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ABSTRACTS

Arieff, Allen I.; Doerner, Tom; Zelig, Harry; and Massry, Shaul G. (Wadsworth V.A. Hosp. Center, Cedars-Sinai Med. Center, and Univ. of Calif., Los Angeles, Calif.): MECHANISMS OF SEIZURES AND COMA IN HYPOGLYCEMIA: EVIDENCE FOR A DIRECT EFFECT OF INSULIN ON ELECTROLYTE TRANSPORT IN BRAIN. J. Clin. Invest. *54*:654-63, September 1974.

In an effort to understand the pathophysiologic events leading to seizures and coma as a result of hypoglycemia, rabbits were given intravenous insulin at a dose of 50 U. per kilogram, while plasma, cerebrospinal fluid, and brain levels of glucose, osmolality, and electrolytes were measured sequentially.

The first change noted after intravenous insulin was an increase in brain potassium and water content with a fall in plasma potassium and osmolality at thirty-five minutes; at this time there were no changes in plasma or brain glucose levels. At 146 minutes, when seizures were occurring, plasma glucose fell, but brain glucose was still unchanged; brain sodium content and osmolality increased and brain potassium and water content continued to elevate. At 208 minutes the animals were in coma, at which time brain glucose as well as lactate and glutamate fell while there was a further rise in brain water. Brain potassium and water returned to normal after correction of the hypoglycemia with intravenous glucose.

The authors suggest that seizures which occurred soon after the onset of hypoglycemia were related to brain edema secondary to insulin-induced transport of potassium and sodium into brain cells and were not a result of lack of fuel for metabolism, while the comatose state was related to both brain edema and depletion of energy-supplying substrate. For unexplained reasons the rabbits in this study had elevated fasting glucose levels (9.1 to 11.4 mM per liter), and, in spite of astronomical levels of circulating insulin (707 mU. per milliliter), they had marked retardation of the glucose-lowering effect of insulin. In these respects, these animals are unique; thus, caution must be exercised in applying these results to the clinical setting. R.R.

Caren, Raymond; and Corbo, Lucille (Cedars-Sinai Med. Res. Inst. and Div. of Med., Cedars-Sinai Med. Ctr.; and Dept. of Med., Univ. of Calif., Los Angeles, Calif.): GLUCAGON AND PLASMA LIPOPROTEIN LIPASE. Proc. Soc. Exp. Biol. Med. *146*:1106-10, September 1974.

Verbatim summary. Subcutaneous administration of 1.0 mg. glucagon to fifteen fasted, normal people caused significant increase of plasma lipoprotein lipase-like activity in one hour. The activity is termed lipase-like since coconut oil emulsion rather than isolated chylomicrons were used as substrate. A linear relationship between lipolysis and time of incubation obtained, indicating zero order kinetics. pH optimum of enzyme activity was 8.4. There was no correlation between depression of plasma triglycerides and increase of plasma lipoprotein lipase-like activity following glucagon administration. This was thought to be due to other effects of glucagon administration which alter plasma lipid levels. Incubation of whole blood with glucagon caused an increase of plasma lipoprotein lipase-like activity and a depression of plasma triglycerides that were significantly correlated. The in vitro action of glucagon when incubated with whole blood suggests that blood cell(s) may be a source of glucagon-induced plasma lipoprotein lipase and that they may play a role in the regulation of plasma triglycerides. Increase of plasma lipoprotein lipase-like activity by glucagon when added to whole blood suggests that the hormone acted by releasing preformed enzyme from blood cell(s) or by enzyme induction in the nucleated blood cells.

Chez, Ronald A.; Mintz, Daniel H.; Epstein, Michael F.; Fleischman, Alan R.; Oakes, Gary K.; and Hutchinson, Donald L. (Pregnancy Res. Branch, Natl. Inst. of Child Health and Human Develop., and the Dept. of Med., Univ. of Miami Sch. of Med., Miami, Fla.): GLUCAGON METABOLISM IN NONHUMAN PRIMATE PREGNANCY. Am. J. Obstet. Gynec. *120*:690-94, November 1974.

