ABSTRACTS

Conn, H. O. (Med. Serv., Veterans Administration Hosp., West Haven, Conn.; and Dept. of Intern. Med., Yale Univ. Sch. of Med., New Haven, Conn.): CIRRHOSIS AND DIABETES. IV. EFFECT OF POTASSIUM CHLORIDE ADMINISTRATION ON GLUCOSE AND INSULIN METABOLISM. Amer. J. Med. Sci. *259*: 394-404, June 1970.

Verbatim summary. Potassium depletion has been associated with glucose intolerance in primary and secondary aldosteronism, in uremia, and after the administration of kaliuretic drugs. The common occurrence of both potassium depletion and diabetes in Laennec's cirrhosis suggested a causal relationship. Serum glucose and insulin responses to oral and intravenous glucose tolerance tests were measured in ten stable cirrhotic patients before and after the administration of 120 to 180 mEq KCl daily for at least ten days. Oral glucose tolerance, which was abnormal in all ten patients before KCl became normal in five after KCl. Total insulin increments, which were greatly increased before potassium in these patients, were not significantly changed after KCl. The five patients whose glucose tolerance improved after KCl were characterized before KCl administration by mild impairment of glucose tolerance and by the presence of an immediate, vigorous insulin response to intravenous glucose, findings compatible with an early abnormality of carbohydrate metabolism. The patients who failed to improve after KCl had had more severely impaired glucose tolerance and a diminished or absent prompt insulin response to intravenous glucose, abnormalities suggestive of more advanced impairment of carbohydrate metabolism. Although the mechanism of the potassium-associated improvement is not known, it was not associated with an increased insulin response, the expected consequence of potassium repletion.

Curry, Donald L. (Dept. of Physiol. Science, Sch. of Vet. Med., Univ. of California, Davis, Calif.): IS THERE A COMMON BETA CELL INSULIN COMPARTMENT STIMULATED BY GLUCOSE AND TOLBUTAMIDE? Amer. J. Physiol. *220*:319-23, February 1971.

Verbatim summary. Studies were done in which pancreatic preparations were subjected to several sequential periods of stimulation, either by glucose (300 mg./100 ml.) or tolbutamide (20 mg./100 ml.). The pattern of insulin secretion and the total amount of hormone released were determined. With either agent the successive periods of stimulation resulted in progressively decreasing rates of insulin secretion. This is probably due to a depletion of insulin from a hormonal storage compartment. When both glucose and tolbutamide were administered to the same preparations, either successively or concomitantly, the insulin secretory pattern and the total quantity of insulin released were similarly depleted. This suggests that the insulin secreted was released from the same storage site within the beta cell, regardless of whether the stimulation was induced by glucose or by tolbutamide.

Daughaday, William; and Boniuk, Isaac (Dept. of Med., Jewish Hosp. of St. Louis; and Washington Univ. Sch. of Med., St. Louis, Mo.): DIABETIC RETINOPATHY. JAMA *214*:1867-72, Dec. 7, 1970.

This is a brief and straightforward Therapeutic Grand Rounds discussion of current concepts of the pathophysiology and treatments for diabetic retinopathy. The references are pertinent and up to date. Pathophysiology and the use of pituitary ablative therapy are discussed by Dr. William Daughaday, and Dr. Isaac Boniuk discusses the ophthalmologic approach including photocoagulation. D.R.C.

Friedman, Meyer; Rosenman, Ray H.; Byers, Sanford O.; and Elevitch, Franklin R. (Harold Brunn Inst., Dept. of Clin. Path., Mount Zion Hosp. Med. Center, San Francisco, Calif.): EFFECT OF LOW SUGAR INTAKE UPON BLOOD LIPIDS AND INSULIN LEVELS OF HYPERLIPEMIC SUBJECTS. Proc. Soc. Exp. Biol. Med. *135*:785-91, December 1970.

Verbatim summary. The intake of simple sugars of six moderately hypertriglyceridemic, hypercholesterolemic subjects was reduced for sixty days. This restriction led to a moderate weight loss, a normalization of their previously elevated pre-beta lipoprotein levels and a moderate decrease in their pre- and postprandial hypertriglyceridemia. The elevated serum cholesterol and pre- and postprandial serum insulin levels were not normalized by the dietary change.

