

# ABSTRACTS

Ammon, H. P. T.; Orci, L.; and Steinke, J. (E. P. Joslin Res. Lab., Peter Bent Brigham Hosp., and Dept. of Med., Harvard Med. Sch., Boston, Mass.): EFFECT OF CHLORPROMAZINE (CPZ) ON INSULIN RELEASE IN VIVO AND IN VITRO IN THE RAT. *J. Pharmacol. Exp. Ther.* 187:423-29, 1973.

These studies were designed to elucidate the mechanism of the diabetogenic effect of CPZ. The authors have shown significant abnormality in glucose tolerance in rats after pretreatment with CPZ at a dose of 32 mg. per kilogram, both in terms of elevated glucose and diminished insulin release at 10, 20, and 60 minutes after glucose administration. A dose of 3.2 mg. per kilogram had no significant effect on glucose tolerance. In vitro studies with isolated rat islets revealed gradual inhibition of glucose-induced insulin release with 0.005, 0.01 and 0.1 mM CPZ in the incubates. Preincubation of islets before glucose stimulation again revealed significant inhibition of insulin release with 0.01 and 0.1 mM CPZ. Ninety minute incubation of islets in 0.1 mM CPZ did not effect total extractable insulin suggesting that the above responses reflect insulin secretion. In a final series of studies, carbon dioxide production during incubation with  $^{14}\text{C}$ -1 glucose was reduced in comparison to studies with  $^{14}\text{C}$ -6 glucose in the presence of CPZ, suggesting some diminution of glucose oxidation via the pentose phosphate shunt. The authors conclude that the diabetogenic effect of CPZ is mediated via decreased insulin response to glucose and, furthermore, that this alteration may result from a change in the oxidative disposition of glucose. T.C.H.

Asplund, K. (Dept. of Histol., Univ. of Uppsala, Uppsala, Sweden): EFFECTS OF INTERMITTENT GLUCOSE INFUSIONS IN PREGNANT RATS ON THE FUNCTIONAL DEVELOPMENT OF THE FOETAL PANCREATIC B-CELLS. *J. Endocrinol.* 59:285-93, 1973.

The author infused either glucose or saline into pregnant rats during the last five days of pregnancy in order to determine if this influenced the fetal pancreas. With the glucose there was approximately a 50 mg. per 100 ml. increase in the blood sugar of the mothers and no change with saline. The immunoreactive insulin content of the fetal pancreases from mothers given glucose or saline was the same. However, the release of insulin by the fetal pancreas in response to a high glucose concentration (3 mg. per milliliter) was much greater in the fetuses whose mothers were given glucose. These studies support two concepts which are important. The first is that the hypoglycemia seen in infants of diabetic mothers following delivery is due to the effect of the mother's hyperglycemia on the fetus during pregnancy. The second concept is that the pancreatic beta cells are responsive to a glucose inducible glucoreceptor. H.M.

Björntorp, Per; de Jonge, Kristina; Krotkiewski, Marcin; Sullivan, Lars; Sjöström, Lars; and Stenberg, Jesper (Clin. Metab. Lab. and Cardiol. Sect., First Med. Service and Dept. of Med. Rehabil. Sahlgren's Hospital, Univ. of Gothenburg, Gothenburg, Sweden): PHYSICAL TRAINING IN HUMAN OBESITY. III. EFFECTS OF LONG-TERM PHYSICAL TRAINING ON BODY COMPOSITION. *Metabolism* 22:1467-75, December 1973.

*Verbatim summary.* Eight severely obese patients with juvenile onset obesity, adipose tissue hypercellularity and elevated body cell mass were placed on a rigorous schedule of physical training for a period of six months without dietary restriction. Body weight, fat, and cell mass showed no significant change during the training program. Fasting blood glucose did not change but plasma insulin levels decreased after three months of training. After six months, plasma insulin levels remained decreased; the glucose tolerance improved and plasma triglycerides tended to be somewhat lower. Improved glucose tolerance may indicate a primary effect of training on glucose removal mechanisms rather than on insulin secretion. The lack of body fat decrease after the long training period might be characteristic for patients with this type of severe obesity as contrasted to the pronounced decrease in fat caused by similar programs in patients without severe obesity.

