ABSTRACTS

Andersen, Ortved O. (Steno Memorial Hosp., Gentofte, Denmark): INSULIN ANTIBODY FORMATION. II. THE INFLUENCE OF SPECIES DIFFERENCE AND METHOD OF ADMINISTRATION. Acta Endocrinol. (Kbh) 72:33-45, January 1973.

The insulin-binding capacity of the plasma samples in sixty-three patients not previously treated with insulin was studied for a period of up to three years during which the patients received (a) Neutral Regular porcine insulin, (b) acid porcine insulin, (c) Neutral Regular bovine insulin, (d) Neutral porcine insulin in Protamine suspension (NPH), or (e) Neutral bovine insulin in Protamine suspensions (NPH). Forty-nine patients developed antibodies during the first six months of treatment. The lowest antibody titers were observed in patients who received Neutral porcine insulin. The titers in this group were significantly lower than those treated with acid porcine insulin, neutral bovine insulin or porcine NPH insulin. The antibody production in response to treatment with porcine NPH insulin was reduced significantly when this treatment was preceded by treatment with Neutral porcine insulin. In general, the capacity of the plasma to bind porcine insulin equaled its capacity to bind bovine insulin, respective of the type or species of the preparation the patients had received. The antigenicity of acid porcine insulin may be related to its possible transient precipitation during passage through the isoelectric zone in the process of neutralization. Furthermore, highly antigenic desamidoinsulin is formed more readily in an acid solution. An additional stimulation of the immune response of the host by corpuscular antigenic elements may explain not only the presence of greater antibody titers in patients receiving acid porcine insulin, but also in those receiving porcine or bovine NPH insulin. The diminution in antibody response to NPH insulin following antecedent therapy with Neutral porcine insulin may be the result of blockade of the receptors on the immunologically competent lymphocytes by a less antigenic form of insulin. The development of antibodies against both porcine and bovine insulin suggests that the antigenic groups within the insulin molecule or the special configuration of the molecule must be similar in these species. S.P.

Avogaro, P.; Capri, C.; Cazzolato, G.; and Pais, M. (Il Divisione Medica, Ospedale Regionale Generale, Venezia, Italy): LIPID DISORDERS IN DIABETES MELLITUS. Acta Diabetol. Lat. 9:540-61, July-August 1972.

Verbatim summary. Eighty-four diabetics were studied in order to ascertain the frequency and type of hyperlipemia in diabetes. In order to elucidate some aspects of the pathogenesis, some of the patients were put on a high-carbohydrate diet (75 to 80 per cent), some on a diet supplemented with saturated fats (butter ration equal to 30 per cent of total caloric intake) and others on nicotinic acid treatment (2 gm. per day for eight days). It was found that hyperlipemia is a very frequent accompaniment of diabetes but rarely attains a high degree; type II hyperlipemia is not very frequent whereas type IV is; there is also a mixed type and some cases of "sinking pre-B." Hyperlipemia, usually accompanied by a slight lipoprotein lipase deficiency, was unaffected by a high-carbohydrate or high-fat diet whereas both hyperlipemia and the pre-B band responded to nicotinic acid treatment. The mild hyperlipemia usually present in diabetes thus seems to be related to an increased influx of NEFA to the liver and to defective removal of VLDL from the plasma. In exceptional cases gross hyperlipemia complicates maturity-onset ketonuric diabetes. Here the responsible factor seems to be a combination of several pathologic genes rather than a pathogenetic interdependence with diabetes.

Barta, L.; Brooser, G.; and Molnar, M. (Semmelweis Orvostudomanyi Egyetem, I. Sz. Gyermekklinika, Budapest, Hungary): DIAGNOSTIC IMPORTANCE OF FLUORESCEIN ANGIOGRAPHY IN INFANTILE DIABETES. Acta Diabetol. Lat. 9: 290-98, March/April 1972.

