diabetes were studied. Disappearance of exogenous insulin in pregnancy was characterized by two compartmental models. A multivariate analysis of variance showed that the kinetics of insulin during pregnancy did not differ from those after pregnancy. The authors conclude that hyperinsulinism observed during pregnancy cannot be explained by changes in insulin kinetics and that it appears improbable that the insulin-degrading enzyme activities of the placenta participate in degradation of circulating insulin. No connection between the decline in glucose tolerance during pregnancy and the kinetics of exogenous insulin was observed. J.E.G.

Breuer, R. I.; Zuckerman, L.; Hauch, T. W.; Green, W.; O'Gara, P.; Lawrence, A. M.; Foa, P. P.; and Matsuyama, T. (Dept. of Med., Evanston Hosp., Evanston, Ill.; Northwestern Univ. Med. Sch., Dept. of Med., Univ. of Chicago, Chicago, Ill.; Dept. of Res., Sinai Hosp. of Detroit, Detroit, Mich.): GASTRIC OPERATIONS AND GLUCOSE HOMEOSTASIS. II. GLUCAGON AND SECRETIN. Gastroenterology *69*:598-606, 1975.

Verbatim summary. Alimentary hyperglycemia in patients who have undergone gastric operations may be due, in part, to altered intestinal signals for glucose disposition. We measured glucose, immunoreactive insulin (IRI), pancreatic glucagon (IRG), and glucagon-like immunoreactivity (GLI) after oral glucose in patients with prior antrectomy or vagotomy and pyloroplasty and in normal individuals. All subjects had normal assimilation coefficients for intravenous glucose, which suggests that the responsiveness of the pancreatic B-cells had not been altered by the surgical procedures. The early hyperglycemic response to oral glucose and the associated elevation of plasma GLI were much greater and the IRI levels slightly higher in both experimental groups in comparison to normal subjects. A decrease in the level of IRG, albeit not statistically significant, was noted in all groups after the ingestion of glucose. In gastrectomy patients, secretin infusion during repeated oral glucose tolerance tests partially corrected the hyperglycemia and lowered plasma GLI and IRI levels. The responses of the vagotomy and pyloroplasty patients and of the normal subjects were not altered by secretin infusion. We conclude that the intolerance to oral glucose after gastric surgery may be related to elevated GLI levels, and that the beneficial effect of secretin may be due to its ability to decrease these levels.

Brunzell, John D.; Porte, Jr., Daniel; and Bierman, Edwin L.; (Dept. of Med., Univ. of Wash. Sch. of Med. & Seattle V.A. Hosp., Seattle, Washington): REVERSIBLE ABNORMALITIES IN POSTHEPARIN LIPOLYTIC ACTIVITY DURING THE LATE PHASE OF RELEASE IN DIABETES MELLITUS (POSTHEPARIN LIPOLYTIC ACTIVITY IN DIABETES). Metabolism *24*:1123-37, October, 1975.

Postheparin lipolytic activity (PHLA) was measured during a high-dose constant heparin infusion in diabetic subjects with hypertriglyceridemia, nondiabetic hypertriglyceridemic patients, and normal subjects. The standard low heparin dose PHLA and the PHLA during the early phase of heparin infusion were the same in all groups. In contrast, the PHLA during the last phase of heparin infusion was lower in untreated diabetics than in the other two groups or in chronically treated diabetic patients. Untreated diabetic patients manifested both lower absolute PHLA levels at the late phase of the heparin infusion and greater decreases in relative PHLA during the infusion with increasing levels of fasting blood sugar. Treatment of diabetes with long-term oral sulfonylurea or insulin therapy corrected the late phase PHLA, with an associated fall in plasma TG levels. Those with deficient PHLA response to standard low-dose heparin also manifested a low PHLA response to heparin infusion. With treatment, the PHLA response to low heparin dose was corrected and the early PHLA response during heparin infusion improved. The late-phase abnormality in untreated diabetics did not return to normal until

after several months of antihyperglycemic therapy. In the untreated diabetic subjects the degree of elevation of plasma TG appeared to result from the interaction of the abnormality in PHLA with the presence or absence of a familial lipid disorder.

Apparently, lipoprotein lipase as an insulin-dependent enzyme is restored to normal activity only after several weeks or months of active antidiabetic therapy in some patients. C.R.S.

Christensen, Niels Juel; Christensen, Stig Engkjoer; Hansen, Aage Prange; and Lundboek, Knud (Second Univ. Clinic of Intern. Med., Kommunehospitalet, Aarhus, Denmark): THE EFFECT OF SOMATOSTATIN ON PLASMA NORADRENALINE AND PLASMA ADRENALINE CONCENTRATIONS DURING EXERCISE AND HYPOGLYCEMIA. Metabolism *24*:1267-72, November 1975.