Blackwell, S. W.; and Burns-Cox, C. J. (Bristol Gen. Hosp., Bristol, England): INTRAVASCULAR HAEMOLYSIS COMPLICATING TREATED NON-KETOTIC HYPERGLYCAEMIC DIABETIC COMA. *Postgrad. Med. J.* 49:656-57, September 1973.

A patient with nonketotic hyperosmolar coma is reported. Intravenous fluid therapy included a liter of normal saline and six liters of very hypotonic (0.18 per cent) saline. During treatment the patient developed cerebral edema and intravascular hemolysis.

This case demonstrates the possible complications of hypotonic fluid therapy. D.K.

Brenner, William L.; Lansky, Zena; Engelman, Richard M.; and Stahl, William M. (Dept. of Surg., New York Univ. Sch. of Med., New York): HYPEROSMOLAR COMA IN SURGICAL PATIENTS: IN IATROGENIC DISEASE OF INCREASING INCIDENCE. *Ann. Surg.* 178:651-55, 1973.

The authors report ten cases of hyperosmolar coma seen over a two year period on their surgical services. Four deaths in the group were attributed to hyperosmolar coma, and four of the patients were known to have diabetes at the time of diagnosis. A series of arbitrary groups are derived to categorize surgical patients susceptible to this complication; however, more importantly a number of clinical surgical problems with multiple predisposing factors are described: Coronary by-pass procedures in a patient population with an increased incidence of diabetes, often using hyperglycemic solutions to prime by-pass pumps; patients receiving both oral and intravenous hyperosmolar hyperalimentering supplements; patients with large surface area burns being treated with topical silver nitrate, a dehydrating agent; and uremics with potent diuretic administration during the intra- and postoperative periods. The authors suggest that hyperosmolar coma could perhaps be prevented in some patients with knowledge of avoidable precipitating events. T.C.H.

Brogard, J-M; Kuntzmann, F.; Touitou, D.; and Dorner, M. (Clinique Médicale B. C. H. U., Strasbourg, France): SEVERE HYPOGLYCEMIA INDUCED BY ANTIDIABETIC SULFONAMIDES ON FIVE CASES OF HYPOGLYCEMIC COMA IN ELDERLY PATIENTS. *Sem. Hop. Paris* 49:2461, 1973.

*Verbatim summary.* Five cases of hypoglycemic reactions follow-

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ing the use of antidiabetic sulfonamides are reported. The following features are pointed out: (1) occurrence in patients generally over the age of sixty; (2) occurrence during the initial period of sulfonamide treatment; (3) the hypoglycemia is persistent, with possible recurrences. It should be possible to limit the number and seriousness of such accidents by preventive measures: careful indications, in order to avoid inappropriate sulfonamide therapy; the initial dosage should be cautious and progressive; choice of sulfonamides suited to the renal condition; special caution during association with drugs liable to potentiate the hypoglycemic effect; an adequate carbohydrate supply should be given.

From the therapeutic point of view, sustained administration of glucose is emphasized. The use of glucagon is discussed.

*Cerchio, G. M.; Persico, P. A.; and Jeffay, Henry* (Vet. Adm. West Side Hosp. and Depts. of Med. and Biol. Chem., Univ. of Ill. Coll. of Med., Chicago, Ill.): INHIBITION OF INSULIN RELEASE DURING HYPOVOLEMIC SHOCK. *Metabolism* 22:1449-58, December 1973.

Hemorrhagic hypotension sustained for two hours in baboons resulted in a rapid and substantial reduction in insulin content of portal and peripheral venous blood which remained below pre-shock levels for the duration of the experiment. Administration of tolbutamide after sixty minutes of shock produced a minimal response in insulin levels compared to that observed in control animals. Disappearance rates of insulin from serum were not significantly different in shocked animals compared to controls. Phentolamine, injected after one hour of shock, produced a rise in serum insulin followed by a decrease in plasma glucose levels. These observations demonstrate that hypoinsulinemia induced during shock is due to a depression of pancreatic insulin release which appears to be under adrenergic control and is not related to an acceleration of insulin degradation. In circulatory failure increased catecholamine activity may lead to a rapid decline in portal and peripheral insulin levels which permits diversion of glucose to noninsulin-dependent tissues, such as the brain, to be used for increased energy needs during the shock state. C.S.

