ABSTRACTS

Abraira, Carlos; Graham, Leonard A.; and Lawrence, Ann M. (Hines Veterans Adm. Hosp., Hines, Ill., the Univ. of Ill. A. Lincoln Sch. of Med., Chicago, Ill., & Loyola Univ. Stritch Sch. of Med., Maywood, Ill.): ABSENCE OF FACILITATED GLUCOSE DISPOSAL (STAUB-TRAUGOTT EFFECT) IN SUBJECTS WITH HYPOPITUITARISM. Metabolism *24*:1145-55, October 1975.

The role of the anterior pituitary in the Staub-Traugott effect was investigated by the administration of three intravenous injections of glucose at hourly intervals in hypopituitary patients receiving replacement thyroid, cortisone, and sex-steroid therapy, and in normal control subjects. The usual augmented glucose disposal rates were seen in the control group; however, in the hypopituitary subjects this phenomenon was conspicuously absent. Patterns of peripheral insulin responses were similar in both groups while FFA levels fell more slowly in the hypopituitary patients. Normal pituitary function appears to be required for the Staub-Traugott effect, which cannot be explained by incremental insulin responses. Reduced suppression of FFA and impaired induction of key glycolytic-glycogenic enzymes are possible explanations for the absence of this effect in hypopituitary subjects. C.R.S.

Anderson, James W.; and Herman, Robert H. (Metab. Res. Unit, San Francisco V.A. Hosp., and Metab. Div., U.S. Army Med. Res. and Nutrition Lab, Fitzsimons Gen. Hosp., Denver, Colo.): EFFECTS OF CARBOHYDRATE RESTRICTION ON GLUCOSE TOLERANCE OF NORMAL MEN AND REACTIVE HYPOGLYCEMIC PATIENTS. Am. J. Clin. Nutr. *28*:748-55, 1975.

Normal individuals ingesting a low carbohydrate diet frequently develop an impairment of glucose tolerance as measured by the oral glucose tolerance test; most of these diets, however, have been high in fat content. Our present studies demonstrate that a low carbohydrate diet (57 gm./day) did not impair the glucose tolerance of normal men if the fat content was similar to values on a standard (301-gm./day) carbohydrate diet. However, a low carbohydrate diet did lead to impaired glucose tolerance when the fat content was 16 per cent higher than that of the control diet. Thus, our present and previous studies demonstrate that normal men maintain normal glucose tolerance on low carbohydrate diets and suggest that the deterioration of the glucose tolerance observed on high fat diets is related to the increased fat content rather than to the reduced carbohydrate content of these diets. Seven patients with reactive hypoglycemia were exquisitely sensitive to carbohydrate deprivation. Whereas the glucose tolerance tests of normal men were not altered by a low carbohydrate, high protein diet, a significant deterioration of glucose tolerance occurred when reactive hypoglycemic patients were changed from control diets to low carbohydrate, high protein diets. These hypoglycemic patients also showed an exaggerated deterioration of the glucose tolerance after a 48-hour fast over that of normal men. Our observations suggest that a low carbohydrate, high protein diet is not the best therapeutic diet for certain patients with reactive hypoglycemia because this diet does not provide symptomatic improvement and, in addition, leads to impaired glucose tolerance. J.E.G.

Baum, J. D.; Jenkins, P.; and Aynsley-Green, A. (Dept. Pediat. Univ. Oxford, John Radcliffe Hosp., Headington, Oxford, England): IMMEDIATE METABOLIC RESPONSE TO A LOW DOSE OF INSULIN IN CHILDREN PRESENTING WITH DIABETES. Arch. Dis. Child. *50*:373-378, May, 1975.

Twenty patients with diabetes (17 new and 3 previously diagnosed) were treated with initial insulin doses ranging from 0.1 to 0.29 U./kg. given intramuscularly and followed to determine their metabolic response. This was considered good (a mean fall in blood glucose from 88-100 mg./dl./hr. with comparable falls in blood ketones). Authors suggest that such doses would obviate such problems as hypokalemia and hypoglycemia while attaining adequate control. A summary of currently recommended dose schedules is included. I.M.B.

Berne, Christian (Dept. of Histology, Biomedical Center, Univ. of Uppsala, Uppsala, Sweden): ANTI-INSULIN SERUM COUPLED TO SEPHAROSE 4B AS A TOOL FOR THE INVESTIGATION OF INSULIN BIOSYNTHESIS IN THE B-CELLS OF OBESE HYPERGLYCEMIC MICE. Endocrinology 97:1241-47, 1975.

