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Batalla, M. A.; Balodimos, M. C.; and Bradley, R. F. (Elliott P. Joslin Res. Lab., Dept. of Med., Harvard Med. Sch., Joslin Clinic and New England Deaconess Hosp., Boston, Mass.): BACTERIURIA IN DIABETES MELLITUS. *Diabetologia* 7:297-301, 1971.

Verbatim summary. One hundred and four diabetic patients with bacteriuria were followed for a mean period of forty-four months. They were divided in two groups "cured" and "persistent" according to the results of treatment. Retinopathy and albuminuria as evidences of microangiopathy were present at the beginning of the study in a greater number of patients and in a greater degree in those with persistent bacteriuria than in those cured. At follow-up the number of patients with and the severity of retinopathy and albuminuria were higher in those with persistent bacteriuria although not statistically different. Microangiopathy usually antedated bacteriuria and may have contributed to its persistence, although the possibility that bacteriuria played a role in the progression of microangiopathy cannot be excluded. No significant deterioration in renal function became apparent in either group, suggesting that persistent bacteriuria had not obviously contributed to the development of pyelonephritis or progressive renal damage.

Bergman, E. N.; and Wolff, J. E. (Dept. of Physiol., New York State Vet. Coll., Cornell Univ., Ithaca, N.Y.): METABOLISM OF VOLATILE FATTY ACIDS BY LIVER AND PORTAL-DRAINED VISCERA IN SHEEP. *Amer. J. Physiol.*, 221:586-92, August 1971.

Net appearance in portal blood and net hepatic utilization of volatile fatty acids (VFA) were measured. Simultaneously, acetate-2-C-14 was infused to measure total body turnover, blood acetate utilization, and production by liver and portal-drained viscera. Mean net rates of appearance in portal blood

were 68, 18, and 2 mmoles/hr. for acetate, propionate, and butyrate when sheep were fed 800 gm./day of alfalfa pellets. These were reduced to 3, 0.8, and 0.6 mmole/hr. after three day's fasting. About one third of arterial acetate-C-14 entering the portal region was removed in both fed and fasted sheep. Portal acetate absorption rates in fed and fasted animals accounted for 76 ± 4 and 22 ± 4 per cent of whole-body acetate turnover, implying a large endogenous acetate production. Only small amounts of acetate were metabolized by liver, while 80 to 100 per cent of both propionate and butyrate were removed by liver. It appeared that measurements of only net appearance in portal blood or rates of acetate turnover incorrectly measure acetate absorption. Substantial fractions of all three VFA produced in the rumen are metabolized during absorption and never do reach the bloodstream. J.D.G.

Bianco, Jesus A.; Shanahan, E. Anne; Ostheimer, Gerard W.; Gunton, Robert A.; Powell, William John, Jr.; and Daggett, Willard M. (Gen. Surg. & Med. Servs., Massachusetts Gen. Hosp., Boston, and Depts. of Surg. & Med., Harvard Med Sch., Boston, Mass.): EFFECTS OF GLUCAGON ON MYOCARDIAL OXYGEN CONSUMPTION AND POTASSIUM BALANCE. *Amer. J. Physiol.* 221:626-31, August 1971.

The effect of 50 μ g/kg. glucagon on myocardial oxygen consumption (MVO_2) was assessed in twelve areflexic canine right heart bypass preparations. When left ventricular end-diastolic pressure (LVEDP) was initially below 15 cm. water, glucagon bolus injection into the pulmonary artery caused a significant increase in MVO_2 , small decrease of LVEDP, and an increase in maximum rate of rise of LV pressure (max dp/dt). When glucagon was injected into animals with LVEDP initially above 15 cm. water, MVO_2 decreased or showed little change, LVEDP fell substantially, and max dp/dt

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increased. In the animals with an initially high LVEDP, the greater fall of LVEDP correlated with a greater decrease in left ventricular end-diastolic circumference in this same group. In four animals glucagon administration was followed by net uptake of K^+ by the myocardium. Data did not support a correlation between myocardial performance, K^+ efflux, and oxygen consumption. Influence of glucagon on MVO_2 was analyzed both in terms of changes in myocardial contractility and in terms of alteration of ventricular dimensions. J.D.G.

Boden, G. (Dept. of Med., Rochester Gen. Hosp. and the Univ. of Rochester Sch. of Medicine, Rochester, N.Y.): HORMONAL AND METABOLIC DISTURBANCES DURING ACUTE AND SUBACUTE MYOCARDIAL INFARCTION IN MAN. *Diabetologia* 2:240-46, 1971.