Gang, Nicholas F. (Jewish Gen. Hosp., Montreal, Quebec, Canada, and Mount Sinai Sch. of Med., City Univ., New York, N.Y.): ULTRASTRUCTURE OF THE GLOMERULAR BASEMENT MEMBRANE AS VISUALIZED BY LANTHANUM. Proc. Soc. Exp. Biol. Med. *135*:223-27, November 1970.

Verbatim summary. Cortical tissues from the kidneys of rats were infused with a suspension of lanthanum hydroxide, or were placed in fixatives containing lanthanum to visualize intermolecular spaces in the glomerular basement membrane. Lanthanum particles were seen in aggregates throughout the basement membrane. The diameter of the aggregates varied between 20 and 200 Å. The diameter of the majority of aggregates ranged from 40 to 75 Å. Aggregates with diameters greater than 150 Å were located mainly in the lamina rara interna, less in the lamina rara externa.

It is concluded that the basement membrane is a random porous molecular filter and the lamina densa is the rate limiting structure in the glomerular filtration of macromolecules.

Halperin, M. L.; and Robinson, B. H. (Univ. of Toronto Sch. of Med., St. Michael's Hosp., Univ. of Toronto, Dept. of Biochem., Toronto, Canada): MECHANISM OF INSULIN ACTION ON CONTROL OF FATTY ACID SYNTHESIS INDEPENDENT OF GLUCOSE TRANSPORT. Metabolism 20:78-86, January 1971.

In white adipose tissue of the rat insulin causes a thirtyfold increase in the rate of glucose conversion to fatty acid in vitro. Glucose conversion to fatty acid is limited by accumulation of cytoplasmic $NADH_2$ which lowers intracellular pyruvate concentration. Insulin in the absence of glucose stimulated pyruvate conversion to fatty acid in adipose tissue of normal fed and starved rats. These data indicate that insulin in the rat augments fatty acid synthesis by increasing substrate levels of pyruvate and also by increasing pyruvate incorporation into fatty acids by a mechanism distinct from the stimulation of glucose transport. C.R.S.

Han, Paul W.; and Frohman, Lawrence A. (Dept. of Physiol., Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.; and Dept. of Med., State Univ. of New York, Buffalo, N.Y.): HYPERINSULINEMIA IN TUBE-FED HYPOPHYSECTOMIZED RATS BEARING HYPOTHALAMIC LESIONS. Amer. J. Physiol. *219*: 1632-36, December 1970.

Verbatim summary. Twenty-one hypophysectomized, hypothalamic rats bearing bilateral VM lesions and ten sham-operated hypophysectomized controls were tube fed equal amounts of a liquid diet for twenty-eight days. Blood samples were collected on the day of hypothalamic operation and on the 5th, 13th, 19th, and 28th postoperative (PO) days for measurement of plasma glucose and insulin levels. Plasma insulin levels of the lesioned rats were consistently higher than those of the control rats beginning with the fifth PO day. Plasma glucose levels of the former were also slightly higher than those of the latter on most of the PO days. Pancreatic insulin concentration was identical in both groups of rats. These results along with the fact that lesioned rats accumulated more fat than did the control rats support the idea that the endocrine pancreas is directly involved in the development of hypothalamic obesity and establish that the hyperinsulinemia can develop in the absence of both hyperphagia and pituitary hormones.

Hendler, E. W. (Laboratory of Biochemistry, National Heart and Lung Inst., Bethesda, Md.): BIOLOGICAL MEMBRANE ULTRASTRUCTURE. Physiol. Rev. *51*:66-97, January 1971.

This is a comprehensive review of the historical development of basic concepts of membrane structure. Considering the well established actions of insulin on the cellular membrane, such a discussion of current problems regarding membrane structure is worthwhile to those working in the research of diabetes mellitus. The authors begin with a consideration of the early proposal of Daneilli and Harvey. They consider the evidence both for and against the Unit-Membrane hypothesis, and present in a concise manner the major modifications and alternative conclusions for the membrane ultrastructure. They conclude that the lipo-bilayer idea remains the best over-all view at the moment. T.J.M.

Hunter D. J. S. (Dept. of Obstet. & Gynec., Univ. of Dundee, Dundee, Scotland): CHANGES IN BLOOD GLUCOSE AND LIVER CARBOHYDRATE AFTER *INTRAUTERINE INJECTION OF* GLUCAGON INTO FOETAL RATS. J. Endocr. *45*:367-74, 1969.