Fluorescein angiography was performed in 111 juvenile diabetic patients with known duration of the disease for zero to fifteen years. Evidence of angiopathy could be found in the earliest stages of this disorder. Whereas the number of cases showing retinopathy on funduscopy increases with the duration of diabetes, the incidence of microaneurysms demonstrated by fluorescein angiography in the cases with normal funduscopic results were almost identical in the various age groups. The authors suggest that the retino-vascular changes revealed by fluorescein angiography must be considered a fundamental sign which appears to be independent of the metabolic changes. D.K.

Bruns, Waldemar (Zentralinstitut fur Diabetes "Gerhardt Katsch", Bereich Klinik Karlsburg, DDR): SIGNIFICANCE OF PYELONEPHRITIS IN DIABETES AND PROBLEMS OF DIAGNOSIS. REVIEW OF THE LITERATURE AND PERSONAL INVESTIGATIONS. Acta Diabetol. Lat. 9:46-73, February 1972.

Verbatim summary. The prevalence of pyelonephritis (PN) and urinary tract infections, the differential diagnosis between PN and diabetic nephropathy (dNP) and factors favoring the development of PN and its influence on diabetic angiopathy are discussed in the light of examinations of 4,074 diabetics, 307 nondiabetics and 106 cases with renal glucosuria. PN was found in 5.8 per cent and urinary tract infections in 19.9 per cent of diabetics, a total of 25.7 per cent; the comparative figures for nondiabetics and cases with renal glucosuria were 11.7 per cent and 12.25 per cent. The most important factor in the greater propensity of diabetics to PN is the existence of renal microangiopathy, i.e. glomerulosclerosis and arteriosclerosis, not glucosuria. Renal failure occurs earlier in cases with combined PN and diabetic nephropathy. The raised blood pressure due to PN makes for the more rapid progress of diabetic retinopathy. Problems of differential diagnosis of latent PN and diabetic nephropathy are described and discussed. Early detection and adequate therapy, plus maximum control of the diabetic metabolism, are the only means of checking the advance of renal lesions in diabetes.

Chowdhury, Faizur; and Bleicher, Sheldon J. (Jewish Hosp. and Med. Center of Brooklyn, Brooklyn, N.Y.): STUDIES OF TUMOR HYPOGLYCEMIA. Metabolism *22*:663-74, May 1973.

Fasting hypoglycemia in a patient with an intrathoracic mesothelioma was corrected by removal of the tumor. The patient had manifested hypoglycemia evolving slowly during fasting and corrected by exogenous glucagon; plasma IRI responses to provocative testing improved postoperatively; circulating insulin-like activity correlated well with IRI; the tumor exhibited a high rate of glucose uptake metabolized by anaerobic glycolysis and was unresponsive to insulin; only trace amounts of IRI or insulin-like activity were present in tumor homogenates. Plasma growth hormone, cortisol and FFA were not elevated before surgery but acute hypoglycemia, during an insulin tolerance test, elicited appropriate responses in these counter-regulatory factors. In this instance of tumor-induced hypoglycemia, it would appear that the rate of blood glucose fall may be too slow to trigger counter-regulatory responses until marked hypoglycemia develops and that an acquired form of glucagon deficiency may impair glucose counter-regulatory processes. C.R.S.

Drury, Michael I.; and Timoney, Francis J. (Mater Misericordiae Hospital, Dublin): ORAL HYPOGLYCAEMIC AGENTS AND CARDIOVASCULAR DEATHS IN DIABETES. Acta Diabetol. Lat. *9*:645-50, July-August 1972.

In this retrospective study, the authors have reviewed 284 deaths in maturity-onset diabetics. The proportion of cardiovascular deaths (approximately 70 per cent) was remarkably similar for the diet, insulin and oral drug-treated groups. D.K.

Eaton, R. P. (Dept. of Med., Univ. of New Mexico Sch. of Med., Albuquerque, N.M.): EFFECT OF CLOFIBRATE ON ARGININE-INDUCED INSULIN AND GLUCAGON SECRETION. Metabolism *22*:763-67, June 1973.