Verbatim summary. To investigate the cause of glucose intolerance (GIT), frequently seen during acute myocardial infarction (AMI), seventeen males without history of diabetes were studied with intravenous glucose tolerance tests within seventy-two hours after uncomplicated myocardial infarction and again three weeks later. Seventy per cent (12/17) of the patients showed GIT during AMI. In seven of these patients (41 per cent) glucose tolerance (GT) remained abnormal after three weeks. In addition, all seven showed markedly diminished insulin responses to glucose during both the acute and subacute phase. Therefore, their GIT was considered to be due to newly-recognized chemical diabetes. In the remaining patients in whom the initially depressed GT improved during SMI elevated serum levels of FFA, insulin, HGH and cortisol suggested the temporary presence of insulin antagonism. Increased adrenal medullary activity was not found to be a major factor inhibiting glucose tolerance.

Brisson, G. R.; Malaisse-Lagae F.; and Malaisse, W. J. (Lab. of Exper. Med., Brussels Univ., Brussels, Belgium): EFFECT OF PHENTOLAMINE UPON INSULIN SECRETION DURING EXERCISE. *Diabetologia* 7:223-26, 1971.

Verbatim summary. Rats were injected with guinea-pig anti-insulin serum and I-131-labeled human albumin. The amount of endogenously secreted insulin was estimated from the progressive reduction in the pool of circulating unneutralized antibodies. In animals compelled to swim, insulin secretion occurred at a much lower rate than in control rats. Prior injection of phentolamine abolished the exercise-induced inhibition of insulin release. These findings support the concept that such inhibition is due to endogenously released catecholamines.

Caspary, W. F.; and Creutzfeldt, W. (Div. of Gastroenter. and Metab., Dept. of Med., University of Göttingen, W. Germany): ANALYSIS OF THE INHIBITORY EFFECT OF BIGUANIDES ON GLUCOSE ABSORPTION: INHIBITION OF ACTIVE SUGAR TRANSPORT. *Diabetologia* 7:379-85, 1971.

Verbatim summary. The effect of biguanides (phenethylbiguanide, butylbiguanide and dimethylbiguanide) on absorption of actively transported sugars was examined by incubating rings of hamster small intestine *in vitro*. Biguanides inhibited transport of D-glucose, D-galactose and 3-O-methyl-D-glucose but had no effect on the transport of D-fructose. Inhibition of D-xylose transport could only be demonstrated if concentrations for below half maximal saturation concentration (K_m) were used (10^{-5} M), but not with concentrations approaching concentrations during a D-xylose tolerance test (18 mM). Formation of lactate by intestinal tissue was increased in

presence of biguanides using D-glucose or D-fructose as substrates. The minimal inhibitory concentrations on transport of D-galactose were 10^{-3} M for phenethylbiguanide, 2×10^{-3} M for butylbiguanide and 6×10^{-3} M for dimethylbiguanide. The metabolite of phenethylbiguanide, 1-(4-hydroxy- β -phenethyl)-biguanide, did not affect glucose uptake but increased glucose metabolism to some extent. The demonstrated inhibition of active intestinal transport *in vitro* may be the mechanism for the decreased absorption of glucose observed by other authors *in vivo* in man and animals after biguanides.

Chlouverakis, C. (Dept. of Med., State Univ. of N.Y. at Buffalo and E. J. Meyer Memorial Hosp., Buffalo, N.Y.): ON THE ORIGIN OF HYPERGLYCEMIA IN THE OBESE-HYPERGLYCEMIC MOUSE (*obob*): EFFECT OF DIET ON BLOOD GLUCOSE AND SERUM INSULIN IN *obob* AND GOLD-THIOGLUCOSE OBESE MICE. *Diabetologia* 7:373-78, 1971.

Verbatim summary. Obese-hyperglycemic mice (*obob*), gold-thiogluco-obese (GTG-obese) and normal control mice were fed a high-carbohydrate and a carbohydrate-free diet. Blood glucose and serum insulin levels were influenced by the diet in all animals studied, but more so in the *obob* and GTG-obese. Blood glucose levels were equally raised in both types of obesity. Serum insulin of GTG-obese showed a marked elevation above normal but failed to reach the serum insulin levels of the *obob*. The blood glucose of *obob* and lean controls remained constant when fed the carbohydrate-free diet. Under these conditions, a trace amount of U-C-14-glucose was injected intravenously. The rate of C-14-glucose disappearance from the blood followed first-order kinetics and did not differ between *obob* and lean mice, suggesting a similar fractional rate of glucose uptake by tissues. The presence of a normal fractional rate of glucose extraction by the tissues of *obob*, together with their hyperglycemia and a normal volume of glucose distribution suggests an increased absolute rate of tissue glucose uptake. This increase is likely to be due to the expanded mass of adipose tissue in these animals.