The biosynthetic activity of the B cells of obese hyperglycemic mice (*ob/ob*) was measured by the incorporation of [^{3}H]leucine into proteins in collagenase-isolated pancreatic islets. To quantitate the incorporation into proinsulin and insulin, an immune binding method was used. For this purpose, anti-insulin serum was coupled to cyanogen-bromide-activated Sepharose 4B. This turned out to be a specific and versatile technic for the measurement of newly synthesized proinsulin and insulin in the B-cells.

The B-cells of *ob/ob* mice appear to be well adapted to a high rate of hormone biosynthesis, since at 16.7 mM glucose 44 per cent of [^{3}H]leucine incorporated into TCA-precipitable proteins was bound to be the insulin antibodies coupled to Sepharose 4B. During a three-hour incubation the insulin biosynthetic rate was stimulated nine times at 16.7 mM glucose that of the basal insulin biosynthesis rate. J.E.G.

Breslow, Jan L.; Spaulding, Duane R.; Lux, Sanuel F.; Levy, Robert I.; and Lees, Robert S. (Dept. of Pediatrics, Harvard Med. Sch., Molecular Disease Branch, NHLI, and the Arteriosclerosis Center, MIT, Boston, Mass.): HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA. N. Engl. J. Med. *293*:900-3, Oct. 30, 1975.

The response of fibroblast from patients with homozygous familial hypercholesterolemia to low-density lipoprotein was studied with respect to inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and binding to the cells. Four of the patients studied were responsive to a treatment combination of cholestyramine, nicotinic acid, and polyunsaturated fatty acids. This resulted in approximately a 50 per cent fall in their plasma cholesterol. In these patients low-density lipoprotein caused a 30 to 58 per cent reduction in HMG-CoA reductase activity in their fibroblast. The fibroblast from two patients whose hypercholesterolemia was unresponsive to therapy did not have a fall in HMG-CoA reductase activity with low-density lipoprotein exposure. The fibroblast from mothers of two patients wtih partial suppression responded normally. The specific binding of low-density lipoprotein to fibroblast was approximately twice as great in the group with a therapeutic response as it was in the unresponsive group. However, the binding was reduced in both groups, in contrast to that of normals. The authors conclude that there are either three alleles for one gene locus or two gene loci with two or more alleles to account for the clinical and biochemical findings in homozygous familial hypercholesterolemia. H.M.

Felig, Philip; and Wahren, John (Dept. of Intern. Med. Yale Univ. Sch. of Med., New Haven; Dept. of Clinical Physiol., Karolinska Inst. at the Serafimer Hosp., Stockholm, Sweden): FUEL HOMEOSTASIS IN EXERCISE. N. Engl. J. Med. *293*:1078-84, Nov. 20, 1975.

This is an excellent review of the changes occurring in fuel utilization by skeletal muscle during exercise and in hepatic metabolism with regard to carbohydrate homeostasis during exercise. In the resting state, muscle utilizes primarily fatty acids as fuel. During exercise glucose becomes an important source of fuel through glycogen breakdown and glucose uptake from the circulation. The increased utilization of glucose with exercise appears to be dependent on the presence of some circulating insulin, although it does not require an increase in insulin level. Alanine output by skeletal muscle is augmented during exercise. This occurs by transamination of pyruvate (the amine group being derived from catabolism of certain amino acids by muscle and purine recycling during exercise). During exercise, splanchnic glucose output is increased severalfold. This results from hepatic glycogen breakdown followed by an increase in gluconeogenesis. The hormonal response to exercise is a fall in insulin and an increase in glucagon. The postexercise period is characterized by repletion of glycogen stores. The exercising diabetic utilizes more free fatty acids than glucose because of his decreased glycogen stores. The utilization of branched-chain amino acids by skeletal muscle is also increased in the diabetic during exercise. H.M.

Frame, Carolyn M.; Davidson, Mayer B.; and Sturdevant, Richard A. L. (Depts. of Physiol. & Med., U.C.L.A. School of Med., & Res. & Med. Serv., V.A. Wadsworth Hospital Center, Los Angeles, Ca.): EFFECTS OF THE OCTAPEPTIDE OF CHOLECYSTOKININ ON INSULIN AND GLUCAGON SECRETION IN DOG. Endocrinology 97:549-53, September 1975.

