ABSTRACTS

Alberti, K. G. M. M.; Hockaday, T. D. R.; and Turner, R. C. (Nuffield Dept. of Clinical Medicine and Division of Med., Radcliffe Infirmary, Oxford, England): SMALL DOSES OF INTRAMUSCULAR INSULIN IN THE TREATMENT OF DIABETIC "COMA." Lancet *2*:515-22, September 1973.

Because there has been little proof that the conventional large doses of insulin used to treat diabetic ketoacidosis are especially efficacious, and because the authors reasoned that smaller regularly administered amounts of insulin would permit a smooth return to the normal state, a new method of treating diabetic "coma" was devised. Seventeen consecutive patients with severe uncontrolled diabetes admitted during three months were studied. In fourteen of them ketoacidosis was established by finding a mean plasma glucose concentration of 637 mg./100 ml. and a mean blood ketone concentration of 12.1 mM/L. These patients received an average initial insulin dose of 16 units intramuscularly and then 5 to 10 units I.M. every hour. Cumulative insulin therapy in this group amounted to 43 units at six hours, 59 units at twelve hours and 98 units at twenty-four hours on the average. Serial observations showed that plasma glucose, plasma free fatty acids and blood glycerol fell significantly within the first hour. The rate of fall of glucose was not influenced by the plasma ketone level or history of previous insulin treatment. Patients with infection required more insulin. A patient with hyperosmolar nonketotic precoma required the same insulin dose as the noninfected ketoacidotic patients. The authors state that low intramuscular doses of insulin are effective in the treatment of diabetic coma regardless of the severity of the metabolic disturbance. They regard the new regimen as simple to follow and advantageous over conventional therapy because it decreases problems with potassium, lactate and growth hormone. T.G.S.

Andreani, D.; Fallucca, F.; Tamburrano, G.; Iavicoli, M.; and Menzinger, G. (Cattedra di Medicina Costituzionale ed Endocrinologia dell' Università degli Studi, Policlinico Umberto I, Roma, Italy): INSULIN, GLUCAGON AND GROWTH HORMONE IN PRIMARY ADULT MYXOEDEMA. Diabetologia *10*:7-12, 1974.

Verbatim summary. Previous studies have shown that in patients with primary adult myxedema (PAM) the rise in blood glucose (BG) and plasma insulin (IRI) after various stimuli is higher and more sustained than in normals, so that in this condition insulin resistance may be hypothesized. In the search for factors involved glucose (BG), insulin (IRI), glucagon (IRG), (assayed with an antiserum which is not specific for pancreatic glucagon) and growth hormone (GH), have been determined in blood during the oral glucose tolerance test, OGTT, (100 g), arginine intravenous infusion, ATT (30 g/30 min.), and insulin-induced hypoglycemia, ITT (0.1 kg.), in patients with PAM, without clinical diabetes, and in normal control subjects. During OGTT, glucose and IRI levels were higher than normal; on the other hand, IRG (probably gut glucagon, or enteroglucagon) levels were lower than in normals. During ATT blood glucose in PAM was slightly higher than normal at 30′ and lower at 90′ and 120′; insulin levels were higher than normal at any time; GH and IRG (very likely pancreatic glucagon, or nesidioglucagon) responses were lower than normal. During ITT, blood glucose levels dropped slowly but progressively and GH levels were lower than normal. It is concluded that in primary adult myxedema glucagon, both enteric and pancreatic, and growth hormone secretions are impaired. The resistance to insulin action observed in PAM does not seem to be due to an excess of growth hormone or (nesidioglucagon).

Bansal, D. D.; Connolly, J. H.; and Vallance-Owen, J. (Depts. of Medi. and Microbiol., The Queens's Univ. of Belfast, Ireland): PRECIPITIN REACTIONS BETWEEN INSULIN, PROINSULIN, INSULIN CHAINS AND INSULIN ANTIBODY. Diabetologia *9*:384-86, 1973.

Verbatim summary. Insulin antibody was produced in guinea pigs and the precipitins tested by double diffusion in agarose gel. Pork, beef and monocomponent insulin produced precipitin lines. Proinsulin also produced a precipitin line with these antisera but no lines appeared with either the A-chain or the B-chain of insulin. There was good correlation between the precipitin titer and the radioimmunoassay titer.

Becker, H. D.; Reeder, D. D.; and Thompson, J. C. (Dept. of Surg., Univ. of Texas Med. Branch, Galveston, Texas): EFFECT OF GLUCAGON ON CIRCULATING GASTRIN. Gastroenterology *65*:28-35, July 1973.