Christophe, J.; Winand, J.; Kutzner, R.; and Hebbelinck, M. (Dept. of Biochem. and Nutrition, Brussels Univ. Sch. of Med., Brussels, Belgium): AMINO ACID LEVELS IN PLASMA, LIVER, MUSCLE, AND KIDNEY DURING AND AFTER EXERCISE IN FASTED AND FED RATS. *Amer. J. Physiol.* 221:453-57, August 1971.

Young male rats were forced to swim for fifteen or thirty minutes as a single exercise or after a ten-day period of training. When swimming for fifteen minutes only, rats were sacrificed immediately or after a fifteen-minute rest. Acute exercise lowered levels of glutamine in plasma and in liver, gastrocnemius, and kidney. Maximum decrease of glutamine was measured in the liver and was 50 per cent of resting level. Changes were usually accompanied by significant depressions of glutamate. Swimming induced increases in aspartate and serine in liver and a decrease of glycine. Data probably relate to increased gluconeogenesis and enhanced activity of glutaminase consequent to metabolic acidosis.

J.D.G.

Clayton, Barbara E.; Tanner, J. M.; and Vince, F. P. (Depts. of Chem. Path. and Growth and Development, Inst. of Child Health; The Hosp. for Sick Children; and The Dept. of Metabolism and Endocr., London Hosp., London, England): DIAGNOSTIC AND PROGNOSTIC VALUE OF SHORT-TERM METABOLIC RESPONSE TO HUMAN GROWTH HORMONE IN SHORT STATURE. *Arch. Dis. Child.* 46:405-13, August 1971.

The diagnostic and prognostic value of acute metabolic response to growth hormone administration was assessed in fifty-five children with short stature. Growth hormone was given for three days and urinary nitrogen, blood urea, and urinary calcium were measured. Diagnoses included isolated growth hormone deficiency, panhypopituitarism, short stature associated with low birth weight, and psychosocial short stature.

While growth hormone deficient children had greater acute metabolic responses to growth hormone than nondeficient children, there was considerable overlap. There was no significant correlation between the acute metabolic response and the increase in growth rate produced by a year of treatment with growth hormone. Measurement of acute metabolic response to growth hormone thus seems of little value in predicting which children will benefit from growth hormone therapy.

P.S.R.

Constam, G. R. (Zürich, Switzerland): IS THE USE OF SULFONYLUREA DERIVATIVES IN THE TREATMENT OF DIABETES MELLITUS DANGEROUS? *Diabetologia* 7:237-39, 1971.

Verbatim summary. Grouping 651 diabetic deaths according to their treatment with diet alone, with diet and sulfonylurea tablets, with diet and small or large doses of insulin, we cannot discover any significant difference in the duration of diabetes from onset till death between patients treated by diet alone and those treated by diet and hypoglycemic tablets. The longer duration of insulin-controlled diabetes is mainly due to the younger age of the patients at onset of the disease. Some other factors which may favor insulin treatment are discussed. Neither overweight nor hypertension explains the disparity in duration of diabetes between patients under diet or tablet therapy and others controlled by insulin.

Hypoglycemia and side effects of sulfonylurea derivatives have been known for a long time and are not included in this study. A critical review of the UGDP report does not give any justification for condemning tolbutamide therapy as dangerous. As in every really efficient medical treatment, sulfonylurea compounds should be used only when necessary, and then with the appropriate dosage, the necessary circumspection and good common sense!

Deconinck, J. F.; Potvliege, P. R.; and Gepts, W. (Dept. of Path., Brugmann Univ. Hosp. and Queen Elizabeth Fndtn., Vrije Universiteit Brussel, Brussels, Belgium): THE ULTRASTRUCTURE OF THE HUMAN PANCREATIC ISLETS. I. THE ISLETS OF ADULTS. *Diabetologia* 7:266-82, 1971.

Verbatim summary. The ultrastructure of the pancreatic islets was studied in seven surgical specimens of human pancreas. The effects of two different fixation methods were compared: osmium tetroxide alone and glutaraldehyde followed by osmium. On the basis of their ultrastructural characteristics, four main types of islet cells were identified: (1) B cells, with polymorphous, often crystalline granules contained in wide sacs. (2) A cells with rounded granules enclosed in tight fitting sacs and composed of an electron-dense core surrounded by a clearer halo. (3) Type III cells, with rounded, large homogeneous granules of varying sizes and electron densities. They presumably secrete gastrin. Comparable cells were found in samples of human gastric and duodenal mucosae. (4) Type IV cells, with rounded, small, homogeneous granules of low electron density. Comparable cells were found

in human gastric and duodenal mucosae. The nature of their secretion remains obscure. A fifth cell type was observed in the pancreas but was not restricted to the islets. Cells of type V have small, polymorphous and very electron-dense granules. They offer a certain resemblance with the serotonin secreting cells which are found in the digestive tract.