Verbatim summary. Maternal blood glucose, fetal blood glucose and liver carbohydrate levels were estimated after fetuses were injected with glucagon through the uterine wall on Days 19½, 20½, and 21½ of gestation in the rat.

Glucagon had a hyperglycemic effect in the fetus on all the days studied but the response was greater and more rapid on Day 21½ of gestation. Glucagon was shown to decrease liver glycogen on Days 20½ and 21½, but again the response was more rapid and more pronounced on Day 21½.

The normal levels of fetal liver glycogen were similar to those previously found but the normal fetal blood glucose values are lower than previous results. Decrease in liver glycogen observed in the control group of fetuses on Day 21½ of gestation together with a loss in feto-maternal blood glucose relationship on that day of gestation suggest that on Day 21½ the fetal rat develops the ability to mobilize hepatic glycogen and therapy to alter its blood glucose level independently from the mother.

The significance of the low blood glucose levels found in the fetus is discussed.

Jungas, Robert L. (Dept. Biological Chem., Harvard Med. Sch., Boston, Mass.): HORMONAL REGULATION OF PYRUVATE DEHYDROGENASE. Metabolism 20:43-53, January 1971.

Fatty acid synthesis in rat epididymal adipose tissue is accelerated by insulin demonstrated by conversion of medium lactate or pyruvate or endogenous glycogen to fatty acids. The activity of pyruvate dehydrogenase affecting conversion of pyruvate to CO_2 and acetyl CoA was elevated in tissues exposed to insulin prior to homogenization. Exposure to epinephrine resulted in an inhibition of the enzyme initially but after thirty minutes led to enhanced activity. This enhancement did not occur when insulin was present with epinephrine. Modification of the activity of pyruvate dehydrogenase in rat adipose tissue by the hormones insulin and epinephrine has been demonstrated as another regulatory factor in glucose conversion to fatty acids. C.R.S.

LaNoue, Kathryn F.; and Williamson, John R. (Johnson Res. Found., Univ. of Pennsylvania, Philadelphia, Pa.): INTERRELATIONSHIPS BETWEEN MALATE-ASPARTATE SHUTTLE AND CITRIC ACID CYCLE IN RAT HEART MITOCHONDRIA. Metabolism 20:119-40, February 1971.

Using rat heart mitochondria the basic control properties of the citric acid cycle were investigated under various metabolic conditions. The results suggest that control properties of the cycle separate it into two spans, one between acetyl CoA entry and α-ketoglutarate and the other between α-ketoglutarate and oxalacetate. Comparison of changes in metabolite levels after addition of pyruvate or acetylcarnitine showed that cycle flux was primarily controlled by citrate synthase which appeared to be regulated by intramitochondrial oxalacetate concentration. Thus greater emphasis has been placed on this level of control and less on acetyl CoA content. The intramitochondrial oxalacetate concentration is regulated by malate and the NAD/NADH ratio and is a key metabolite affecting both α-ketoglutarate and aspartate efflux. NADH transport via the malate-aspartate shuttle was investigated under a variety of conditions. Using mitochondria supplemented with the extramitochondrial components of the malate-aspartate shuttle verification of the role of these factors in regulation of the transport of reducing equivalents was obtained. C.R.S.

Malaisse, Willy J.; Brisson, Guy; and Malaisse-Lagae, Francine (Labs. of Exp. Med., and Anatomo-Path., Université Libre de Bruxelles, Brussels, Belgium): THE STIMULUS-SECRETION COUPLING OF GLUCOSE-INDUCED INSULIN RELEASE. I. INTERACTION OF EPINEPHRINE AND ALKALINE EARTH CATIONS. J. Lab. Clin. Med. 76:895-902, December 1970.