Verbatim summary. The effect of glucagon on basal and food-stimulated gastrin release, measured by radioimmunoassay, was studied in normal persons, patients with duodenal ulcer, patients with Zollinger-Ellison syndrome, and Heidenhain pouch dogs. Intravenous glucagon (30 μg per kg. per hr.) diminished the basal serum gastrin values and the gastrin response to a standard meal in normal persons, in duodenal ulcer patients, and in dogs. In patients with the Zollinger-Ellison syndrome, glucagon caused an immediate increase in basal gastrin concentrations, and did not diminish the gastrin response to a meal. Lowering the glucagon dosage to 0.5 μg per kg. per hr. did not influence the inhibitory effect on basal values of gastrin or on stimulated gastrin release in normal persons. The effects of glucagon on gastrin are not related to the hypoglycemic effects of glucagon. These effects of glucagon on serum gastrin closely parallel the effects of secretin.

Brown, M.; Doron, M.; and Laron, Z. (Department of Statistics, and Institute of Pediatric and Adolescent Endocrinology Beilinson Hospital, Petah Tikva, Tel Aviv University, Israel): APPROXIMATE CONFIDENCE LIMITS FOR THE CONCENTRATION OF INSULIN IN RADIOIMMUNOASSAY. Diabetologia *10*:23-25, 1974.

Verbatim summary. In radioimmunoassays confidence limits for the concentration of insulin in the serum assayed are of value to the laboratory as an aid in quality control and to the doctor as an aid in differentiating high from low concentrations and in the reliability to be placed on the result. We present a method of deriving approximate confidence intervals for the concentrations by approximating the nonlinear standard curve by a straight line (its tangent) at the estimated concentration. A similar approach may be used for other nonlinear standard curves.

Buckman, M. T.; Conway, M. J.; Seibel, J. A.; and Eaton, R. P. (Dept. of Med., Univ. of New Mexico Sch. of Med. and the Lovelace Clinic, Albuquerque, N. M.): EFFECT OF FASTING ON ALANINE-STIMULATED INSULIN AND GLUCAGON SECRETION. Metabolism *22*:1253-62, October 1973.

Glucose and alanine tolerance tests were performed on dogs in control and fasted states to determine the effect of alanine upon insulin and glucagon secretion. Fasting was shown to inhibit the insulin secretory response to glucose administration. In contrast, both insulin and glucagon secretion after alanine challenge were unaltered by fasting. This amino acid, as a gluconeogenic precursor and glucagon secretogogue, may be partially responsible for the regulation of insulin secretion in the fasting state. C.R.S.

Chakrabarti, R.; and Fearnley, G. R. (Gloucester Royal Hospital, Gloucester, England): PHARMACOLOGICAL FIBRINOLYSIS IN DIABETES MELLITUS. Diabetologia *10*:19-22, 1974.

Verbatim summary. The fibrinolytic activity, plasma fibrinogen and blood sugar levels of twenty maturity-onset diabetics were measured before treatment with (a) phenformin and (b) phenformin plus ethylestrenol; subsequently fortnightly estimations of these parameters were made. After a period of stabilization, treatments were interchanged between the two groups. It has been shown that phenformin alone only partially increases fibrinolytic activity; the maximum effect was obtained with the combined therapy of phenformin plus ethylestrenol. This treatment also effected a reduction of nearly 40 per cent in the plasma fibrinogen level from pretreatment levels. If enhanced fibrinolytic activity in diabetic patients is to be achieved, the results indicate that combined therapy is essentially more effective than therapy with phenformin alone. Blood sugar levels were adequately controlled, as expected, with diet and phenformin alone, addition of ethylestrenol making no difference.

Chick, William L.; Lauris, Vilma; Soeldner, J. Stuart; Tan, Meng H.; and Grinbergs, Marta (Elliott P. Joslin Res. Lab., Joslin Diab. Found., Inc., Harvard Med. Sch. & Peter B. Brigham Hosp., Boston, Mass.): MONOLAYER CULTURE OF A HUMAN PANCREATIC BETA-CELL ADENOMA. Metabolism *22*:1217-24, September 1973.

Monolayer cultures, prepared from a human beta-cell adenoma, were maintained through three subcultures over a period of two months. Insulin release from the primary culture declined gradually and became stabilized prior to subculture. Subcultures became rapidly overgrown with fibroblasts with significant decrease in insulin release. Reducing the glucose concentration from 300 to 100 mg. per 100 ml. produced only a 7 per cent reduction in insulin release which may reflect the high fasting insulin to glucose ratios observed in patients with beta-cell adenoma. These data confirm that cell cultures derived from such tumors may provide a suitable model for studying human beta cells. C.S.

Christensen, N. J.; and Iversen, J. (Second Univ. Clin. of Intern. Med., Kommunehospitalet, Aarhus, Denmark): RELEASE OF LARGE AMOUNTS OF NORADRENALINE FROM THE ISOLATED PERFUSED CANINE PANCREAS DURING GLUCOSE DEPRIVATION. Diabetologia 9:396-99, 1973.