*Chase, H. P.; Marlow, R. A.; Dabiere, C. S.; and Welch, N. N.* (Univ. of Colo. Med. Center, Denver, Colo.): HYPOGLYCEMIA AND BRAIN DEVELOPMENT. *Pediatrics* 52:513-20, October 1973.

*Verbatim summary.* Though hypoglycemia has been a common clinical condition known to affect human brain development, little has been done to define the resultant brain biochemical alterations. Because a controlled study of hypoglycemia in the newborn human infant is impossible, the infant rat was chosen as a model. Hypoglycemia induced once daily for eighteen days following birth resulted in a generalized diminution of brain weight, cellularity, and protein content. The rate of formation of the myelin lipid sulfatide was decreased, as was the quantity of cerebroside-sulfatide in brains of hypoglycemic animals. Phospholipids, gangliosides, and cholesterol were decreased only in proportion to the decrease in brain weight. Brain glucose and glycogen concentrations were low in the brains of hypoglycemic animals, although ATP and phosphocreatine levels were not decreased.

*Garcia, M. J.; Czerwinski, C.; De Santis, R.; Lan, V. V.; Ramey, E.; and Penhos, J. C.* (Endocr. Res. Unit, V. A. Hosp., Dept. of Physiol. and Biophys., Geo. Wash. Univ., Wash., D.C.): HYPERGLYCEMIC AND INSULINOGENIC EFFECTS OF INTRAVENOUS GLUCAGON AT DIFFERENT BLOOD GLUCOSE LEVELS. *Proc. Soc. Exp. Biol. Med.* 143:707-10, July 1973.

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The insulin and glucose responses to intravenous glucagon are reported in beagle dogs. Glucagon administered to fasting animals produced an expected rise in the insulin and glucose concentrations. A hyperglycemic state was produced by 50 per cent glucose infusion. Glucagon injection during hyperglycemia induced a marked increase in insulin concentration and a delayed disappearance of blood glucose. It is suggested that both blood glucose levels and glucagon act together to produce the maximal beta cell response. D.K.

*Grabner, W.; Phillip, J.; and Strigl, P.* (Dept. of Med., Univ. of Erlangen, Nuremberg, Germany): THE DIAGNOSTIC VALUE OF ORAL GLUCOSE TOLERANCE TEST AND COMBINED B-CELL STIMULATION IN CHRONIC PANCREATITIS. *Am. J. Dig. Dis.* 18:1055-60, December 1973.

*Verbatim summary.* The secretory capacity of the B-cells in forty patients with chronic or chronic relapsing pancreatitis was examined by means of the oral glucose tolerance test (100 gm. of glucose, orally) and combined stimulation (100 gm. of glucose, orally, 1 mg. of glucagon, and 0.5 gm. of tolbutamide intravenously). Under both the test conditions, the immunologically measurable insulin was significantly reduced compared to that of controls. The maximal insulin differences and the insulinogenic index (thirty-five-minute value) of the combined stimulation method were most satisfactory for the diagnosis of the secretory B-cell insufficiency. In addition to these parameters, the constancy of insulin levels in the period between thirty-five and sixty minutes indicated a dysfunction of the endocrine pancreas.

*Kongtabworn, C.; Foster, E.; Mason, E. E.; and Printen, K. J.* (Dept. of Surg., Univ. Hosp., Iowa City, Iowa): HEPARIN-INDUCED ELEVATION OF FREE FATTY ACIDS IN DIABETIC PATIENTS. *Surgery* 74:30-33, July 1973.

Postheparin free fatty acid responses in four groups of patients are presented: controls, morbid obesity, cardiopulmonary bypass and diabetics. Free fatty acid levels were significantly higher in the diabetics preheparin and at four time intervals up to ninety minutes postheparin. On the basis of these data the authors conclude that heparin therapy in diabetics may be harmful, assuming that free fatty acids are toxic. T.C.H.