Ekholm, R.; Ericson, L. E.; and Lundquist, I. (Dept. of Anat., Univ. of Göteborg, and Dept. of Pharm., Univ. of Lund, Sweden): MONOAMINES IN THE PANCREATIC ISLETS OF THE MOUSE. *Diabetologia* 7:339-48, 1971.

Verbatim summary. By application of autoradiographic technique the cellular and subcellular distribution of radioactivity in mouse pancreatic islets was investigated following intravenous administration of 3-H-5-hydroxytryptophan. Autoradiographic silver grains, most of which probably represent 5-hydroxytryptamine formed from the labeled precursor, appeared over A₂ and B cells, whereas very few grains were recorded over A₁ cells at any time investigated (20 min.—16 hrs). and also when monoamine oxidase was inhibited. Quantitative analysis of autoradiographic sections revealed that the concentration of silver grains over the specific granules of A₂ and B cells was five to ten times higher than over the remaining parts of these cells. In A₂ cells the highest grain count was recorded at twenty minutes, in B cells at one hour after the injection of label. After eight hours very few, and after sixteen hours no silver grains appeared over islet cells. Inhibition of monoamine oxidase caused an increased retention of label over islet cells, most pronounced over A₂ cells. Pretreatment with reserpine abolished the autoradiographic reaction.

Giombetti, Robert; Hagstrom, Jack W. C.; Landey, Stephanie; Young, Margaret C.; and New, Maria I. (Dept. of Pediat., New York Hosp.-Cornell Med. Center, New York, N.Y.): CUSHING'S SYNDROME IN INFANCY. *Amer. J. Dis. Child.* 122:264-66, September 1971.

A six-week-old female infant presented with hypertension, cardiomegaly, obesity, moon facies, buffalo hump, hirsutism, and ecchymosis. A right upper quadrant mass was palpated. Laboratory studies revealed hyperglycemia, glycosuria, and markedly elevated plasma cortisol concentrations. A 61 gm. right adrenal adenoma was surgically resected. The patient improved initially, with regression of the manifestations of Cushing's Syndrome, but eventually succumbed to monilial endocarditis.

Osteoporosis, polycythemia, and striae, commonly observed in adult Cushing's Syndrome, are rarely seen in children. Virilization is common. Adrenal tumors frequently are the cause of the disorder in infancy and malignancy is common. The presence of diabetes mellitus and glucocorticoid excess favor development of infection, and sepsis is a frequent cause of death. Careful attention to asepsis in the perisurgical period is essential. P.S.R.

Heath, H.; Bridgen, W. D.; Canever, J. V.; Pollock, J.; Hunter, P. R.; Kelsey, J.; and Bloom, A. (Dept. of Biochem. Path., Univ. Col. Hosp. Med. Sch., London, Eng.): PLATELET ADHESIVENESS AND AGGREGATION IN RELATION TO DIABETIC RETINOPATHY. *Diabetologia* 7:308-15, 1971.

Verbatim summary. Platelet adhesiveness, ADP-activated platelet aggregation and the activity of the ADP-splitting enzymes in blood and plasma have been studied in twenty-two diabetics with severe retinopathy, twenty-two long-duration dia-

betics with minimal or no retinopathy and twenty-eight control subjects. The rate of platelet aggregation under the influence of 5, 3, 2 and 1 μ M ADP, the maximum aggregation attained and the rate of disaggregation of these aggregates were measured. The platelets from actively deteriorating retinopathies were found to be more sensitive to the effect of low concentrations of ADP; a significant increase in the extent of aggregation and a decrease in the rate of disaggregation of platelet aggregates formed under the experimental conditions, *in vitro* were observed. If this should occur *in vivo*, then capillary occlusion might ensue. This increased sensitivity to ADP and inability to disaggregate, was not due to any differences in the activity of the ADP-splitting enzyme systems in blood. Significant differences in the parameters were not observed when the large diabetic groups were compared with the control subjects. Contrary to some reports, an increase in platelet adhesiveness was not apparent in either diabetic group.