The effects of intravenous infusion of synthetic C-terminal octapeptide of cholecystokinin (OP-CCK) on concentrations of insulin and glucagon in peripheral venous plasma of conscious dogs were studied. Both hormones increased in response to 160 and 480 ng./kg./hr. of OP-CCK. The increases after 480 ng./kg./hr. were larger than those after 160 ng./kg./hr. Peripheral venous concentrations of glucose and intestinal glucagon-like immunoreactivity were not altered by OP-CCK. OP-CCK, 160 ng./kg./hr., did not increase insulin and glucagon responses to intravenous infusion of amino acids. The results suggest that insulin- and glucagon-releasing actions of porcine cholecystokinin preparations should not be attributed entirely to gastric inhibitory polypeptide or other impurities contained in these preparations, since the synthetic active fragment of cholecystokinin alone increases insulin and glucagon concentrations in peripheral plasma. J.E.G.

Goldfine, Ira D. (Diabetes Branch, National Inst. of Arthritis, Metabolism & Digestive Diseases, National Institutes of Health, Bethesda, Md.): BINDING OF INSULIN TO THYMOCYTES FROM SUCKLING AND HYPOPHYSECTOMIZED RATS: EVIDENCE FOR TWO MECHANISMS REGULATING INSULIN SENSITIVITY. Endocrinology 97:948-54, October 1975.

Insulin more effectively increased amino acid influx into thymocytes isolated from insulin-sensitive suckling and hypophysectomized rats than into cells obtained from normal adult animals. Thymocytes from hypophysectomized adult rats bound more insulin than did cells from sham-operated controls, suggesting that insulin sensitivity in this condition was due to an increase in the number of insulin receptors. In contrast, thymocytes from suckling rats bound the same amount of insulin as did cells from adult animals, suggesting that in this instance insulin sensitivity was the result of changes in events subsequent to the binding of insulin. J.E.G.

Goldsmith, P. C.; Rose, J. C.; Arimura, A.; and Ganong, W. F. (Dept. of Physiol., Univ. of California, San Francisco, & Veterans Administration Hosp. & Tulane Univ. Sch. of Med., New Orleans, La.): ULTRASTRUCTURAL LOCALIZATION OF SOMATOSTATIN IN PANCREATIC ISLETS OF THE RAT. Endocrinology 97:1061-64, 1975.

In order to determine the precise localization of somatostatin (SRIF) in the pancreas, electron-microscopic immunocytochemistry was performed on thin sections of whole pancreas and isolated pancreatic islets of the rat with the peroxidase antiperoxidase technic. SRIF was localized in secretory granules concentrated in cells sparsely distributed near the periphery of the islet. The granules were closely applied to their limiting membrane, exhibited moderate electron density, and were smaller than those in other islet cells. The location and relative number of SRIF-containing cells as well as the morphology of the granules suggest that SRIF is present in delta cells or a subgroup with small granules. These results provide evidence that SRIF is present in a discrete granule population in a specific type of secretory cell in the pancreatic islets. J.E.G.

Grodsky, Gerold M.; Fanska, Rudolph; and Lundquist, Ingmar (Metabolic Res. Unit & Dept. of Biochemistry & Biophysics, Univ. of California, San Francisco, Calif.): INTERRELATIONSHIPS BETWEEN α AND β ANOMERS OF GLUCOSE AFFECTING BOTH INSULIN AND GLUCAGON SECRETION IN THE PERFUSED RAT PANCREAS. II. Endocrinology 97:573-80, September 1975.

Temporal and quantitative relationships between the α and β anomers of glucose on insulin and glucagon secretion were studied in two surgical preparations of the in-vitro perfused rat pancreas. α-Glucose was a more effective stimulator of insulin release. β-Glucose, however, though less effective, was a positive modulator when admixed with α-glucose. Dose-response studies showed that α-glucose probably had a smaller apparent K_m for insulin secretion, while the V_{max} for the two anomers was the same—the effects of the two anomers being indistinguishable at high glucose concentrations (300 mg./dl.). α-Anomeric stereospecificity was demonstrable equally on both phases of insulin release and was maintained throughout 60-minute perfusions. Spontaneous or arginine-stimulated glucagon release was also preferentially inhibited by α-glucose. Since others have shown that glucose uptake and phosphorylation in islets are not α-stereospecific, the data suggest that the initial signal for the first and second phases of insulin release and glucose suppression of glucagon secretion is at the level of a glucoreceptor prior to, or independent of, major pathways of glucose metabolism. J.E.G.