Extracellular calcium is a prerequisite for insulin secretion by the perfused rat pancreas or slices of pancreas. This investigation studies the role of calcium in permitting insulin release. Pieces of rat pancreas weighing about 8 mg. each were incubated for sixty to ninety minutes in buffered bicarbonate-albumin medium containing guinea pig anti-insulin serum and the rate of insulin secretion during incubation was estimated by measuring the fall in insulin antibody concentration in the medium. Concentrations of Ca^{++}, Mg^{++} or Ba^{++} were varied during different runs and various substances such as epinephrine, theophylline, 3':5'-c AMP and ATP were added to certain flasks. Glucose 200 to 300 mg. per 100 ml. was usually added. When Ca^{++} was omitted insulin release was markedly reduced but this effect was obviated by adding as little as 0.5 mEq. of Ca per L. Omission of Mg did not influence insulin secretion but high concentrations of Mg^{++} (20 mEq./L.) inhibited secretion. Because the inhibitory effect of epinephrine on insulin secretion has been attributed to a decrease in c AMP, the combined effects of adding epinephrine and db-c-AMP were studied. Epinephrine alone markedly reduced glucose induced insulin secretion but db-c-AMP did not reverse this. When theophylline was used to increase c-AMP the addition of epinephrine abolished its stimulatory effect. Addition of Ba^{++} restored normal secretion with either absent Ca^{++} or high Mg^{++}. It is hypothesized that Ca^{++} influx in the beta cell might trigger the release of insulin and that epinephrine might suppress insulin secretion by blocking that influx. T.G.S.

Mehlman, Myron A.; Therriault, D. G.; and Tobin, R. B. (Dept. of Biochem., Univ. of Nebraska Coll. of Med.; Veterans Administration Hosp., Omaha, Neb.; and U.S. Army Res. Inst. for Environmental Med., Natik, Mass.): CARNITINE-C-14 METABOLISM IN CHOLINE-DEFICIENT, ALLOXAN-DIABETIC CHOLINE-DEFICIENT AND INSULIN-TREATED RATS. Metabolism 20:100-07, January 1971.

The body pool, turnover time and tissue levels of carnitine were measured in choline-deficient animals. The muscle carnitine of choline-deficient and alloxan diabetic choline-deficient animals was greatly decreased below that of normal rats and insulin-treated alloxanized choline-deficient animals. The turnover time for carnitine in all choline-deficient animals was lower than that of normal rats. The results indicate that the decreased body pool of carnitine in choline deficiency in rats is due to a decrease in turnover time and an increased metabolism of carnitine. C.R.S.

Milunsky, Aubrey; Bray, George A.; Londono, Javier; and Loridan, Liliane (Depts. of Pediat. and Endocr., Tufts-New England Med. Center and Tufts Univ. Sch. of Med., Boston, Mass.): INSULIN, GLUCOSE, GROWTH HORMONE, AND FREE FATTY ACIDS. Amer. J. Dis. Child. 121:15-19, January 1971.

Fifteen pediatric patients with cystic fibrosis (CF) who ranged in age from two to seventeen years received oral glucose tolerance tests. Plasma glucose, insulin, free fatty acid (FFA) and growth hormone responses were compared to values of twenty-eight control subjects.

The majority of CF patients demonstrated subnormal increments of plasma insulin, which did not correlate very well with carbohydrate tolerance. Plasma FFA responses were similar to patterns of control patients, but growth hormone concentrations were higher throughout the test in CF subjects.

Factors thought to be responsible for hormonal changes in the CF group included physical damage to the pancreas, possible genetic predisposition to diabetes and malnutrition. R.K.K.

Plackova, Anna; Waterhouse, J. P.; and Meyer, Julia (Dept. of Oral Path., Coll. of Dentistry, Univ. of Illinois at the Med. Center, Chicago, Ill.): GLYCOGEN IN CLINICAL LEUKOPLAKIA. DISTRIBUTION AND FINE STRUCTURE IN HUMAN BUCCAL MUCOSA. Arch. Derm. 102:291-99, September 1970.

Verbatim summary. The distribution of glycogen was studied in preparations for light and electron microscopy of nine surgical specimens of clinical leukoplakia in normally nonkeratinized parts of human oral mucosa and in two clinically normal areas of buccal mucosa. Over-all ratings of tissue content of glycogen in electron microscopic and light microscopic preparations were in good agreement. The glycogen content of the epithelium of the nine lesions was found to be unrelated to the degree of inflammation present and to be inversely related to the degree of keratinization. No exception was found at the cellular level to an inverse relation between the content of glycogen and the degree of keratinization.