Fasting plasma glucagon levels and pancreatic alpha-cell responses to alanine and insulin-induced hypoglycemia were studied in near-term pregnant monkeys and in the simian fetus and newborn. Fasting plasma glucagon levels (picograms per milliliter, mean ± SEM) in nonpregnant adult females (196 ± 20), in near-term females (114 ± 17), in the simian fetus (136 ± 21), and in the four- to nine-hour newborn (180 ± 25) were not significantly different. Neither hypoglycemia nor infusion of alanine (150 mg. per kilogram) into the fetus stimulated fetal glucagon secretion, whereas these were adequate stimuli for maternal glucagon secretion. In the twenty-four-hour neonate, however, alanine did stimulate glucagon secretion. Infusion of glucagon into the mother did not raise fetal plasma glucagon levels, and infusion of glucagon into a fetal vein did not alter maternal plasma glucagon levels.

These studies indicate apparent unresponsiveness of the simian fetal pancreatic alpha cell to alanine and hypoglycemia and demonstrate that there is no transplacental exchange of glucagon. J.E.G.

Gerich, John E.; Lorenzi, Mara; Schneider, Victor; Karam, John H.; Rivier, Jean; Guillemin, Roger; and Forsham, Peter H. (Dept. of Med., Univ. of California, San Francisco, Calif., and Dept. of Neuroendocrin., Salk Institute, San Diego, Calif.): EFFECTS OF

SOMATOSTATIN ON PLASMA GLUCOSE AND GLUCAGON LEVELS IN HUMAN DIABETES MELLITUS. N. Engl. J. Med. *291*:544-47, September 1974.

The effect of somatostatin was investigated in ten adult diabetic patients with ketonuria, one of whom had been surgically hypophysectomized for retinopathy. During somatostatin infusion, plasma glucose fell from 260 to 191 mg. per 100 ml. and plasma glucagon fell from 150 to 77 pg. per milliliter. Serum growth hormone levels were low during the infusion but rose to 6 ng. per milliliter after the infusion. Subcutaneous administration of 4 mg. of somatostatin had a similar effect on plasma glucose and glucagon which lasted for approximately two hours. The response of the hypophysectomized diabetic was the same as that of the other diabetic patients. Somatostatin administration along with insulin prevented a rise in plasma glucagon and glucose following breakfast. These studies very nicely demonstrate that somatostatin inhibits glucagon secretion in the diabetic and that this is associated with approximately a 25 per cent fall in the plasma glucose level. This peptide may be of real therapeutic value in controlling the hyperglycemic effects of excessive glucagon in the diabetic. H.M.

Hamby, Robert I.; Zoneraich, Samuel; and Sherman, Lawrence (Cardiology Div. and Cardiac Catheterization Lab., Dept. of Med., Long Island Jewish-Hillside Med. Center, Jamaica, N.Y.; Sch. of Med., Health Sciences Center, State Univ. of New York at Stony Brook, and Dept. of Med., Queens Hosp. Center Affiliation): DIABETIC CARDIOMYOPATHY. JAMA *229*:1749-54, September 1974.

Verbatim summary. Seventy-three patients with idiopathic primary myocardial disease, sixteen of whom had diabetes mellitus, were compared to matched patients without cardiomyopathy. A statistically significant increase was observed in the frequency of diabetes in patients with idiopathic cardiomyopathy. Evolution of cardiomyopathy in a patient with pre-existing diabetes and angina pectoris was also established. Four diabetic patients died; autopsies were performed on three. In these patients, the large coronary arteries were patent and free of arteriosclerosis, but small vessel changes were present in the myocardium. In contrast, autopsy findings in twenty-eight patients who had cardiomyopathy without diabetes showed small coronary vessel disease in only one patient.

Diabetics can develop myocardial disease without large coronary artery involvement (diabetic cardiomyopathy) possibly due to pathologic changes in small coronary vessels.

Kolanowski, J.; Desmecht, P.; and Crabbé, J. (Unite d'endocrinologie, Universite catholique de Louvain, Belgium): REPERCUSSIONS METABOLIQUES ET HORMONALES DU JEUNE TOTAL DE COURTE DUREE CHEZ L'OBESE. Schweiz. Med. Wochenschr. *104*:1022-28, 1974.

Thirty-two adult nondiabetics were given 1500 calories a day for five days followed by seven days of total fast. In addition to a decrease in blood sugar and total CO2 which was anticipated, a significant, negative water and salt balance occurred during fasting. The natriuresis was associated with a proportional chloride loss, and these resulted in volume depletion. The mean weight reduction was 0.47 ± 0.09 kg. per day during the first and 0.69 ± 0.05 kg. per day during the second study period. Since the weight changes were regarded as excessive in relation to the calculated loss of energy, these were therefore attributed to the water and salt losses. During the fast, plasma insulin levels decreased slowly and plasma glucagon rose dramatically. No changes in plasma cortisol and HGH or in the urinary free cortisol and catecholamine concentrations could be detected throughout the fasting period. N.K.