Serum insulin and glucagon levels rose promptly in the rat following arginine administered subcutaneously and intraperitoneally. Clofibrate therapy prevented arginine-stimulated insulin secretion while potentiating the simultaneous glucagon response. Other effects were noted, including a reduction in serum triglyceride, FFA, and VLDL protein. Clofibrate may induce a fall in the insulin/glucagon molar ratio which mediates in part the hypolipemic effects that occur simultaneously. C.R.S.

Ellenberg, Max (Dept. of Med., Mt. Sinai Hosp., New York, N.Y.): CURRENT STATUS OF DIABETIC NEUROPATHY. Metabolism *22*:657-62, May 1973.

Among the pathologic changes described in diabetic neuropathy are (1) thickening of the vasa nervorum and ischemic infarcts in mononeuropathies implicating the vascular system, (2) abnormalities in motor end-plates, and (3) segmental demyelination of the peripheral nerve fiber suggesting metabolic alterations in the Schwann cell. Electrophysiologic measurements have revealed early involvement of the nervous system (even at onset) in juvenile as well as in adult diabetes. Biochemical activity in spinal cord and peripheral nerves, dependence of insulin response on the presence of an intact axon and myelin sheath, and involvement of the polyol pathway in intermediary metabolism of diabetic neural tissue have been shown. The variability of nervous system involvement in diabetes suggests that neuropathy is a concomitant rather than a complication of the disease. C.R.S.

Federspil, G.; Zaccaria, M.; Reffo, G. C.; and De Palo, C. (Instituto di Semeiotica Medica, Universita di Padova, Padova, Italy): METABOLIC EFFECTS OF NEUTRAL RED IN RATS. Acta Diabetol. Lat. *9*:562-76, July-August 1972.

Verbatim summary. Metabolic responses to neutral red administration were studied in normal and hypophysectomized rats. In normal animals neutral red causes a marked increase in blood glucose and lactic acid. The plasma glycerol increases very slightly but significantly, whereas the plasma FFA do not show a significant increase. After DHE—an adrenergic blocking agent of hepatic glycogenolysis—neutral red induces a decreased but still evident hyperglycemic response. In hypophysectomized rats all metabolic responses to neutral red are abolished. These results suggest that neutral red causes hyperglycemia by releasing glucagon from A_2-cells, the glucagon in its turn causing the release of catecholamines from the adrenals. Both glucagon and catecholamines might be responsible for the lipolytic effect of neutral red. The influence of the hypophysis on these metabolic phenomena is discussed.

Ghidoni, A.; Sanesi, E.; Melogli, O.; Tognetti, A.; Pappalettera, A.; and Pozza, G. (Instituto di Clinica Medica, I dell' Universita, Milano, Italy): IN VITRO METABOLISM OF ISOLATED HUMAN FAT CELLS. IV. EFFECT OF THE INSULIN OF OTHER SPECIES ON NOREPINEPHRINE-INDUCED LIPOLYSIS. Acta Diabetol. Lat. *9*:595-602, July-August 1972.

The authors studied the antilipolytic effect of insulin on norepinephrine-induced lipolysis. Minimum insulin concentration of human insulin capable of exerting a definite antilipolytic action was determined. At this concentration, the antilipolytic activity varied with the change in species source of insulin. Human insulin was most effective (93 per cent) and bovine was least (67.5 per cent). Porcine insulin was intermediate (70.8 per cent). Dealanated porcine was better than porcine but less efficacious than human insulin. D.K.

Goldner, Andrew M. (Dept. of Human Physiol., Univ. of Calif. Med. Sch., Davis, Calif.): SODIUM-DEPENDENT SUGAR TRANSPORT IN THE INTESTINE. Metabolism *22*:649-56, May 1973.

Transport of sugars across the brush border membrane of intestinal epithelial cells is dependent on the presence of sodium in the mucosal bathing medium. In the absence of sodium, the reactions of cellular accumulation, transmural transport and unidirectional influx of sugars are inhibited. Sodium influx is stimulated by the influx of sugar suggesting that sugar binds to a membrane site in the presence of sodium for translocation into the epithelial cell. The driving force for sugar transport is postulated as the electrochemical gradient for sodium or other ions across the membrane and not a direct input of metabolic energy. Sodium-dependent sugar transport in the intestine can be considered an example of co-transport. C.R.S.