Hobenegger, M.; and Rudas, B. (Inst. for Gen. and Exper. Path. of the Univ. of Vienna, Vienna, Austria): KIDNEY FUNCTION IN EXPERIMENTAL DIABETIC KETOSIS. *Diabetologia* 7:334-38, 1971.

Verbatim summary. Rats both with streptozotocin and alloxan diabetes were used. Ketosis developed in the first days following the application of the diabetogenic agents, and also in rats with long term diabetes in the first days after the insulin previously administered daily had been withdrawn. The rats with more elevated blood ketone levels also demonstrated strikingly high serum urea levels, oliguria and a diminished food intake. In the groups of rats which in spite of insulin deficiency revealed no or only mild ketonemia, food intake was increased, and marked polyuria as well as near to normal serum urea levels were observed. Our results showed that the symptoms of uremia occurred independently of the nature of the diabetic agent, and also of the time at which these agents were administered. Thus it can be concluded that in that case acute renal insufficiency was not due to the nephrotoxicity of the agents employed but rather to the severity of diabetic ketosis.

James, Albert L.; and Ockner, Robert K. (Depts. of Med. and Anat., Univ. of California Med. Center and V.A. Hosp., San Francisco, Cal.): AN ELECTRON MICROSCOPIC STUDY OF ENDOGENOUS VERY LOW DENSITY LIPOPROTEIN PRODUCTION IN THE INTESTINE OF RAT AND MAN. *J. Lipid Res.* 12:580-89, September 1971.

Electron microscopic studies of fasted rat and human jejunal absorptive cells revealed osmiophilic particles the size of very low density lipoproteins (VLDL), covered with endoplasmic reticular membranes, often near the luminal surface. The Golgi complex also was a frequent site for these lipid particles. Biliary diversion or cholestyramine treatment resulted in a virtual disappearance of the VLDL-sized particles from mucosal cells. The authors offer this as evidence for the necessity of intraluminal lipid in the formation of these non-dietary lipoproteins by intestine. P.H.S.

Jansen, F. K. (Diabetes-Forschungsinstitut, Düsseldorf, Germany): TOLERANCE TO HIGH AND LOW DOSES OF NATURAL CRYSTALLINE INSULIN. *Diabetologia* 7:290-92, 1971.

Verbatim summary. In order to examine the induction of

an immunological tolerance to insulin, six different doses of once-crystallized insulin were injected *i.p.* into NMRI mice three times a week for three months. The doses were: 100 μ g, 10 μ g, 1 μ g, 100 ng, 10 ng and 1 ng per injection. A test immunization of 100 μ g insulin in complete Freund's adjuvant was given at the end of the immunization period to test the immunologic reactivity. It was found that one dose (1 μ g) had stimulated antibody production, and that two doses had induced tolerance: a low dose of 100 ng and a high dose of 100 μ g. In the tolerant animals at three and five weeks after the test immunization the antibody level was less than 10 per cent of that present in the controls.

Kanazawa, Yasunori; Orzi, Lelio; and Lambert, André E. (Institut de Biochimie Clinique and Institut d'Histologie et d'Embryologie, Univ. of Geneva, Geneva, Switzerland): ORGAN CULTURE OF FETAL RAT PANCREAS. IV. EFFECTS OF METABOLIC INHIBITORS ON INSULIN RELEASE. *Endocrinology* 89:576-83, August 1971.

Observations are reported on the effects of four metabolic inhibitors, mannoheptulose, 2-deoxyglucose, iodoacetate and oligomycin, upon insulin secretion in the cultured fetal rat pancreas stimulated by each of four substrates, glucose, pyruvate, xylitol, citrate, and by tolbutamide, with and without the further addition of caffeine. Glucose-induced IRI release was suppressed by all metabolic inhibitors while none significantly altered the IRI release induced by citrate. Pyruvate- and tolbutamide-induced IRI releases were inhibited by iodoacetate and oligomycin and were stimulated by mannoheptulose and 2-deoxyglucose. Xylitol-induced IRI release was enhanced by 2-deoxyglucose but not mannoheptulose. Since low concentrations of iodoacetate inhibited glucose-induced IRI release but not that of pyruvate, it appears that intermediates beyond the level of glyceraldehyde-3-phosphate are involved in the stimulation of insulin release. The stimulatory effects of mannoheptulose and 2-deoxyglucose on pyruvate- and tolbutamide-induced IRI suggest that the releasing mechanisms for insulin may be dependent also on other types of metabolic events. The activation of membrane receptor sites or specific transport sites by these glucose analogues may contribute to stimulation of IRI releasing mechanisms in an action independent of their effects on glycolysis. C.R.S.