L'age, M.; Langholz, J.; Fechner, W.; and Salzmann, H. (Dept. of Endocr., Med. Clinic, Klinikum Steglitz, Free Univ. of Berlin, Federal Republic of Germany): DISTURBANCES OF THE ADRENOCORTICAL SYSTEM IN THE ALLOXAN DIABETIC RAT. Endocrinology *96*:760-65, September 1974.

Verbatim summary. In insulin-treated alloxan diabetic rats, some parameters of the hypothalamo-hypophysial-adrenocortical (HHA) system are normal: half-life and circadian rhythm of plasma corticosterone, maximal and submaximal stimulation of the adrenal cortex by exogenous and endogenous ACTH, dexamethasone suppression of stress stimuli of different strengths. If insulin treatment is withheld, at forty hours after the last insulin injection, morning levels of plasma corticosterone are elevated, adrenocortical response to exogenous ACTH is increased, the onset of dexamethasone inhibition of weak stress signals is delayed, and different stress stimuli overcome the dexamethasone blockade. These disturbances of the regulation of the HHA-system could be interpreted as counterregulation in insulin-deficient alloxan diabetic rats.

Mörchen, R.; Damschen, G.; and Oehme, J. (Kinderklinik der Stadt Braunschweig): MAURIAC SYNDROME WITH VILLOUS ATROPHY. Deutsch. Med. Wschr. *99*:1446-48, July 1974.

In two children with Mauriac syndrome—characterized by early-onset and difficult to control diabetes mellitus, dwarfism, abdominal distension, and changing hepatomegaly—jejunal biopsy revealed subtotal villous atrophy. Gluten-free diet for one year and six months, respectively, produced an improved histologic picture of partial villous atrophy in one case. Further studies will be required to define the role of such villous atrophy of Mauriac syndrome, whose pathogenesis remains unexplained. J.P.A.

Nuttall, F. Q.; Barbosa, J.; and Gannon, M.C. (V. A. Hosp., Univ. of Minn., Minneapolis, Minn.): THE GLYCOGEN SYNTHASE SYSTEM IN SKELETAL MUSCLE OF NORMAL HUMANS AND PATIENTS WITH MYOTONIC DYSTROPHY: EFFECT OF GLUCOSE AND INSULIN ADMINISTRATION. Metabolism *23*:561-68, 1974.

Glycogen synthase and glycogen phosphorylase systems were studied in muscle tissue obtained by needle biopsy in normal individuals and in patients with myotonic dystrophy before and after oral glucose or intravenous insulin administration. Total synthase activity and the percentage in the I form were similar in both groups. Glucose or insulin administration produced a significant rise in the I form in normal females but not in normal males. In patients with myotonic dystrophy, the response was reduced and more variable with no sex difference noted. Similar findings were observed in the measurement of phosphorylase. After glucose and insulin, a modest decrease in the per cent of phosphorylase in a form was noted in the myotonic dystrophy patients but not in the normal subjects. C.R.S.

Ozawa, K.; Yamaoka, Y.; Nanbu, H.; and Honjo, I. (Dept. of Surgery, Kyoto Univ. Faculty of Med., Kyoto, Japan): INSULIN AS THE PRIMARY FACTOR GOVERNING CHANGES IN MITOCHONDRIAL METABOLISM LEADING TO LIVER REGENERATION AND ATROPHY. Am. J. Surg. *127*:669-75, June 1974.

Verbatim summary. Ligation of a branch of portal vein in rabbits resulted in a depression of phosphorylation rates of mitochondria from the ligated lobe and a marked enhancement of phosphorylation rates of mitochondria from the nonligated lobe supplied with excess portal blood. However, when liver slices from the ligated

lobe were incubated in a medium containing insulin, serum albumin, and citrate for ten minutes at 22° C., the respiratory control ratio, state 3 respiration, P:O ratio, and phosphorylative activity of the mitochondria increased to maximal levels, nearly equaling those of mitochondria from the nonligated lobe. However, the addition of glucagon to the incubation mixture did not appreciably enhance the phosphorylative activity of the mitochondria of liver slices from the ligated lobe. It is suggested that insulin may play an important regulatory role in the mechanism by which portal factor stimulates oxidative phosphorylation of liver mitochondria.