Hansen, Aage Prange (Second Univ. Clinic Intern. Med., Aarhus, Denmark): SERUM GROWTH HORMONE PATTERNS IN FEMALE JUVENILE DIABETICS. J. Clin. Endocrinol. Metab. *36*:638-46, April 1973.

Dr. Hansen finds higher than normal concentrations of serum growth hormone in twenty young nonobese women with juvenile diabetes matched with twenty-four young non-

obese control females. These groups included normally menstruating women as well as women taking oral contraceptives. Serum growth hormone level in the daytime was three to four times higher and more fluctuating and the exercise response occurred earlier and was higher in the diabetics than in the controls. In previous studies Dr. Hansen has clearly shown that growth hormone levels are higher than normal in male juvenile diabetics under various circumstances than in normal males. It can be concluded from this study that women likewise are exposed throughout their daily life to elevated and rapidly changing levels of human growth hormone. T.J.M.

Hilwig, I. (Farbwerke Hoechst AG, Gewebezuchtung H 811, Bundesrepublik, Germany): MONOLAYER CULTURES OF PANCREATIC TISSUE. IV. INVESTIGATIONS OF INSULIN SECRETION AND THE INFLUENCE OF HETEROLOGOUS INSULIN. Acta Diabetol. Lat. 9:577-94, July-August 1972.

Verbatim summary. This article deals with the insulin secretion of monolayer cultures of pancreatic tissue of adult rats and newborn pigs. The amount of insulin released diminishes with increasing age of the cells growing in vitro. The insulin content of the nutrient medium is a function of the insulin released and the insulin metabolized by the cells. The amount of insulin yielded during the growth period in vitro depends on the frequency with which the nutrient medium is changed. Adding heterologous insulin to the culture medium influences, i.e. inhibits, insulin release, provided the cells consume insulin at a constant rate. The inhibitory concentration (we assume) depends on the metabolic condition of the cells in vitro.

Ishii, Hiromasa; Joly, Jean-Gil; and Lieber, Charles S. (Dept. of Med., Mt. Sinai Sch. of Med. of the City Univ. of N.Y. and Section of Liver Disease and Nutrition, V.A. Hosp., Bronx, N.Y.): INCREASE OF MICROSOMAL GLUCOSE-6-PHOSPHATASE ACTIVITY AFTER CHRONIC ETHANOL ADMINISTRATION. Metabolism *22*:799-806, June 1973.

The effect of chronic ethanol administration on the activity of hepatic microsomal glucose-6-phosphatase was examined in pair-fed rats receiving part of their total calories either as ethanol or isocaloric carbohydrate. In another experiment, fat was substituted isocalorically in place of carbohydrate for the control group. The ethanol-fed rats exhibited a significant increase in glucose-6-phosphatase activity over that observed in both control groups. Ultracentrifugation to separate rough and smooth microsomes revealed that the increase in enzyme activity after ethanol feeding occurred mainly in the smooth microsomal membranes. C.R.S.

Johansen, Klaus (Second Univ. Clinic of Intern. Med. and the Neurolog. Dept., Aarhus Univ. Sch. of Med., Aarhus, Denmark): GLUCOSE-SUPPRESSIBLE GROWTH HORMONE RELEASE AFTER L-DOPA ADMINISTRATION TO NORMAL SUBJECTS. Metabolism *22*:773-78, June 1973.

Oral doses of L-dopa increased the levels of plasma growth hormone in normal subjects, an effect which is suppressed by oral glucose ingestion. Glucose-induced suppressibility of growth hormone secretion after L-dopa administration suggests that dopamine may play a role in the normal regulation of growth hormone release from the pituitary. C.R.S.

Johnson, P. R.; Stern, J. S.; Greenwood, M. R. C.; Zucker, L. M.; and Hirsch, J. (Rockefeller Univ., New York, N.Y., and Harriet G. Bird Memorial Lab., Read Acre Rd., Stowe, Mass.): EFFECT OF EARLY NUTRITION ON ADIPOSE CELLULARITY AND PANCREATIC INSULIN RELEASE IN THE ZUCKER RAT. J. Nutr. *103*:738-42, May 1973.