Verbatim summary. Six fasting male mongrels served as pancreas donors. The pancreas was perfused without recirculation with a synthetic medium. The noradrenaline and adrenaline concentration in the efflux perfusate was determined by a double-isotope derivative technique. (1) The noradrenaline concentration in the efflux perfusate rose considerably (from 0.25 ng./ml. to 10.0 ng./ml.), when the pancreas was perfused with a glucose deprived perfusing medium. The concentration rose almost linearly with time. After the addition of very small amounts of glucose (2 mg./100 ml.) to the perfusing medium there was a considerable decrease in catecholamine concentration and a further decrease with higher glucose concentrations. (2) No change in catecholamine concentration in the efflux perfusate was observed if the pancreas was perfused with a high glucose concentration during the whole experiment. (3) Glucagon release was also high during perfusion with a glucose deprived solution while insulin release was low. These experiments raise the question whether an increased catecholamine release may, at least partially, be responsible for the change in insulin and glucagon secretion during glucose deprivation.

Cuatrecasas, Pedro (Dept. of Med. and Dept. of Pharm., Johns Hopkins Univ. Sch. of Med., Baltimore, Md.): INSULIN RECEPTOR OF LIVER AND FAT CELL MEMBRANES. Fed. Proc. *32*:1838-46, August 1973.

Verbatim summary. The basis and significance of the biological activity of insulin-agarose polymers are discussed. The interaction between insulin and intact fat cells is described, and the kinetics of binding, number of binding sites, structural specificity patterns, and the possible role of hormone degradation are presented. The nature of the insulin receptor and the importance of cell surface receptor density in various insulin resistant states (prednisone administration, obesity, starvation, diabetes) are considered. The receptor can be shown to be located exclusively on the surface of the cell, and membrane preparations derived from the cell homogenates contain all of the insulin-binding activity in relatively unaltered form. Inside-out membrane vesicles do not bind insulin unless they are disrupted, indicating that membrane asymmetry with respect to the insulin receptor exists and is stable despite changes in the polarity of the membrane vesicles. A number of enzymic digestions of cells and membranes give some insight into the possible contribution of carbohydrate, protein, and lipid components of the membrane to the insulin receptor. The receptor can be quantitatively extracted from membranes with nonionic detergents. Some physical, kinetic, and chemical properties of the water-soluble receptor are presented. The soluble receptor can be purified extensively, especially by affinity chromatography in insulin-agarose adsorbents. It is not yet possible to determine if the inhibition by insulin of adenylate cyclase activity is the basis for all of the metabolic effects of the hormone, or whether insulin primarily alters another process (generalized change in membrane conformation, or production of unknown mediator) which in turn can modify this enzyme as well as other perhaps unrelated metabolic events.

Devis, G.; Van Obberghen, E.; Somers, G.; Malaisse-Lagae, F.; Orci, L.; and Malaisse, W. J. (Laboratory of Experimental Medicine, Vrije Universiteit Brussel and Université Libre de Bruxelles, Brussels, Belgium and Institutes of Histology and Biochimie Clinique, Université de Genève, Geneva, Switzerland): DYNAMICS OF INSULIN RELEASE AND MICROTUBULAR-MICROFILAMENTOUS SYSTEM. II. EFFECT OF VINCRISTINE. Diabetologia *10*:53-59, 1974.

Verbatim summary. In order to document the participation of microtubules in the dynamics of insulin release, the secretory response of the isolated perfused rat pancreas was measured after various times of exposure to vincristine (2×10^{-5}M). After a short

exposure time (25 min.), both phases of glucose-induced insulin release were increased. After longer pretreatment (60 min.), this facilitating effect disappeared and a slight, insignificant reduction of both phases of the secretory response to glucose was observed. A still longer exposure time (120 min.) provoked a more marked and significant inhibition of the early and late phases of insulin release. The same enhancing effect after short pretreatment with vincristine was noticed when gliclazide was used as the insulinotropic agent. The ultrastructural studies indicated a progressive disappearance of microtubules concomitantly with an increase in number and size of vincristine-induced paracrystalline deposits. These findings suggest that microtubules indeed participate in the dynamics of insulin release, a reduction of both phases of insulin secretion being caused by an extended disruption of the microtubular apparatus, whereas a more limited disturbance of the microtubular system appears to be associated with facilitated insulin release in response to either glucose or sulfonylurea.

Kazdová, L.; Fábry, P.; and Vrána, A. (Research Centre of Metabolism and Nutrition of the Institute for Clinical and Experimental Medicine, Prague, Czechoslovakia): EFFECT OF SMALL DOSES OF INSULIN IN VIVO ON THE PROLIFERATION AND CELLULARITY OF ADIPOSE TISSUE. Diabetologia *10*:77-83, 1974.