Rey, Francoise; Drillet, Francoise; Schmitz, Jacques; and Rey, Jean (Unité de Recherches de Génétique Médicale, INSERM, Hôpital des Enfants Malades, Paris, France): INFLUENCE OF FLOW RATE ON THE KINETICS OF THE INTESTINAL ABSORPTION OF GLUCOSE AND LYSINE IN CHILDREN. Gastroenterology 66:79-85, January 1974.

Verbatim summary. We studied the influence of flow rate on the kinetics of glucose and lysine absorption in twenty normal children, ages seven months to five years, by using a double lumen tube. In certain substrate concentrations and flow rate ranges, absorption was found to increase proportionally to the flow rate without altering the maximum capacity of the segment and without significant decrease of the concentration gradient along the segment; this proves that in these conditions, perfusion rate does not increase the surface of mucosa really perfused. It was also shown that this effect is related to modifications of the apparent affinity constants. It is proposed that the flow rate altered the thickness of the unstirred water layers lining the microvilli, and consequently the substrate concentrations at the contact of the transport sites. Assuming this, our results could further suggest that molecular diffusion through these water layers may be rate-limiting in the over-all process of absorption, even for hydrosoluble substrates such as glucose and amino acids.

Stefanini, Paride; Carboni, Manlio; Patrassi, Neri; and Basoli, Antonio (2nd Surg. Clin. and Surg. Anat., Univ. of Rome Med. Sch., Rome, Italy): HYPOGLYCEMIA AND INSULAR HYPERPLASIA: REVIEW OF 148 CASES. Ann. Surg. *180*:130-35, 1974.

The authors review 148 cases of hypoglycemia secondary to B-cell hyperplasia (as distinct from adenoma and carcinoma), five from their clinic, sixty-five from personal communications and seventy-eight from the literature. The average age of the series was thirty-five years and 56 per cent were female, 44 per cent male. In the authors' group, three of five had fasting hyperinsulinemia and five of five became hypoglycemic during prolonged fasting. The authors conclude from the data that 71 per cent recovered following operative intervention, while 24.5 per cent had persistent hypoglycemia. The operative mortality was 4.5 per cent. It is unclear whether occult adenomas remained in the treatment failure group. T.C.H.

Tavassoli, Fattaneh A.; and Lynch, Richard G. (Dept. of Pathol., Washington Univ. Sch. of Med., and Barnes Hosp., St. Louis, Missouri): OCCULT ADENOCARCINOMA OF THE PANCREAS IN A SEVENTEEN YEAR OLD PATIENT WITH IMMUNOSUPPRESSED LEUKEMIA. Gastroenterology 66:1054-57, 1974.

Verbatim summary. A case of an occult adenocarcinoma of the pancreas in a seventeen year old leukemic girl on immunosuppressive therapy is reported. Although the presence of two primary neoplasms in this case may be purely coincidental and unrelated to therapy, the rarity of pancreatic adenocarcinoma at this age suggests that the neoplasm may be an undesired complication of immunosuppressive therapy. These findings add to the increasing evidence of the role of immunosuppression in facilitating tumor growth in experimental animals and man.

Turner, R.C.; and Harris, E. (Nuffield Dept. of Clin. Med., Radcliffe Infirmary, Oxford, England): DIAGNOSIS OF INSULINOMAS BY SUPPRESSION TESTS. Lancet *2*:188-90, 1974.

Endocrine tumors characteristically secrete hormones autonomously. For example, glucose concentrations usually control the secretion of insulin by the beta cells. The authors postulated that hypoglycemia would not suppress the secretion of insulin by an insulinoma. They investigated this hypothesis by giving 0.2 U. of fish insulin intramuscularly every forty-five minutes to twelve patients with insulinoma. They then measured plasma glucose and serum immunoreactive insulin by a method which essentially did not detect fish insulin but was capable of measuring human insulin at very low concentrations. They then compared human insulin levels in the insulinoma patients with normal subjects who were made about equally hypoglycemic with fish insulin. The normal subjects had insulin levels below 2 μU. per milliliter of plasma when their glucose levels were below 50 mg. per 100 ml. The insulin levels were not nearly this well suppressed in insulinoma patients. Three insulinoma patients displayed complete failure of insulin suppression with fish insulin-induced hypoglycemia. In four there was only partial suppression and in five there was a paradoxical increase in insulin concentration. It was thought that the increased insulin could have been caused by the presence of a small amount of glucagon in the fish insulin. In four of the insulinoma patients, both the serum insulin and fasting glucose levels were normal. In each of these, the test revealed autonomous insulin secretion. The fish insulin test is recommended as a means of diagnosing or excluding insulinoma. T.G.S.