Porter, Robert D.; and Hartman, Charles R. (Dept. of Intern. Med., Kansas Univ. Med. Center, Kansas City, Kan.; Fitzsimons' Gen. Army Hosp., Denver, Colo.): ARTHUS REACTIONS FROM INSULIN ASSOCIATION WITH LUPUS ERYTHEMATOSUS CELL PHENOMENA. JAMA 214:1884-85, Dec. 7, 1970.

This is a brief case report describing an obese patient with diabetes who developed insulin hypersensitivity as manifested by Arthus phenomenon eosinophilia, and hypergammaglobulinemia. Tolbutamide, 500 mg. twice daily was added to improve control; and some time following this, while on therapy with both insulin and tolbutamide, positive LE cells were noted. Insulin and tolbutamide therapy were stopped and control maintained on a 1200-calorie, 100-gm. carbohydrate diet. Four months later, the eosinophilia and the LE test had disappeared. The authors believe this may be a unique report of the association of both the Arthus and LE phenomenon with insulin therapy. D.R.C.

Raptis, S.; Schroder, K. E.; Faulhaber, J. D.; and Pfeiffer, E. F. (Dept. of Endocr. and Metabolism, Centre of Internal Medicine and Paediatrics, University of Ulm, Ulm, Germany): STIMULATION OF INSULIN SECRETION BY SECRETIN IN DIABETICS. Germ. Med. Mth. 15:206-10, April 1970.

Verbatim summary. Secretin stimulates the secretion of insulin in metabolically normal subjects, persons with subclinical diabetes, maturity-onset diabetics and, to a lesser extent, also juvenile diabetics. Maturity-onset diabetics with deficient insulin release after intravenously injected glucose react almost normally when secretin is administered simultaneously. Even glucose assimilation is greatly improved, even though not completely normalized. These findings suggest that the reaction of the pancreas to glucose is disturbed in diabetics even when adequate reserves of insulin are available, as demonstrated by an injection of secretin. Deficient secretion of intestinal hormones could be one of the factors contributing to the delayed insulin response after oral glucose administration in the diabetic.

Salmon, William D., Jr.; and DuVall, Margaret (Med. and Radioisotope Serv., Veterans Administration Hosp., Dept. of Med., Vanderbilt Univ. Sch. of Med., Nashville, Tenn.): IN VITRO STIMULATION OF LEUCINE INCORPORATION INTO MUSCLE AND CARTILAGE PROTEIN BY A SERUM FRACTION WITH SULFATION FACTOR ACTIVITY: DIFFERENTIATION OF EFFECTS FROM THOSE OF GROWTH HORMONE AND INSULIN. Endocrinology *87*:1168-80, December 1970.

Effects of growth hormone (GH), insulin and serum with sulfation factor activity on leucine incorporation into muscle proteins and cartilage of hypophysectomized rats were compared. Cartilage was insensitive to GH in vitro but responded significantly in vivo. This tissue was very sensitive to sulfation factor but not to insulin in vitro. In the muscle studies, the maximum effect of GH in vivo and that of sulfation factor or insulin exceeded the effects of high concentration of GH in vitro. Sulfation factor stimulated both muscle and cartilage from hypophysectomized rats in vitro; these effects were not augmented by GH and only slightly by insulin. Serum from GH-treated hypophysectomized rats in producing in vivo stimulation of muscle and cartilage contained sulfation factor in a concentration effective on muscle and cartilage from hypophysectomized rats in vitro. Anti-insulin serum inhibited the effects of insulin but not those of sulfation factor. GH apparently exerts its effects upon protein synthesis in muscle and cartilage through the activity of sulfation factor. C.R.S.

Scrutton, Michael C. (Dept. of Biochem., Rutgers Med. Sch., New Brunswick, N.J.): POSSIBLE REGULATORY FACTORS FOR PYRUVATE CARBOXYLASE WITH PARTICULAR REFERENCE TO ENZYME FROM CHICKEN LIVER. Metabolism *20*:168-86, February 1971.

The regulatory factors involved in the activity of pyruvate carboxylase were investigated in the context of its metabolic roles involving gluconeogenesis, glycerogenesis and the anaplerotic replenishment of citric cycle intermediates. It is suggested that acetyl-CoA, acetoacetyl-CoA, K+, and H+ are the effectors which are most likely responsible for the regulation of pyruvate carboxylase in a gluconeogenic tissue. C.R.S.