Verbatim summary. The effect of insulin in vivo on the proliferation and cellularity of epididymal adipose tissue of growing rats was investigated. Following the intraperitoneal administration of small amounts of insulin (500 *u* U/rat, twice a day), which did not influence the blood sugar level and food intake, it was found that repeated administration of insulin for 48-72 hours leads in adipose tissue to an enhanced incorporation of ^{14}C-2-thymidine into DNA and to an increase of the total amount of DNA and RNA in the fat body. The enhanced DNA synthesis in adipose tissue of insulin-treated rats was marked in nuclear DNA and absent in mitochondrial DNA. After fractionation of adipose tissue by collagenase an enhanced DNA synthesis was found in the fraction of adipose and stromavascular cells. Morphological examination of adipose tissue of insulin-treated rats revealed cells in the phase of mitotic division and an increased ratio of fat cells of smaller size. Calculation of the number of cells in the epididymal fat body revealed that, after administration of insulin, the number of adipose and stromavascular cells increased.

Pense, G.; Panzram, G.; Pissarek, D.; Meinhold, J.; Müller, W.; Leder, H.; Kaselow, D.; and Adloph, W. (Medizinische Poliklinik der Medizinischen Akademie, DDR-50 Erfunt): QUALITAT DER STOFFWECHSELFUHRUNG UND ANGIOPATHIE BEI 180 LANGZEITDIABETIKEN MIT MINDESTENS 20 JAHRIGER KRANKHEITSDAUER. Schweiz. Med. Wochenschr. *103*:1125-29, 1973.

Verbatim summary. As part of a clinicoepidemiologic study, 180 long-term diabetics from a closed diabetic population and having diabetes of twenty to forty-two years' standing were investigated on a multidisciplinary basis with special reference to the vascular system. The quality of diabetic control was carefully assessed on the basis of objective data on metabolic values throughout the duration of the diabetes. Macroangiopathy and retinopathy proved to be largely independent manifestations of diabetic angiopathy. Although there was no relation between the macroangiopathy and diabetes, statistically highly significant correlations were found between the incidence or severity of retinopathy and the quality of the metabolic conditions followed-up over decades. For the present a consistent and disciplined metabolic control offers the only chance of effectively counteracting diabetic microangiopathy.

Petkov, Petko; and Donev, Stojco (Institut po Histologija i Embriologija, Medicinski Fakultet, Sofija, Bulgaria): THE PROBLEM OF *B*-GRANULE ULTRASTRUCTURE IN THE ENDOCRINE PANCREAS. Acta Diabetol. Lat. *10*:54-88, January-February 1973.

Verbatim summary. The ultrastructure of the granules of the endocrine pancreas in different mammals has been investigated by applying fixation with glutaraldehyde, osmium tetroxide, and potassium permanganate. The core of the granules has a globular, tubular, and crystalloid structure. The protein substance is preserved by fixation with glutaraldehyde and it "masks" the ultrastructure of granules. The ultrastructure of granules can best be observed after osmium fixation. The authors consider the ultrastructure of the core to be dependent on the molecular organization of the "carrier substance" to which insulin is bound. Insulin release is accompanied by changes both in the granule core and in the "halo," and especially in the elementary membrane.

Rayfield, E. J.; Curnow, R. T.; George, D. T.; and Beisel, W. R. (U.S. Army Med. Res. Inst., Frederick, Md.): IMPAIRED CARBOHYDRATE METABOLISM DURING A MILD VIRAL ILLNESS. N. Engl. J. Med. *289*:618-21, September 20, 1973.

The authors studied the effects of a viral illness, sandfly fever, on glucose tolerance in man. During the febrile phase of this illness there was impairment of the glucose tolerance. This was accompanied by increased insulin values, growth hormone values, plasma free fatty acids, and cortisol values. The basal glucagon values were also increased. The exact mechanism leading to the relative insulin resistant impairment in glucose tolerance was speculated on but no definite conclusion drawn concerning this matter. H.M.

Rogers, P. H.; Boden, Guenther; and Tourtellotte, C. D. (Temple Univ. Hospital, Philadelphia, Pa.): RELAPSING POLYCHONDRITIS WITH INSULIN RESISTANCE AND ANTIBODIES TO CARTILAGE. Am. J. Med. 55:243-48, August 1973.

The authors describe a patient with relapsing polychondritis associated with marked insulin resistance requiring up to 1,400 units of insulin a day. The patient had evidence of widespread immunologic dysfunction in addition to insulin antibodies, manifested by anticollagen antibodies, ANA presence, and a probably biologically false positive FTA-ABS test. The authors discuss in detail the possible relationship between the serologic abnormalities and the pathogenesis of relapsing polychondritis. R.P.E.