Kasperska, Teresa; Lawecki, January; Rogala, Henry K.; and Czyzyk, Artur (Dept. III of Intern. Dis., Med. Acad., Warsaw, Poland): THE BEHAVIOR OF INSULINEMIA IN PATIENTS WITH LIVER CIRRHOSIS AFTER INTRAVENOUS ADMINISTRATION OF GLUCOSE, TOLBUTAMIDE AND GLUCAGON. *Diabetologia* 7:391-94, 1971.

Verbatim summary. The response of both blood glucose and serum immunoreactive insulin to glucagon, glucose and tolbutamide was studied in ten patients with well-documented, advanced liver cirrhosis and in ten healthy subjects without history indicative of liver impairment or diabetes. Glucose was administered as a rapid intravenous injection in a dose of 0.33 gm./kg. of body weight, tolbutamide in a dose of 1.0 gm. and glucagon in a dose of 1.0 mg. The mean fasting serum insulin levels of cirrhotic patients did not differ significantly from the values obtained in healthy subjects. However, after administration of glucose or tolbutamide the rise of insulinemia was significantly higher in cases of liver cirrhosis

than in normal subjects. The increase of serum insulin values after intravenous administration of glucagon was similar in both groups; thus glucagon failed to induce hyperinsulinemia as observed after glucose or tolbutamide. The possible causes of this phenomenon have been discussed.

Keller, U.; and Froesch, E. R. (Metab. Unit, Dept. of Med., Univ. of Zurich, Switzerland): METABOLISM AND OXIDATION OF U-C-14-GLUCOSE, XYLITOL, FRUCTOSE AND SORBITOL IN THE FASTED AND IN THE STREPTOZOTOCIN-DIABETIC RAT. *Diabetologia* 7:349-56, 1971.

Verbatim summary. (1) Twenty-four-hr.-fasted rats exhaled 35 to 37 per cent of i.v. administered loads of labeled glucose, xylitol and fructose, and 20 per cent of a sorbitol load as CO₂-14 within a period of six hours. (2) Streptozotocin-diabetic rats exhaled under similar conditions only 11 to 18 per cent of these substrates as CO₂-14. The rate of glucose oxidation was similar in both groups of animals when a correction for the different glucose pool size was applied. It is concluded that glucose oxidation to CO₂-14 takes place mainly in tissues which are not sensitive to insulin. (3) Urinary excretion of all substrates was 39 to 55 per cent of the given dose in diabetic rats. The large difference of urinary carbon-14 between fasted and diabetic rats was due to the excretion of glucose-C-14 by the diabetic rats. (4) Six hours after the administration of all four substrates, similar amounts of carbon-14 were recovered in serum, serum osazones, liver glycogen and total lipids and diaphragm glycogen within each group of animals. It is concluded that the similarities of the metabolism of all substrates is due to the rapid conversion of the substitute sugars to glucose.

Kitabchi, Abbas E.; Duckworth, William C.; Brush, James S.; and Heinemann, Martha (Labs. of Endocr. and Metabolism, Res. Serv. V.A. Hosp.; and Depts. of Med. and Biochem., Univ. of Tennessee Med. Units, Memphis, Tenn.): DIRECT MEASUREMENT OF PROINSULIN IN HUMAN PLASMA BY THE USE OF AN INSULIN-DEGRADING ENZYME. *J. Clin. Invest.* 50:1792-99, September 1971.

A proteolytic enzyme which effectively degrades insulin but not proinsulin was isolated from rat skeletal muscle, using a previously described method. Total immunoreactive insulin was assayed by a conventional "double-antibody" method, using radioiodinated insulin and an antiporcine insulin serum which adequately cross-reacted with proinsulin. When plasma samples were incubated with the enzyme, 80 to 95 per cent of the immunoreactivity which corresponded to the insulin fractions eluted from a biogel column was lost. The residual immunoreactivity represented proinsulin or proinsulin-like compounds. Thus, immunoreactive proinsulin in human plasma could be estimated without prior fractionation in gel columns. Proinsulin levels estimated by this method were somewhat higher than those observed by column fractionation. In four healthy subjects, 26 to 75 per cent, and in a patient with insulinoma, 50 per cent of fasting plasma total immunoreactivity corresponded to proinsulin. After the ingestion of glucose proinsulin levels rose more slowly than those of total immunoreactive insulin. S.P.

Koschinsky, Th.; Gries, F. A.; and Herberg, L. (Sec. Med. Clin. and Diabetes Res. Inst., Univ. of Düsseldorf, Düsseldorf, Germany): REGULATION OF GLYCEROL KINASE BY INSULIN IN ISOLATED FAT CELLS AND LIVER OF BAR HARBOR OBESE MICE. *Diabetologia* 7:316-22, 1971.