*Marco, Jose; Diego, Javier; Villanueva, Maria; Diaz-Fierros, Maruxa; Valverde, Isabel; and Segovia, Jose* (Clinica Puerta de Hierro, Universidad Autonoma de Madrid, Madrid, Spain): ELEVATED PLASMA GLUCAGON LEVELS IN CIRRHOSIS OF THE LIVER. *N. Engl. J. Med.* 289:1107-11, Nov. 22, 1973.

Immunoreactive glucagon levels were studied in cirrhotic patients, some of whom had portacaval shunts. The basal glucagon values and the response to arginine stimulation were found to be greater in the cirrhotic patients than in the control group. The increase in glucagon was apparently due to a decrease in the degradation of glucagon by the liver of these patients. However, the authors point out that the liver disease lessens the effect of glucagon so that its role in the carbohydrate intolerance of cirrhosis is not clear at this time. H.M.

*Mason, Edward E.; Gordy, Dennis D.; Chernigoy, Franz A.; and Printen, Kenneth J.* (Dept. of Surg., Univ. Hosp., Univ. of Iowa, Iowa City, Iowa): FATTY ACID TOXICITY. *Surg. Gynec. Obstet.* 133:992-98, December 1971.

This report details one obese female in whom free fatty acid (FFA) levels ranged from 1 to 1.5 mEq. per liter during periods of fasting and fell to below 0.5 mEq. per liter while the subject

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received 1000 cal. per day on numerous occasions during a seventy-five day study period. Three groups of patients were studied during bypass surgical procedures for obesity, thirteen receiving intravenous glucose and six receiving intravenous glucose and amino acids with infusions starting two hours into the operation. The third group of eight patients received intravenous glucose starting at the fifth hour of operation. FFA levels fell significantly at five hours into the operation in the group receiving glucose and amino acids in comparison to the group first receiving glucose at the fifth hour. In two of the operated patients, thrombus formation time and FFA levels demonstrated a reciprocal relationship.

The authors conclude that circulating FFA levels may relate to thromboembolic phenomena and, furthermore, adequate provision of carbohydrate and protein minimize these levels. T.C.H.

*Novin, Donald; VanderWeele, Dennis A.; and Rezek, Milan* (Dept. of Psych. and Brain Inst., Univ. of Calif., Los Angeles): INFUSION OF 2-DEOXY-D-GLUCOSE INTO THE HEPATIC-PORTAL SYSTEM CAUSES EATING: EVIDENCE FOR PERIPHERAL GLUCORECEPTORS. *Science* 181:858-60, August 31, 1973.

*Verbatim summary.* Injections of 2-deoxyglucose into the hepatic-portal system of normal rabbits increased eating to a greater extent and with shorter latency than comparable injections of 2-deoxyglucose into the jugular vein or into the hepatic-portal circulation of the vagotomized rabbit. These differences suggest the existence of vagally mediated peripheral glucoreceptors important in the initiation of food intake.

*Permutt, Marshall Alan; and Kipnis, David M.* (Dept. of Med., Washington Univ. Sch. of Med., St. Louis, Mo.): GLUCOSE REGULATION OF INSULIN BIOSYNTHESIS IN ISOLATED RAT ISLETS. *J. Mount Sinai Hosp., N.Y.* 40:323-33, May-June 1973.

*Verbatim summary.* Insulin biosynthesis in isolated rat pancreatic islets has been studied to determine the mechanisms whereby alterations in glucose concentrations alter biosynthetic rates. Glucose stimulated the uptake, phosphorylation, and incorporation of islet RNA precursors, as well as the species of RNA synthesized. Islet messenger RNA was stripped from polysomes and analyzed by sucrose gradients and polyacrylamide gel electrophoresis. Islet m-RNA synthesized at 2.8 mM or 16.6 mM glucose was qualitatively indistinguishable by these methods. I-125-labeled anti-insulin antibody bound to polysomes from a hamster insulinoma. Highest specific activity was in the small polysome region, thus giving the first estimate of the size of proinsulin m-RNA.