Preweaning nutritional manipulation in the Zucker rat interacts with genotype to influence growth and adipose tissue morphology but not pancreatic insulin release. Zucker obese and nonobese male rats were over- or underfed prior to weaning by placement in large or small litters, respectively. During the first thirty days of life the nutritional effect and not the genotype was the predominant influence on the animals' growth. By twelve weeks of age genotypic differences became the major determinant of body weight. While early overfeeding significantly increased adipocyte number in both the obese and nonobese rats, early underfeeding reduced adipocyte number only in the nonobese. The release of immunoreactive insulin from isolated pancreatic islets was a function of the animal's genotype and was uninfluenced by the early nutritional treatment. Obese rats released three to four times as much immunoreactive insulin as did their nonobese controls. T.J.M.

Lucke, C.; Kagan, A.; and Glick, S.M. (Coney Island Hosp., Brooklyn, N.Y.): BIOLOGICAL AND IMMUNOLOGICAL ACTIVITY OF BOILED INSULIN. Acta Diabetol. Lat. 9:651-54, July-August 1972.

Commercially available Regular beef insulin was exposed for twenty minutes to 100° C. The immunological and biological potencies of this insulin remained unaffected. D.K.

Moses, Arnold M.; Numann, Patricia; and Miller, Myron (V.A. Hosp. and Dept. of Med. and Surg., State Univ. of N.Y., Upstate Med. Center, Syracuse, N.Y.): MECHANISM OF CHLORPROPAMIDE-INDUCED ANTIDIURESIS IN MAN: EVIDENCE FOR RELEASE OF ADH AND ENHANCEMENT OF PERIPHERAL ACTION. Metabolism *22*:56-66, January 1973.

An antidiuretic effect of chlorpropamide was demonstrated in healthy subjects receiving a water load. During these experiments, urinary antidiuretic hormone (ADH) measured by radioimmunoassay was undetectable or low without drug treatment. When chlorpropamide was given, ADH excretion was significantly increased. Administration of the drug to patients with diabetes insipidus receiving intravenous Pitressin did not increase urinary excretion of ADH. Three patients with absence of ADH activity were found to have a greater response in urine osmolality in response to ADH when chlorpropamide was given than when the drug was withheld. Water-loaded patients with diabetes insipidus given chlorpropamide had a significant decrease in their ability to excrete a dilute urine than did normal subjects. These experiments indicate that chlorpropamide acts centrally in augmenting the release of ADH or preventing the inhibitory effect of water loading on the release of ADH, and augments the renal effects of ADH. In addition, patients with impaired ability to synthesize and release ADH were found to be more responsive than normal subjects to the antidiuretic action of chlorpropamide. C.R.S.

Muggeo, M.; Fedele, D.; Bagnariol, G.; Tiengo, A.; and Crepaldi, G. (Clinica Medica-Policlinico, Padova, Italy): INSULIN PRODUCTION IN THE POST-GASTRECTOMY HYPOGLYCEMIC SYNDROME. Acta Diabetol. Lat. 9:603-30, July-August 1972.

Verbatim summary. Seven postgastrectomy patients suffering from the late hypoglycemic syndrome were subjected to

oral (100 gm.) and intravenous glucose (20 gm.) tolerance tests. Nine symptom-free postgastrectomy patients and ten normal subjects were tested as controls. The OGTT induced a more marked plasma IRI response in the postgastrectomy patients with hypoglycemia than in both those without and in normals. This hyperinsulinism preceded the hypoglycemic phase, which became manifest three to four hours after loading. The blood glucose curve presented an earlier and more marked rise in the postgastrectomy patients with the hypoglycemic syndrome compared to patients without this syndrome and to normals (lag storage effect). The hyperinsulinism does not, however, seem to correlate with the initial hyperglycemia only since there was no relation between blood glucose and IRI levels. Further, the hyperglycemia induced by intravenous glucose, though similar in extent to that induced by the oral test, induced a smaller IRI response, not different from that obtained in the symptomless postgastrectomy patients. Other insulin-stimulant factors, such as enteroglucagon and other gut hormones, produced by the intestine in abnormal quantity, together with hyperglycemia, are the most probable cause of the late hypoglycemic syndrome of postgastrectomy patients.