Senyk, George; Niteck, Danute; and Goodman, Joel W. (Dept. of Microbiol., Univ. of California Med. Center, San Francisco, Calif.): IMMUNOGENICITY OF GLUCAGON: DETERMINANTS RESPONSIBLE FOR ANTIBODY BINDING AND LYMPHOCYTE STIMULATION. Science *171*:407-08, Jan. 29, 1971.

Verbatim summary. Bovine glucagon, a polypeptide of 29 amino acids, is immunogenic in rabbits and guinea pigs. The antigenic determinants of glucagon were investigated with isolated tryptic peptides of the hormone. Antibodies from virtually all of more than a dozen animals tested had specificity primarily for the amino-terminal heptadecapeptide. However, only intact glucagon and its carboxy-terminal dodecapeptide stimulated spleen or lymph node cells to synthesize DNA. It thus appears that glucagon was cleaved along functional lines into two parts, one of which contained the major antigenic determinant for serum antibody and the other of which was "recognized" by antigen-reactive cells.

Trenkle, Allen (Dept. of Animal Sci., Iowa State Univ. of Science and Technology, Ames, Ia.): EFFECTS OF SHORT-CHAIN FATTY ACIDS, FEEDING, FASTING AND TYPE OF DIET ON PLASMA INSULIN LEVELS IN SHEEP. J. Nutr. *100*:1323-30, November 1970.

Experiments were conducted with sheep to study the effects of intravenous injection of short-chain fatty acids, feeding, fasting, and type of diet on plasma insulin levels. Injection of propionate, butyrate or glucose increased the secretion of insulin. The injection of either propionate or butyrate caused a greater insulin response than the injection of glucose. Fasting resulted in a decrease of plasma insulin concentration; feeding grain produced 50 to 60 per cent increases of plasma propionate and butyrate. The authors conclude that diet affects plasma insulin levels in sheep by altering the short chain fatty acid pattern of plasma. T.J.M.

Vince, F. P.; Boucher, Barbara J.; Cohen, R. D.; and Godfrey, Jeand (Dept. of Metabolism and Endocr. and Clin. Lab., The London Hosp., Whitechapel, London, England): THE RESPONSE OF PLASMA SUGAR, FREE FATTY ACIDS, 11-HYDROXYCORTICOSTEROIDS AND GROWTH HORMONE TO INSULIN-INDUCED HYPOGLYCEMIA AND VASOPRESSIN IN PRIMARY MYXEDEMA. J. Endocr. *48*:389-400, November 1970.

Verbatim summary. The plasma sugar, free fatty acids (FFA), 11-hydroxycorticosteroids (11-OHCS) and growth hormone (GH) response to insulin-induced hypoglycemia, have been studied in nineteen patients with primary myxedema and thirteen normal subjects. Nine of the myxedematous patients were restudied after treatment. The plasma 11-OHCS response to lysine vasopressin (LVP) was studied in the myxedematous subjects and again in eight of them after treatment.

In myxedema the plasma sugar falls to a lesser extent and more slowly in response to insulin than normal and takes longer to recover. The fall in plasma FFA is not different from normal, but recovery of plasma FFA is delayed. The responses to insulin-induced hypoglycemia of plasma GH and 11-OHCS may be smaller than normal in myxedema and tend to improve on treatment. Altered GH and 11-OHCS responses to insulin-induced hypoglycemia in myxedema are not necessarily due to pituitary or hypothalamic dysfunction. No difference was found in the response of plasma 11-OHCS to LVP before and after treatment. Pituitary function cannot be fully assessed in the presence of hypothyroidism.

Wright, Peter H.; and Makulu, David R. (Dept. of Pharmacol., Indiana Univ. Med. Center, Indianapolis, Ind.): REACTIONS OF PROINSULIN AND ITS DERIVATIVES WITH ANTIBODIES TO INSULIN. Proc. Soc. Exp. Biol. Med. *134*:1165-69, September 1970.

Verbatim summary. The reactions of porcine proinsulin and degradation products with insulin antibodies in guinea pig anti-insulin serum can be shown to vary with the immunological system used for study. From the results obtained with two such systems it is concluded that the connecting chain of amino acids in the molecule of proinsulin must mask sites on the insulin molecule which are capable of reacting with insulin antibodies.