Glucose stimulates islet protein synthesis on preformed m-RNA as well. Activation of islet polyribosomes by glucose occurs in the presence or absence of actinomycin D and by the increase of initiation. NaF (10 mM) and lowered temperature (37° C. → 22° C.) reduce the glucose-stimulated activation of islet polysomes. Islets incubated in 16.6 mM glucose incorporated about six times as much <sup>3</sup>H-guanosine into GTP as islets incubated in 2.8 mM glucose, and the per cent of the total nucleotide pool in GTP rose from 21 per cent to 55 per cent.

*Simon, M.; Vongsavanthong, S.; Hespel, J.-P.; Lecornu, M.; and Bourel, M.* (Hosp. Pontchaillou, 35077 Rennes, France): DIABETE ET HEMOCHROMATOSE (I and II). *Sem. Hop. Paris* 49:2125, 1973.

Within 130 cases of idiopathic hemochromatosis, an over-all frequency of 81 per cent of diabetes was recorded (22 per cent in

the latent form). Diabetes occurred in 34 per cent of all the cases as the initial sign of illness. Eighty-one per cent of the diabetic patients required insulin (average 73.7 U. daily as compared to a mean of 52.2 U. in a control group of common diabetes). This fact indicates some degree of insulin resistance in this type of diabetes. In ten cases of latent diabetes, insulinemia was studied during an oral glucose tolerance test, and seven had low serum levels. Histologic examination of the pancreas (eleven cases) revealed a considerable decrease of the number of the islets of Langerhans in nine patients.

The group of patients with hemochromatosis and diabetes was compared to a matched group of patients with common diabetes with respect to complications. In contrast to other studies the incidence of atherosclerosis, neuropathy, nephropathy, and retinopathy did not differ significantly in the two groups. N.K.

*Spech, H.-J.; Wernze, H.; and Brunswig, D.* (Medizinische Universitätsklinik Würzburg West Germany): STREPTOZOTOCIN IN INSULIN-PRODUCING, METASTATIC ISLET CELL CARCINOMA. *Med. Klin.* 68:555, April 1973.

*Verbatim summary.* A seventy-one year old woman with metastatic insulinoma and hypoglycemia was treated with streptozotocin. A rapid and complete disappearance of hypoglycemia and hypoglycemic shocks occurred. Nephrotoxic side effects were characterized by an increase in urea nitrogen, creatinine, glucosuria, proteinuria, a high alkaline urine output and disturbances in electrolytes and acid-base-balance. In part the renal complications contributed to the lethal outcome. Application of each single dose of streptozotocin must be well controlled by renal and liver function tests as well as electrolytes and acid-base-balance studies.

*Volk, B. W.; Wellmann, K. F.; and Brancato, P.* (Isaac Albert Research Institute of the Kingsbrook Jewish Medical Center, Brooklyn, New York 11203, U.S.A.): FINE STRUCTURE OF RAT ISLET CELL TUMORS INDUCED BY STREPTOZOTOCIN AND NICOTINAMIDE. *Diabetologia* 10:37-44, 1973.

*Verbatim summary.* Young male Holtzman rats were injected intravenously with 50 mg./kg. of streptozotocin, preceded and followed by a single intraperitoneal injection of 350 mg./kg. of nicotinamide, according to the method of Rakieten *et al.* After 245 to 323 days, twenty-seven pancreatic islet cell tumors measuring up to 0.6 cm. were demonstrable in twenty of forty-one rats so treated; they were solitary in fifteen and multiple (two or three neoplasms each) in five animals. It was not possible to distinguish between tumor-bearing and tumor-free rats on the basis of periodic blood sugar determinations and serum insulin assays. Mean insulin concentration in grossly tumor-free pancreatic specimens was 0.661 units of insulin/g of wet tissue, but amounted to 5.385 units/g in specimens containing tumor. The islet cell tumors were rounded and well delineated. They were located in all parts of the pancreas. In general, their cells stained deeply with aldehyde-fuchsin. Ultrastructurally, most tumors consisted of well granulated B cells. A or D cells were not encountered while occasional EC cells were identified. Nucleoli were frequently prominent. Some necrotic B cells and others with few or unusually small secretory granules were present. Extravasated erythrocytes as well as hemosiderin deposits were seen in many tumors, and tumor cell particles were occasionally noted within the lumina of capillaries. Distant metastases were not demonstrable in this group of animals.