Oseid, Svein (Pediatric Res. Inst., Rikshospitalet, Univ. of Oslo, Oslo, Norway): STUDIES IN CONGENITAL GENERALIZED LIPODYSTROPHY (SEIP-BERARDINELLI SYNDROME). I. DEVELOPMENT OF DIABETES. Acta Endocrinol. (Kbh) *72*:475-94, March 1973.

Six patients with this entity have been studied at different ages from infancy to adolescence. During the first few years of life, fasting plasma glucose was normal and fasting plasma insulin was normal or slightly increased. In response to oral glucose, plasma glucose curve was normal but the increases in plasma insulin were exaggerated and prolonged. Some degree of insulin resistance was already present. Between the ages of eight and ten years, fasting plasma glucose was normal or only moderately elevated, while marked increases in fasting plasma insulin occurred. Glucose tolerance diminished; insulin release evoked by oral or intravenous glucose or by tolbutamide was exaggerated. Cortisone-provocative glucose tolerance tests became abnormal, and marked insulin resistance became manifest. In one patient, who was followed beyond the age of twelve, fasting hyperglycemia and fasting hyperinsulinemia were present; the plasma insulin response to oral glucose diminished. These findings indicate that the insulinogenic capacity of the pancreatic islets diminishes with age. The mechanism of insulin resistance seen in these patients may be causally related to the lack of adequate amounts of fat tissue necessary for the disposal of glucose. S.P.

Pagliara, Anthony S.; Karl, Irene E.; DeVivo, Darryl C.; Feigin, Ralph D.; and Kipnis, David M. (Dept. of Med. and Edward Mallinckrodt Dept. of Pediatr., Washington Univ. Sch. of Med., St. Louis, Mo.): HYPOALANINEMIA: A CONCOMITANT OF KETOTIC HYPOGLYCEMIA. J. Clin. Invest. *51*: 1440-49, June 1972.

Eight ketotic hypoglycemic children were studied to determine whether the primary defect in this condition is a deficiency of one or more gluconeogenic precursors or an abnormality in the hepatic gluconeogenic enzyme system. On a normal diet, overnight fasting plasma alanine and glucose were significantly lower and plasma β-hydroxybutyrate significantly higher in ketotic hypoglycemic children than in controls. All patients had symptomatic hypoglycemia and ketosis eight to sixteen hours after starting a hypocaloric low-carbohydrate diet containing 68 per cent fat; plasma alanine declined even further. Normal children, even after thirty-six hours on this diet, maintained higher plasma glucose and alanine and had lower β-hydroxybutyrate levels. Intravenous infusion of alanine uniformly restored the hypoglycemic plasma glucose levels to normal. Oral cortisone acetate treatment combined with the diet produced a marked increase in plasma alanine within four to six hours and completely prevented the development of hypoglycemia and ketosis. When amino acid profiles were determined quantitatively, alanine was found to be the only amino acid which differed significantly between the two groups. Plasma insulin and blood lactate and pyruvate levels were similar in both groups under all conditions examined. These results support the hypothesis that a deficiency in gluconeogenic precursor, such as alanine, rather than a defect in the hepatic gluconeogenic enzyme apparatus represents the most likely factor in the pathogenesis of ketotic hypoglycemia. S.P.

Phang, James M.; Downing, Sylvia J. (Metabolism Branch, Natl. Cancer Inst., Nat. Inst. of Health, Bethesda, Md.): AMINO ACID TRANSPORT IN BONE: STIMULATION BY CYCLIC AMP. Am. J. Physiol. *224*:191-96, January 1973.