Verbatim summary. Glycerol kinase was measured by a modification of the radiochemical enzyme test described by Newsholme and coworkers in isolated epididymal and parametrial fat cells and liver tissue of obese hyperglycemic Bar Harbor mice (obob) and their lean littermates (ob+ob+). The specific activity of glycerol kinase was independent of age in the control animals. It was about 90 times greater in liver than in fat cells. In obese animals glycerol kinase was dependent on age. Compared with the controls, the activity was significantly increased in fat cells of two to twelve-month old mice and in liver of five-month old mice. In fat cells of two to twelve-month old mice fed ad libitum, glycerol kinase activity was significantly correlated to serum IRI-levels. Glycerol kinase activity decreased during fasting or experimental insulin deficiency, induced by streptozotocin. It was significantly increased in fat cells and liver by insulin substitution. This insulin effect was suppressed by actinomycin D. It is concluded that insulin regulates glycerol kinase activity by enzyme induction. The significance of these results for the adipose tissue metabolism in obob mice is discussed.

Larkins, R. G. (Univ. of Melbourne Dept. of Med., Royal Melbourne Hosp., Victoria, Australia): PLASMA GROWTH HORMONE IN THE NEW ZEALAND OBESE MOUSE. *Diabetologia* 7:302-07, 1971.

Verbatim summary. Plasma growth hormone was measured by radioimmunoassay under basal conditions and after glucose administration in the New Zealand Obese (NZO) mouse and in a control strain. There was greater variability of plasma IRGH in the NZO mice than in the control strain under basal conditions, but there was no significant difference between the mean log plasma IRGH in the two strains. Moreover, in both strains rapid suppression of plasma IRGH occurred following glucose administration. It appears unlikely that pituitary hypersecretion of growth hormone accounts for the metabolic abnormalities observed in the NZO mouse.

Massara, F.; Strumia, E.; Camanni F.; and Molinatti, G. M. (Istituto di Clinica Medica dell'Università di Torino, Italy): DEPRESSED TOLBUTAMIDE-INDUCED INSULIN RESPONSE IN SUBJECTS TREATED WITH PROPRANOLOL. *Diabetologia* 7:287-89, 1971.

Verbatim summary. The effect of propranolol on 1 gm. i.v. tolbutamide-induced insulin response was studied in eleven subjects. The drug depressed this response, the effect being more noticeable in the patients receiving 200 mg./day per os for three days. The corresponding blood glucose curves, however, were unaffected by propranolol. The findings suggest that the beta-receptors play a part in sulfonylurea-induced insulin secretion in man.

Paasikivi, J.; and Wahlberg, F. (Dept. of Med., Karolinska Inst. at Serafimerlasarettet, Stockholm, Sweden): PREVENTIVE TOLBUTAMIDE TREATMENT AND ARTERIAL DISEASE IN MILD HYPERGLYCEMIA. *Diabetologia* 7:323-27, 1971.

Verbatim summary. In a study at the Serafimerlasarettet, Stockholm, it was found that low intravenous glucose tolerance (IVGT) in survivors from a first myocardial infarction without manifest diabetes reflected a chronic state and implied a poor long term prognosis. In a controlled study of secondary pre-

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ventive treatment with tolbutamide in 178 such patients the survival rate improved significantly over one-and-one-half to two years. This applied particularly to those with abnormal IVGT, who during the hospitalization had revealed signs suggestive of heart failure. Also, the results of a controlled trial of primary preventive antidiabetic treatment performed in Bedford, England, showed that in 248 borderline hyperglycemic individuals the incidence of new arterial events over five to seven years was significantly lower in those treated with tolbutamide. These findings indicate that progress of arterial disease assumed to be enhanced by impaired carbohydrate metabolism may be retarded by early tolbutamide treatment.

Pirart, J. (Allgemine Belgische Diabetesbond, Brussels, Belgium): FAILURE OF THE BIGUANIDES TO IMPROVE THE CONTROL OF UNSTABLE DIABETES TREATED WITH INSULIN. *Diabetologia* 7:283-86, 1971.