Somatostatin suppressed plasma growth-hormone response to exercise and insulin-induced hypoglycemia in normal subjects. Plasma norepinephrine was reduced but not significantly during exercise while somatostatin was being infused. The secretion of epinephrine was increased during somatostatin infusion both with exercise and hypoglycemia. The epinephrine levels were higher during hypoglycemia following insulin injection despite somatostatin administration. These data demonstrate that the secretion of catecholamines is not inhibited by a dose of somatostatin that is capable of suppressing the secretion of growth hormone. C.R.S.

Greenfield, Sheldon; Lewis, Charles E.; Kaplan, Sherrie H.; and Davidson, Mayer B. (Dept. of Med., Sch. of Med. and Sch. of Public Health, Univ. of California, Los Angeles, California): PEER REVIEW BY CRITERIA MAPPING: CRITERIA FOR DIABETES MELLITUS. Ann. Intern. Med. *83*:761-70, November 1975.

Verbatim summary. The UCLA Experimental Medical Care Review Organization (EMCRO), in an attempt to minimize the problem of applying a general list of criteria to each patient with a specific condition, has developed a method called Criteria Mapping. This method uses sequential judgments based on the specific clinical data for the individual patient to assess the quality of care by medical record audit. The method does not penalize the physician for omitting unnecessary procedures by allowing alternative decisions when appropriate, and it provides supporting reference materials to allow nonphysicians to make reliable medical interpretations of the data in medical records. It is expected that this method will more accurately reflect the physician's intentions, and that process, when measured by this approach, may correlate better with the outcome of medical care.

Harrison, L.C.; King-Roach, A.P.; and Sandy, K.C. (Depts. of Med. and Endocr., Univ. of Melbourne, Royal Melbourne Hosp., Victoria, Australia): EFFECTS OF MAZINDOL ON CARBOHYDRATE AND INSULIN METABOLISM IN OBESITY. Metabolism *24*:1353-61, December 1975.

A single oral dose of the anorectic agent mazindol given to obese subjects led to improvement in oral glucose tolerance and reduced insulin secretion but had no effect on blood glucose or on plasma insulin responses to intravenously administered glucose. In long-term studies using mazindol with a hypocaloric diet, these subjects manifested progressive weight loss with reductions in the fasting levels of blood glucose, plasma insulin, serum TG, and cholesterol. When oral glucose tolerance was retested, blood glucose and plasma insulin responses were significantly lower than

the intial control values. The data suggest that an acute effect of mazindol is to inhibit intestinal glucose absorption. Changes in carbohydrate metabolism after chronic administration of mazindol are consistent with weight loss per se, although a separate effect of the drug has not been excluded. C.R.S.

Jain, Adesh K.; Ryan, Jerome R.; and McMahon, F. Gilbert (Therapeutics Sect., Dept. of Med., Tulane Univ. Sch. of Med., New Orleans, La.): POTENTIATION OF HYPOGLYCEMIC EFFECT OF SULFONYLUREAS BY HALOFENATE. N. Engl. J. Med. *293*:1283-86, Dec. 18, 1975.

The authors found that the drug halofenate (used to lower serum lipids) potentiated the hypoglycemic effect of tolbutamide in a group of volunteers. This was associated with an increase in serum tolbutamide levels. In a double-blind study of diabetics with type IV hyperlipoproteinemia there was a potentiate of sulfonylurea effect by halofenate but not by clofibrate. Thus this interaction appears to be significant clinically. H.M.

Karl, Richard C. (A summary of the Kroc Foundation Conference held at Santa Ynez, Calif., Dec. 8-11, 1974): ANIMAL MODELS OF INAPPROPRIATE HYPERGLYCEMIA. Metabolism *24*:1305-09, November 1975.

This summary of the Kroc Foundation Conference entitled "Swine as a Model in Diabetes Mellitus," held in December, 1974, provides a description of the various examples of spontaneously occurring inappropriate hyperglycemia in animals. Reference is made to studies of inbred colonies of mice and Chinese hamsters as well as the Celebes ape and Yucatan pig. A selected breeding stock of the latter has yielded progeny with glucose intolerance that may provide a valuable animal for investigations of phenomena central to our understanding of diabetes. C.R.S.