Verbatim summary. Cyclic adenosine 3',5'-monophosphate, N^6-2'-0-dibutyryl cyclic adenosine 3',5'-monophosphate (DB-cAMP), as well as parathyroid hormone and prostaglandin E_1, activators of skeletal adenylate cyclase, all stimulate amino acid uptake in fetal rat calvaria. Increased collagen synthesis accompanied the cyclic nucleotide-mediated increase in proline uptake. Characteristics of the stimulatory effect on amino acid uptake suggest that DB-cAMP augments the synthesis of a component of the sodium-dependent transport mechanism. Although insulin and DB-cAMP stimulate the same transport mechanism, evidence suggests that they act at different sites.

Podolsky, Stephen; and Pattavina, Catherine G. (Dept. of Med., Boston Univ. Sch. of Med., and the Medical and Nuclear Med. Serv., V.A. Hosp., Boston, Mass.): HYPEROSMOLAR NONKETOTIC DIABETIC COMA: A COMPLICATION OF PROPRANOLOL THERAPY. Metabolism *22*:685-93, May 1973.

A hypertensive patient treated with apresoline and propranolol was observed on two occasions to develop hyperosmolar nonketotic diabetic coma. Studies revealed a diabetic tolbutamide tolerance test, which was repeated following intravenous propranolol resulting in a further diminution of the insulin response. When all treatment was withheld, the patient developed hyperglycemia and an elevation of FFA. Propranolol was then administered resulting in marked hyperglycemia without a similar elevation of FFA. These observations suggest that propranolol may precipitate hyperosmolar nonketotic coma in an untreated diabetic by blockage of lipolysis and impairment of insulin responses. C.R.S.

Reaven, Eve P.; Peterson, Daniel T.; and Reaven, Gerald M. (Dept. of Med., Stanford Univ. Sch. of Med., and Palo Alto V.A. Hosp., Palo Alto, Calif.): THE EFFECT OF EXPERIMENTAL DIABETES MELLITUS AND INSULIN REPLACEMENT ON HEPATIC ULTRASTRUCTURE AND PROTEIN SYNTHESIS. J. Clin. Invest. *52*:248-62, February 1973.

Verbatim summary. The following study was conducted in order to define the specific alterations in hepatic ultrastructure

responsible for the decrease in hepatic protein synthesis associated with experimental diabetes. Rats received intravenous alloxan (70 mg. per kilogram) and forty-eight hours later were either sacrificed or given insulin for 1, 2, 4, 6, or 24 hours. Specimens for electron microscopic evaluation and morphometric analysis were taken from the same livers used to isolate ribosomes for measurement of in vitro protein synthesis. Our results show that hepatocytes from animals with untreated alloxan diabetes show varying degrees of disorganization and loss of rough endoplasmic reticulum (RER) which is directly related to the severity of the alloxan diabetes. A significant correlation existed between the severity of ultrastructural changes as judged by the loss of both membrane and polysome components of the RER and degree of inhibition of protein synthesis ($P < 0.001$). Abnormalities of hepatic ultrastructure and protein synthesis were reversed within twenty-four hours of insulin administration. The data are consistent with the view that it is the relative decrease in hepatic polysomes that results from the loss of RER in alloxan diabetes that is responsible for the decrease in hepatic protein synthesis.

Reese, Andy C.; Landau, Bernard R.; Craig, James W.; Gin, Gary; and Rodman, Harvey M. (Dept. of Med., Case Western Reserve Univ. Sch. of Med., Cleveland, Ohio): GLUCOSE METABOLISM BY RAT PANCREATIC ISLETS IN VITRO. Metabolism *22*:467-72, March 1973.

The uptake of labeled glucose and its oxidation to CO_2 by isolated rat islets were in accord with linear increments associated with increasing concentrations of glucose in the medium. Saturation of glucose uptake was observed at high concentrations. Between 62 and 76 per cent of glucose uptake was converted to CO_2 and lactate. The amounts of labeled CO_2 and lactate were similar at low glucose concentrations, but lactate decreased to less than one-half the amount of CO_2 at high glucose concentrations, indicating that lactate is not the major product of glucose metabolism in this preparation. Localization of carbon 1 of glucose in carbon 3 of lactate indicates that lactate was formed without randomization via pyruvate in the Krebs cycle. C.R.S.