Verbatim summary. Twenty-five insulin-dependent diabetics had marked instability despite optimal treatment. These highly cooperative patients alternately received a placebo and the biguanide. They were aware that they were being treated with a new drug in the hope of reducing their instability. Long before this trial they were trained to record in a booklet their four daily urine tests (Clinitest + Acetest) and their hypoglycemic reactions (occurrence, timing, causes if any) and to adjust their daily dose of insulin(s) to the results of the preceding days. They were seen about once or twice a month, carefully questioned and their booklets were examined and discussed. A slight insulin-sparing effect was observed in one half of the cases. Some patients declared that the oral treatment improved their condition. However, the percentage of the urine tests and hypoglycemic reactions recorded in their booklets, as well as the objective data gained on each visit, did not make it possible to differentiate between the degree of control obtained before and that obtained during or after the oral treatment, and between that obtained with a biguanide and that obtained with its placebo. It is concluded that the addition of biguanide to insulin is of *no* value in the treatment of unstable diabetes.

Pirart, J.; and Barbier, P. (Hôpital St. Pierre, Service de Médecine Interne, Bruxelles, Belgium): PROTECTIVE EFFECTS OF HEMOCHROMATOSIS AGAINST MICRO- AND MACRO-ANGIOPATHY ASSOCIATED WITH DIABETES. A COMPARISON WITH COMMON CIRRHOSIS. *Diabetologia* 7:227-36, 1971.

Verbatim summary. (1) Signs of common vascular sclerosis and of specific diabetic angiopathy have been sought in thirty-nine cases of proved hemochromatosis with diabetes, in twenty-two cases of proved hemochromatosis without diabetes, in eighty-four cases of common cirrhosis with overt diabetes, in sixty-five cases of common cirrhosis without diabetes, in sixty-five control subjects and in two groups of patients with common diabetes, each case being carefully paired with a corresponding diabetic either with common cirrhosis or with hemochromatosis as far as sex, age, duration and severity of diabetes as well as body weight are concerned. One out of three cases has been examined at autopsy. The striking protective effect of hemochromatosis was confirmed in five arterial areas (retinae, kidneys, coronary, lower limbs, aorta), and in

two areas where diabetic microangiopathy (glomeruli and retinae) is typical. This protection is closely related to hemochromatosis, and is not due to the shorter survival of patients with bronze diabetes. Common cirrhosis, despite marked hypocholesterolemia and better control of the diabetes has but a slight protective effect. Various explanations are suggested, none of them being fully satisfactory. At least two out of three cases of patients with common cirrhosis have a reduced glucose tolerance. In cirrhosis the values of fasting and of postprandial blood sugar are widely spaced out in a unimodal pattern varying from complete normality to full insulin-dependency. Just as in the general population, the limits of diabetes are quite arbitrary (> 180 mg. per cent two hours after a meal in the present study). According to this definition, diabetes in our series required insulin in only one out of five cases of diabetes associated with cirrhosis, no less in fact than in diabetes without cirrhosis when age and body weight were taken into account. Clinical features (heredity, evolution, typical vascular complications) do not indicate that diabetes associated with cirrhosis differs markedly from ordinary diabetes of the same severity (glycosuria plus hyperglycemia > 180 mg. per cent in the fasting state or two hours after a meal).

Scheynius, A.; and Täljedal, I. B. (Dept. of Hist., Univ. of Umeå, Umeå, Sweden): ON THE MECHANISM OF GLUCOSE PROTECTION AGAINST ALLOXAN TOXICITY. *Diabetologia* 7: 252-55, 1971.

Verbatim summary. The modifying effects of some sugars and amino acids on the diabetogenic action of alloxan were studied in mice. The severity of diabetes was assessed by measuring the blood glucose level 48 hr. after the alloxan injection. In accordance with earlier reports, D-glucose and D-mannose, but not D-galactose, protected against alloxan diabetes. No such effect was observed with D-mannoheptulose, L-alanine, or L-leucine. The protective action of glucose was abolished by prior treatment with mannoheptulose. It is concluded that alloxan and glucose do not compete for a common biochemical site in the β -cell membrane. Protection against alloxan toxicity may, however, result from a conformational change in the β -cell membrane induced by glucose, glucose transport, or glucose metabolism.

Walaas, E.; Wille, L.; and Haugen, H. N. (Inst. of Med. Biochem., Univ. of Oslo and Univ. Hosp., Medical Dept. B, Univ. of Oslo, Norway): SERUM PHOSPHOLIPIDS IN DIABETIC PATIENTS WITH LATE MANIFESTATIONS. *Diabetologia* 7:360-66, 1971.

Verbatim summary. Serum phospholipid constituents in a selected group of hyperlipemic diabetic patients with late manifestations have been investigated. In these patients the concentrations of serum lecithin as well as the cephalin fraction were increased. The absolute and relative increase of the cephalin fraction amounted to three to four times. It is indicated that the disturbances in serum phospholipids are due to insufficient metabolic control in these patients. The possible significance of the increase of serum cephalin for the occurrence of vascular complications is discussed.