Hofeldt, Fred D. (The Endocrine Serv., Dept. of Med., Fitzsimons Army Med. Center, Denver, Colorado): REACTIVE HYPOGLYCEMIA. Metabolism *24*:1193-1208, October 1975.

In this review a useful classification of the hypoglycemoses is presented with guidelines for the clinical, physiologic approach to these disorders. Particular emphasis is given to reactive hypoglycemic disorders characterized by postprandial onset, adrenergic-mediated symptoms, and benign etiologies, including the entities of alimentary-reactive, diabetic-reactive, hormonal deficiency, fructose 1-6 diphosphatase enzyme deficiency, and idiopathic hypoglycemia. It is emphasized that many normal subjects will manifest a normal transitional low blood glucose state, with blood glucose values below 50 mg./100 ml. There are no symptoms associated with this phase of intermediary metabolism, which marks the transition between the fed and fasting state. The various types of hypoglycemic states are described with reference to the timing of the onset of symptoms correlated with abnormalities in insulin-secretory rates and those of the counterregulatory hormones. Therapeutic programs are presented based on the classification as to the type of hypoglycemia, with emphasis on familiar dietary modifications and the use of such drugs as diphenylhydantoin, sulfonylureas, phenformin, and anticholinergic agents. C.R.S.

Jobansen, Klaus; Soeldner, J. Stuart; Gleason, Ray E.; Gottlieb, Marise; Park, Byung N.; Kaufmann, Robert L.; and Tan, Meng H.: (Joslin Research Lab., Dept. of Med., Harvard Med. Sch. Boston, Mass.; Peter Bent Brigham Hospital; and New England Deaconess Hosp.): SERUM INSULIN AND GROWTH HORMONE RESPONSE PATTERNS IN MONOZYGOTIC TWIN SIBLINGS OF PATIENTS WITH JUVENILE-ONSET DIABETES. N. Engl. J. Med. *293*:57-61, July 10, 1975.

Three groups of individuals—(1) monozygotic twin siblings of juvenile-onset diabetics, (2) normal individuals, and (3) offspring of two diabetic parents—were studied by oral glucose tolerance testing. The twins and normals were also compared with regard to intravenous glucose tolerance, tolbutamide tolerance, and cortisone glucose tolerance testing. The incidence of abnormal glucose tolerance was the same in the twins and the normal group but was much higher in the offspring of two diabetic parents. The twins had higher mean serum insulin levels during all tests, but this difference was statistically significant only during the cortisone glucose tolerance test.

The authors suggest that the failure to find a delayed or decreased insulin response in these "prediabetic" monozygotic twins of juvenile diabetics, as others have reported in offspring of two diabetic parents, may well be due to a variation in genetic and environmental factors that result in clinical diabetes mellitus. H.M.

Kaneto, Akio; Miki, Eishi; and Kosaka, Kinori (The 3rd Dept. of Internal. Med., Faculty of Med., Univ. of Tokyo, Tokyo, Japan): EFFECT OF BETA AND BETA$_2$ ADRENORECEPTOR STIMULANTS INFUSED INTRAPANCREATICALLY ON GLUCAGON AND INSULIN SECRETION. Endocrinology 97:1166-73, 1975.

L-Isoproterenol was infused at a dose of 20 pmol/kg./min. for 10 min. into the cranial pancreaticoduodenal artery in anesthetized dogs. Arterial plasma glucose, blood flow, and plasma concentrations of both glucagon and insulin in the cranial pancreaticoduodenal vein were significantly enhanced during the infusion, resulting in a greater increase of bihormonal output. Intrapancreatic pretreatment with propranolol abolished all of the isoproterenol-induced increases except for glucagon secretion, which was suppressed only in part. Pretreatment with practolol, a specific receptor blocker of the beta$_1$ type, did not exert any discernible inhibiting effect on the isoproterenol-induced enhancement. Intrapancreatic infusion of trimetoquinol, a selective receptor stimulant of the beta$_2$ type in some mammals, at an equimolar dose caused increases in plasma glucose, pancreatic venous blood flow, and bihormonal output similar to those induced by isoproterenol. Pretreatment with a larger dose of propranolol totally abolished the trimetoquinol-induced enhancement of both glucagon and insulin secretion. Pretreatment with

an isomolar dose of practolol, in contrast, did not show any suppressive effect on the parameters investigated. There was a dose dependency in the bihormonal responses to trimetoquinol. Another beta$_2$ receptor agonist, salbutamol, also significantly raised plasma glucose, pancreatic venous blood flow, and bihormonal concentrations during its intrapancreatic infusion, although to a lesser extent than did trimetoquinol. These results indicate that the adrenergic control over the function of the endocrine pancreas through beta adrenoreceptors may be mediated mainly by those of the beta$_2$ type. J.E.G.