Sando, Hiroyuki; Borg, Jo; and Steiner, Donald F. (Dept. of Biochem., Univ. of Chicago, Pritzker Sch. of Med., Chicago, Ill.): STUDIES ON THE SECRETION OF NEWLY SYNTHESIZED PROINSULIN AND INSULIN FROM ISOLATED RAT ISLETS OF LANGERHANS. J. Clin. Invest. *51*:1476-85, June 1972.

Rat pancreatic islets were incubated for two hours in low glucose and for two additional hours in high glucose medium. During the first hour of incubation the medium contained 3-H-leucine. The islets were extracted with acid alcohol. Total insulin activity in the media and islet extracts were determined by radioimmunoassay. Proinsulin and insulin components of insulin immunoreactivity were identified by gel filtration.

Amount of proinsulin and insulin released into the incubation medium increased progressively. Concentration of proinsulin in the medium and in the extracts of the islets was approximately 6 per cent of that of insulin. The extent of conversion of proinsulin to insulin increased during incubation. The specific radioactivity of proinsulin was the same in the medium and in the islet extracts; it decreased progressively during incubation. The specific activity of insulin was always higher in the medium than in the islet extract; the greatest difference was observed at the third hour of incubation.

Similar experiments were conducted with the addition of cycloheximide to the incubation medium after the first hour, thus inhibiting protein synthesis. With cycloheximide less proinsulin was released than without cycloheximide; the pattern of insulin release was not altered. The contribution of proinsulin to the total immunoreactivity declined progressively in the medium as well as the islet extracts. Islet extracts contained less proinsulin than the medium during all phases of incubation with cycloheximide. The conversion of proinsulin to insulin was not altered. The specific radioactivity of proinsulin failed to decline in the medium or in the islet extracts. The specific activity of insulin was essentially unaltered by cycloheximide.

During further experiments with the addition of dibutyryl cyclic AMP to the incubation medium during the post-labeling period, the release of insulin was augmented while other parameters were not altered.

These results suggest that the major portion of insulin released by isolated islets in response to glucose is derived from pre-existing stores in the secretory granules. There were no indications of the existence of independent pathways of secretion of proinsulin or insulin not associated with the secretory granules. S.P.

Woo, Yin-Tak; and Manery, J. M. (Dept. of Biochem., Univ. of Toronto, Toronto, Canada): CYCLIC AMP PHOSPHODIESTERASE ACTIVITY AT THE EXTERNAL SURFACE OF INTACT SKELETAL MUSCLE AND STIMULATION OF THE ENZYME BY INSULIN. Arch. Biochem. Biophys. *154*:510-19, February 1973.

There is ample evidence that cyclic AMP participates in many cellular reactions and is the intracellular agent which mediates the actions of a number of hormones. The concentration of intracellular cyclic AMP is regulated by its formation from ATP by adenylcyclase, its degradation to AMP by cyclic AMP phosphodiesterase and possibly by its extrusion into extracellular fluid. In the present work experiments were carried out to characterize phosphodiesterase activity utilizing the surface of isolated intact frog muscles. Small intact frog skeletal muscles were exposed to radioactively labeled cyclic AMP during incubation in frog Ringer's solution buffered with Tris. The fate of the nucleotide was followed by measuring the products in the incubation medium. Paper chromatography was used for the separation and identification of these products. The amounts were measured using liquid scintillation spectrophotometry. It was found that cyclic AMP was degraded and then converted to IMP and to some extent, inosine. The degradation of cyclic AMP to AMP was markedly inhibited by theophylline (10 mM.) suggesting the presence of cyclic AMP phosphodiesterase activity at the muscle surface. Kinetic studies of enzyme activity in situ revealed two K_m values: .33 μmoles and 55 μmoles. Insulin (.3 U. per milliliter) increased the phosphodiesterase activity at concentrations of cyclic AMP ranging from 2 to 17 μmoles. T.M.