Larsson, Bo; Bjorntorp, Per; Holm, Jan; Schersten, Tore; Sjostrom, Lars; and Smith, Ulf (Clin. Metab. Lab. of the First & Second Med. Serv. & from the Second Surg. Serv., Sahlgren's Hosp., Univ. of Gothenburg, Gothenburg, Sweden): ADIPOCYTE METABOLISM IN ENDOGENOUS HYPERTRIGLYCERIDEMIA. Metabolism *24*:1875-89, December 1975.

Patients with endogenous hyperlipidemia (EH) were compared with normolipidemic controls matched for body fat and fat-cell size with respect to adipocyte metabolism studied in vitro. The enlarged fat cells of EH were found to have increased basal and norepinephrine-stimulated lipolysis with blunting of insulin inhibition of lipolysis when compared with cells of the same size from normolipidemic controls. Lipoprotein lipase activity of these cells was depressed and basal TG synthesis from labeled glucose was low in relation to plasma insulin. The results from insulin tolerance tests in vivo showed that the lowering of FFA was smaller in the EH group than in the controls. These data suggest that the hyperinsulinemia and decreased glucose tolerance of EH may be responsible for some of the abnormalities of adipocyte metabolism seen in these patients. Decreased responsiveness to insulin and low lipoprotein lipase activity are, however, findings not typical of enlarged fat cells exposed chronically to insulin and may be characteristic for the fat cells of EH. The factors responsible for these aberrations require further definition because the abnormalities of adipocyte metabolism in EH may provide an explanation for the pathogenesis of that condition. C.R.S.

Nelson, P.G.; Pyke, D.A.; Cudworth, A.G.; Woodrow, J.C.; and Batchelor, J.R. (Diabetic Dept., King's College Hosp. SE5, Dept. of Med., Liverpool L69, and McIndoe Research Laboratory, Queen Victoria Hosp., East Grinstead, Sussex, England): HISTOCOMPATIBILITY ANTIGENS IN DIABETIC IDENTICAL TWINS. Lancet *2*:193-94, August 2, 1975.

Recent studies demonstrating an increased frequency of histocompatability antigens HL-A8 and W15 in juvenile diabetics provide evidence that there is an important locus for a diabetogenic gene closely linked to the HL-A loci. This study observed the frequency of HL-A antigens in identical twins concordant and discordant for diabetes. When 22 pairs of maturity-onset concordant (both had diabetes) twins were HL-A typed, no disturbance of HL-A frequencies was disclosed. In 62 pairs, 31 were concordant juvenile-onset diabetics and 31 were discordant (only one twin had diabetes). The frequency of W15 antigen was equally increased in both concordant and discordant pairs, but HL-A8 antigen was increased only in the concordant pairs. The fact that W15 is increased in the discordant pairs shows that there is genetic predisposition to diabetes even in these twins; the fact that HL-A8 is not increased suggests that different alleles may underlie susceptibility in the two groups of twins. There is evidence that genes in the HL-A chromosomal region may influence immune responses and susceptibility to viruses and thus viral-immunologic mechanisms may have important pathogenic roles in the onset of juvenile diabetes. T.G.S.

Sakurai, Hideo; Dobbs, Richard E.; and Unger, Roger H. (V. A. Hosp., Dallas, Tex. and Depts. of Intern. Med. and Physiol., Univ. of Texas Southwestern Med. Sch., Dallas, Tex.): THE ROLE OF GLUCAGON IN THE PATHOGENESIS OF THE ENDOGENOUS HYPERGLYCEMIA OF DIABETES MELLITUS. Metabolism *24*:1287-97, November 1975.

Experimental insulin deficiency produced in dogs by alloxan, total pancreatectomy, and diazoxide administration permitted studies on the influence of glucagon suppression by somatostatin on endogenous hyperglycemia. In alloxan-diabetic dogs, insulin withdrawal resulted in hyperglycemia, which was significantly reduced by glucagon suppression. Discontinuance of somatostatin was associated with a prompt rise in glucagon and plasma glucose levels. During alanine infusion in these animals, glucose declined, in contrast to the increase observed in unsuppressed controls. In depancreatized dogs withdrawal of insulin resulted in a rise in extrapancreatic glucagon and a marked increase in plasma glucose. Glucagon suppression produced a lowering of plasma glucose; when somatostatin was discontinued, glucagon and glucose rose promptly. In each of these experiments the rises in plasma glucagon and glucose were significantly correlated. Glucagon suppression during diazoxide-induced blockade of insulin secretion reduced hyperglycemia significantly but did not prevent it. These data suggest that a relative or absolute excess of glucagon, as well as insulin deficiency, is etiologically important in the endogenous hyperglycemia of diabetes mellitus, the hyperglucagonemia probably mediating the glucose overproduction. C.R.S.