Koerker, Donna J.; Harker, Laurence A.; and Goodner, Charles J. (Regional Primate Res. Centr. and the Robert H. Williams Lab. for Clinical Investigation; Dept. of Medicine, Harborview Med. Center; Univ. of Wash. School of Med.): EFFECTS OF SOMATOSTATIN ON HEMOSTASIS IN BABOONS. N. Engl. J. Med. *293*:476-79, 1975.

Male baboons repeatedly infused over a two-hour period with somatostatin at a rate of 0.8 μg. per kg. per min. were found to develop thrombocytopenia and evidence of pulmonary hemorrhage at autopsy. Platelet function was also found to be impaired during the infusion as measured by glass bead retention of platelets and ADP-induced aggregate of platelets. The authors use these data to sound a note of caution concerning long-term use of somatostatin. H.M.

Mielke, C. Harold; Gerich, John E.; Lorenzi, Mara; Tsalikian, Eva; Rodvein, Robert; Forsham, Peter H. (Inst. of Health Research, Inst. of Med. Sciences, Pacific Med. Center, Dept. of Med., Univ. of Calif., San Francisco): THE EFFECT OF SOMATOSTATIN ON COAGULATION AND PLATELET FUNCTION IN MAN. N. Engl. J. Med. *293*:480-83, 1975.

The authors found no effect of a four-hour infusion of 500 μg./hr. of somatostatin in five patients or an 18-hour infusion in three patients on hemostasis. Platelet aggregation induced by collagen, ADP, or epinephrine was not altered. The dose of somatostatin used was about one eighth that found to alter platelet function in monkeys. H.M.

Noe, Bryan D.; and Bauer, G. Eric (Depts. of Anat., Emory Univ., Atlanta, Georgia; Univ. of Minnesota, Health Science Centr., Minneapolis, Minn.; and Marine Biological Lab., Woods Hole, Mass.): EVIDENCE FOR SEQUENTIAL METABOLIC CLEAVAGE OF PROGLUCAGON TO GLUCAGON IN GLUCAGON BIOSYNTHESIS. Endocrinology 97:868-77, October 1975.

Following a 30-minute preincubation in medium containing no isotopes, anglefish islet tissue was incubated in the presence of [^{3}H]tryptophan and [^{14}C]isoleucine for 20 minutes. The glucagon immunoreactive molecules, one larger than proinsulin (mol. wt. near 11,400) and the other slightly smaller than proinsulin (mol. wt. near 9,000), were the primary proteins labeled with [^{3}H]tryptophan following the 20-minute pulse. During chase incubations of increasing duration, ^{3}H-radioactivity appeared in a glucagon immunoreactive molecule with the approximate molecular size of glucagon and increased with chase time while radioactivity in the 11,400-mol.-wt. tryptophan-labeled molecule decreased. With increasing chase time, the ^{3}H-radioactivity attributable to the 9,000-mol.-wt. tryptophan-labeled molecule initially increased and subsequently decreased, which is consistent with the pattern that would be expected for a conversion intermediate.

The presence of glucagon immunoreactivity in [^{3}H]tryptophan-labeled molecules having molecular weights near that of proinsulin was established by radioimmunoassay of alternate gel slices following electrophoresis of labeled proteins recovered from the proinsulin-containing portions of gel filtration eluates. That [^{14}C]isoleucine became incorporated into insulin and [^{3}H]tryptophan became incorporated into glucagon was established by determination of the distribution of radioactivity in polyacrylamide gels following electrophoresis of labeled proteins recovered from the insulin- and glucagon-containing portions of gel-filtration eluates. These results provide preliminary evidence for sequential metabolic cleavage of proglucagon in glucagon biosynthesis. J.E.G.

Olefsky, Jerrold; Crapo, Phyllis A.; Ginsberg, Henry; and Reaven, Gerald M. (Dept. of Med., Stanford Univ. Sch. of Med., Stanford, Calif., and Palo Alto V.A. Hosp., Palo Alto, Calif.): METABOLIC EFFECTS OF INCREASED CALORIC INTAKE IN MAN. Metabolism *24*:495-503, April 1975.

During periods of increased caloric intake, normal subjects manifested significant increases in fasting plasma insulin, glucose, and triglyceride levels as well as an increased insulin response to oral glucose. Since these changes occurred prior to significant weight gain they could be ascribed only to increased caloric consumption and not to obesity. Although longer periods of high caloric intake were marked by a return of the measured values toward baseline, small but significant elevations remained for fasting plasma glucose, insulin, and cholesterol levels. On the other hand, insulin resistance, as estimated by direct measurement of insulin responsiveness, did not change during the hypercaloric dietary period. These results indicate that increases in caloric intake can lead to elevated plasma glucose, insulin, cholesterol, and triglyceride levels and that these changes occur before significant weight gain takes place. Although these abnormalities occur in carbohydrate and lipid metabolism with increased caloric intake, insulin responsiveness remains intact—unlike the situation seen in obesity, wherein insulin resistance is often observed in association with these metabolic abnormalities. C.R.S.

Pagliara, Anthony S.; Hover, Barbara A.; Ellerman, Jeanette; and Matschinsky, Franz S. (Edward Mallinckrodt Depts. of Ped. & Pharmacol., Washington Univ. Sch. of Med., St. Louis, Mo.): IODOACETATE AND IODOACETAMIDE-INDUCED ALTERATIONS OF PANCREATIC α- AND β-CELL RESPONSES. Endocrinology 97:698-708, September 1975.

Iodoacetate and iodoacetamide were compared as to their capacity to block islet glycolysis and interfere with glucose inhibition of glucagon release and glucose stimulation of insulin release. Glycolysis was measured in isolated rat islets by the rate of lactate formation from 27 mM glucose. Hormone release was investigated by perfusing isolated rat pancreas with a 10-mM mixture of 19 amino acids, with and without 5 mM glucose. In perfusion experiments, lactate (2.5 mM) and pyruvate (0.5 mM) were present to provide an alternative source of energy independent of glycolysis. Iodoacetate was about twice as potent as iodoacetamide in blocking glycolysis in islets, 0.2 and 0.5 mM, respectively, being

needed for complete inhibition of lactate production. Levels of either agent lower than 0.05 mM did not affect lactate accumulation. Iodoacetate, at the level that completely inhibited glycolysis, did not interfere with the permissive action of glucose for insulin release. In contrast, iodoacetamide, at a level (0.05 mM) that had no effect on lactate production, changed the response of the β-cell dramatically: amino acids now released insulin even in the absence of glucose, and insulin release by 5 mM glucose alone was greatly augmented. Both thiol reagents at 0.025 mM concentration completely prevented glucose from suppressing amino-acid-stimulated glucagon release, iodoacetamide being more potent than iodoacetate. These data indicate that the opposite physiologic actions of glucose in α and β-cells are in each case dissociable from the fuel function of the sugar molecule, and the results best support the concept that glucose and thiol reagents effect insulin and glucagon secretion by acting on sulfhydryl groups related to receptor sites in the α- and β-cell membrane. J.E.G.

Posner, Norman A.; Silverstone, Felix; Tobin, Ellis H.; and Boyer, Joseph (Dept. of Obstet. and Gyne. and Med., Maimonides Hospital, Dept. of Obstet. and Gyne., Downstate Medical Center, New York): CHANGES IN CARBOHYDRATE TOLERANCE DURING LONG-TERM ORAL CONTRACEPTION. Am. J. Obstet. Gynec. *123*:119-27, 1975.

A prospective study was undertaken in 116 women starting oral contraception with Ovulen to determine the effect of this contraceptive agent on glucose tolerance as assessed serially by means of the intravenous glucose tolerance test. Subjects were followed for one to four years during Ovulen therapy. Women using intrauterine devices for contraception served as a control group and showed no changes in glucose tolerance during the observation period. Women receiving Ovulen were divided into two groups—those with prediabetes (a positive family history of diabetes, glycosuria during prior pregnancy, or the birth of a child weighing more than 4.5 kilograms) and normal controls. During the course of the study no overt diabetes occurred. However, a prompt significant decline in glucose tolerance (K value) was noted in the normal group. This persisted for the duration of the study. At least one abnormal glucose tolerance test was noted in 13 per cent of this group. In the suspect diabetic group, a decline in glucose tolerance was also noted, but this was not statistically significant. At no time during the study did mean K values decline below 1.6. Since in nondiabetic subjects as well as those suspected of having prediabetes no overt diabetes developed during the period of observation, it appears that this oral contraceptive has no clinically significant effects on glucose tolerance. J.E.G.

Raskin, Philip; Fujita, Yoshikuni; and Unger, Roger H. (VA Hosp., Dept. of Med. Univ. of Texas S. W. Med. School, Dallas, Texas): EFFECT OF INSULIN-GLUCOSE INFUSIONS ON PLASMA GLUCAGON LEVELS IN FASTING DIABETICS AND NONDIABETICS. J. Clin. Invest. *56*:1132-38, November 1975.

A previous report from the authors' laboratory (Diabetes *21*:301-07, 1972) demonstrated that glucagon levels could not be normally suppressed when adult diabetics were given insulin during a carbohydrate meal; this finding was in contrast to the prompt suppression of glucagon with insulin in alloxan-diabetic dogs and suggested that insulin lack alone may not explain the alpha-cell abnormality in human diabetics. This problem was re-examined in adult and juvenile-onset diabetics given a continuous insulin infusion while blood glucose was maintained with intravenous glucose; two levels of insulin infusion were used, resulting in insulin levels of 25 to 35 μU./ml. and 300 to 600 μU./ml. The results were compared with those in normal controls who were given the low level of insulin infusion together wtih glucose to maintain normoglycemia or to induce hyperglycemia. All groups showed a significant reduction in plasma glucagon levels; although there was a significantly greater reduction at some time points in hyperglycemic nondiabetics, these differences were present only at the lower insulin-infusion rate. These results suggest that the alpha cell in the diabetic is at least partially responsive to the suppression effects of insulin but does not exclude a quantitative defect in insulin sensitivity or an insulin-independent defect. R.R.

Rayfield, Elliot J.: George, David T.; Eichner, Harvey L.; and Hsu, T. H. (Dept. of Med. Mt. Sinai Sch. of Medicine of the City Univ. of New York; U.S. Army Med. Research Inst. of Infect. Dis.; Dept. of Med. Johns Hopkins Univ. Sch. of Med. Baltimore, Md.): L-DOPA STIMULATION OF GLUCAGON SECRETION IN MAN. N. Engl. J. Med. *293*:589-91, September 18, 1975.

An oral dose of L-dopa (0.5 mg.) was found to almost double the plasma glucagon level at 30 minutes. Concomitant with this, the plasma glucose increased 20 per cent and plasma insulin values doubled. The plasma-growth hormone was not altered until 45 minutes after the L-dopa, showing that the glucagon effects were independent of the growth hormone changes. This study emphasizes the influence of the autonomic nervous system on islet cell function. H.M.

Schade, David S.; and Eaton, R. Philip (Dept. of Med., Univ. of New Mexico Sch. of Med., Albuquerque, N. M.): GLUCAGON REGULATION OF PLASMA KETONE BODY CONCENTRATION IN HUMAN DIABETES. J. Clin. Invest. *56*:1340-44, November 1975.

Recent studies have suggested that the necessary conditions for ketogenesis include increased free fatty acid substrate availability and increased hepatic conversion of free fatty acids to ketone bodies. While pharmacologic levels of glucagon have been demonstrated to increase both lipolysis and hepatic ketone body production, the authors assessed the effects of a physiologic elevation of glucagon on these factors. Insulin-dependent diabetics were infused with glucagon, resulting in a rise in mean glucagon levels from 63 pg./ml. to 215 pg./ml., which is within the physiologic glucagon range; the same subjects given a saline infusion served as controls. Intravenous heparin was then administered after 30 minutes and resulted in a similar acute rise in free fatty acids during saline and glucagon infusion. During glucagon infusion alone there were no significant changes in free fatty acids or total ketone bodies; however, following heparin-induced free fatty acid release, ketone levels were increased by 80 per cent during glucagon infusion as against 20 per cent during saline infusion. Thus, the authors have demonstrated that at physiologic levels, glucagon induces an increased ketone body concentration when the availability of free fatty acid substrate has been increased; this effect of glucagon is presumably secondary to increased hepatic ketogenesis, although there are no data on the effect of glucagon on ketone body utilization. R.R.

Soll, Andrew H.; Kahn, C. Ronald; Neville, David M., Jr.; and Roth, Jesse (Diabetes Branch, National Inst. of Arthritis, Metabolism, & Digestive Diseases, N.I.H., Bethesda, Md.; and the Section on Biophysical Chemistry; Lab. of Neurochemistry N.F.H., National Institute of Health, Bethesda, Md.): INSULIN RECEPTOR DEFICIENCY IN GENETIC AND ACQUIRED OBESITY. J. Clin. Invest. 56:769-80, October 1975.

The authors have extended their previous observations on the insulin receptor in obesity. In two forms of inherited insulin-resistant obesity in mice (ob/ob and db/db) and in normal mice made obese with gold thioglucose, the well-recognized hyperinsulinemia and hyperglycemia were associated with a decrease in insulin binding on isolated liver plasma membranes; insulin binding was normal in mice heterozygous for the ob gene. After dieting to a normal body weight, insulin binding increased in both the obese-gold-thioglucose and the ob/ob mice but reached normal only in the former group. Exogenous insulin resulting in sustained hyperinsulinism prevented the increase in insulin binding normally seen in fasted ob/ob mice. There was excellent correlation between the fasting insulin level and insulin binding among all groups studied; these changes in insulin binding could be fully accounted for by changes in the insulin receptor concentration. The authors propose that a decrease in insulin binding is characteristic of obesity and that insulin levels control the concentration of insulin receptors on target cells. R.R.

Szabo, Olga; and Szabo, Andrew J. (Dept. of Med., New York Med. Coll., New York, New York, & The Sect. of Metabolism, Med. Serv., Metropolitan Hosp. Cent., New York): THE EFFECT OF HYPOPHYSECTOMY ON THE FUNCTION OF THE INSULIN-SENSITIVE CENTRAL NERVOUS SYSTEM GLUCOREGULATOR RECEPTOR. Endocrinology 97:734-38, September 1975.

Hypophysectomized and healthy control rats were studied to investigate the mechanism of action of the insulin-sensitive glucoregulator receptor of the central nervous system (CNS). Glucagon-free insulin (500 μU.) was injected into the carotid artery, and the peripheral blood glucose was monitored. An immediate significant fall in the blood sugar was observed in intact as well as in hypophysectomized rats. To control these experiments, buffer was injected into the carotid artery, or 500 μU. insulin was given through the jugular vein of intact and hypophysectomized animals. The systemic blood sugar level remained unchanged for 10-15 minutes in the control experiments. The results indicate that the function of this insulin-sensitive glucoregulator CNS receptor is not impaired in the hypophysectomized state. The initial phase of its effect, the sudden decrease of the blood sugar level, appears to be independent of pituitary hormone secretion. J.E.G.

Taradash, Michael R.; and Jacobson, Lester B. (Dept. of Med., Cardiovascular Div. Moffit Hospital, Univ. of Calif., San Francisco, Calif.): VASODILATOR THERAPY OF IDIOPATHIC LACTIC ACIDOSIS. N. Engl. J. Med. *293*:468-71, September 4, 1975.

The authors report an elderly patient with respiratory distress, cardiomegaly, pulmonary congestion, and lactic acidosis (20 mEq./L. of lactate) who was initially treated with sodium bicarbonate. This therapy precipitated pulmonary edema and a worsening of the acidosis. The patient was then treated with nitroprusside to reduce afterload. The pulmonary artery wedge pressure fell from 28 to 12 mm. Hg, arterial blood pressure fell from 140/50 to 120/50, and the patient's skin became pink. With this therapy his acidosis rapidly reverted to an alkalosis without any further bicarbonate. The authors postulate that the patient developed lactic acidosis in the absence of hypoxia or shock because of regional vasoconstriction, especially with regard to the liver. This report points out the efficacy of trying to treat the cause of lactic acidosis rather than the acidosis itself. H.M.

Erratum

The legend to figure 1 of "Insulin Adsorbance to Polyvinylchloride Surfaces with Implications for Constant-infusion Therapy," by Peterson et al., on page 74 of DIABETES, Vol. 25, January, 1976, should have read:

FIG. 1. Insulin recovered from the infusion apparatus for 50 mU. ^{125}I-insulin plus 25 U. regular insulin in 500 ml. normal saline with a 50-ml. wash-out prior to the start of sample collection (▲-▲); the same solution without a 50-ml. wash-out (■-■); the same solution with 1.25 gm. per cent albumin added, with no wash-out prior to sample collection (●-●). Each figure represents a 1-ml. sample, with radioactivity in each sample represented as per cent of radioactivity in a 1-ml. sample of the initial volumetric control.

ORGANIZATION SECTION

THIRTY-SIXTH ANNUAL MEETING

The Thirty-sixth Annual Meeting of the American Diabetes Association will be held at the Hilton Hotel, San Francisco. An outline of procedures for submission of abstracts of papers to be presented at the Scientific Sessions, June 20-22, has been mailed to the membership. Physicians, allied health personnel, and other scientists who would like to present papers may submit abstracts