ABSTRACTS

Ahuja, M. M. S. (Dept. of Med., All-India Institute of the Med. Sci., New Delhi, India): KETOSIS-RESISTANT YOUNG DIABETICS. Lancet *1*:1254-55, June 12, 1965.

Plasma insulin-like activity (glucose uptake by rat diaphragm) and clinical responsiveness to oral sulfonylurea treatment was assessed in fifteen patients with ketosis resistant "growth-onset" diabetes. The subjects averaged twenty-three years of age and one year of diabetes duration. ILA averaged 6.8 ± 1.4 mg. per gm. dry weight of rat diaphragm in control subjects and was normal or above normal (range 4.6 to 25.0) in all but one diabetic. Despite these findings, only two diabetics could be controlled with sulfonylurea treatment alone and doses of insulin ranging from 70 to 144 U. per day were necessary to control the diabetes in nine patients. The discrepancy between the apparently adequate insulinogenic reserve and the lack of response to sulfonylurea agents is not explained. T.G.S.

Aylett, Pamela (Westminster Hosp. Group, London, England): EFFECTS OF TOLBUTAMIDE UPON GASTRIC SECRETION AND EMPTYING. Brit. Med. J. *1*:1464-66, June 5, 1965.

The effects upon gastric secretion and emptying in eight duodenal ulcer patients following intravenous tolbutamide were studied by use of a test meal as described by Hunt (Hunt, J. N.: Guy's Hosp. Rep. *103*:161, 1954). The test meal was given through a polyvinyl tube in the stomach, allowed to "digest" for twenty minutes, and the unemptied gastric contents recovered by suction, using an electric pump. Each meal was preceded and followed by a 250-ml. "washout" of tap water. Estimations were made on the recovered gastric contents of the concentrations of acid, chloride, potassium, sodium, and phenol red, with additional phenol-red contents of the final washout also being noted. Using Hunt's equations, these measurements together with the volume of recovered gastric contents and the final washout enabled the twenty-minute output of these gastric electrolytes and acid to be calculated. "Control" meals were obtained after intravenous injection of 10 ml. of saline, and on separate days at thirty minutes after intravenous injection of 10 ml. of 1 per cent sodium tolbutamide. Venous blood for glucose was obtained fasting and at ten minutes after the start of each meal.

In four of the eight duodenal ulcer patients there were mild hypoglycemic symptoms after intravenous tolbutamide. In the remaining four subjects, there were no symptoms noted.

The results indicated that after intravenous sodium tolbutamide in duodenal ulcer subjects there was an increase in gastric secretion of acid, chloride, and potassium, as well as in volume of secretion. Concentrations of potassium and sodium fell. These effects were similar to, but milder than, those producible in reported studies utilizing insulin. Tolbutamide led to an increased rate of gastric emptying similar to that reported to occur after insulin. An associated fall in blood glucose level is produced in these nondiabetic subjects, but degree of gastric secretion was not quantitatively correlated with blood glucose level. On the other hand, there was a relation between gastric emptying rate and a change in blood glucose level with a tendency to an increase in emptying with an increase in the degree of fall of blood glucose from the fasting values. R.F.B.

Benner, Ernest J.; Partridge, John W.; and Holcomb, Blair (Univ. of Wash. Sch. of Med., Seattle, Wash., and Univ. of Oregon Med. Sch., Portland, Ore.): AN EVALUATION OF LONG-TERM CHLORPROPAMIDE THERAPY. JAMA *193*:763-66, Sept. 6, 1965.

This is a study of a well-selected group of 147 private diabetic patients over forty years of age who had succeeded on therapy with chlorpropamide for eighteen months each and then followed for a total of twenty-four to sixty-three months. Subsequent failure of regulation occurred in twenty-five patients but none of the sixty-two patients who were successfully treated for forty-two months (or of the forty-seven patients treated for more than four years) subsequently had delayed failure. Only three out of the twenty-five early failures were attributable to true drug failure; the remainder were due to stress, lack of tolerance to the drug, or dietary failure; mainly the latter. This was evidence for remarkable persistence of drug action provided patient cooperation is present. Degenerative vascular changes were present in 42 per cent of the patients and were not considered contra-indications to the use of the drug. S.B.B.

Berkowitz, Donald (Dept. of Med., Hahnemann Med. Coll., and the Albert Einstein and Sidney Hillman Med. Centers, Philadelphia, Pa.): THE EFFECTS OF CHLOROPHENOXYISOBUTYRATE WITH AND WITHOUT ANDROSTERONE ON THE SERUM LIPIDS, FAT TOLERANCE, AND URIC ACID. Metabolism *14*:966-75, September 1965.

A group of thirty-five patients with elevated serum cholesterol was treated with chlorophenoxyisobutyrate (CPIB) and androsterone for sixteen weeks after a four-week control period. This was followed by an eight-week period with no medication and an additional sixteen-week interval of CPIB alone. The CPIB alone and the mixture produced the same significant decreases in serum cholesterol and triglyceride. During the period of no drug administration the serum lipids showed a gradual return to the control levels. During the treatment periods there was an improvement in fat tolerance tests and a decrease in serum uric acid levels both of which appear to be related to the degree of hypertriglyceridemia. No significant side effects or toxicity have been noted with this agent. C.R.S.

Bloom, Walter Lyon (Ferst Res. Center, and Piedmont Hosp., Dept. of Med., Med. Coll. of Georgia, Augusta, Ga.): A MECHANICAL DEVICE FOR MEASURING HUMAN ENERGY EXPENDITURE. Metabolism *14*:955-58, September 1965.

A simple mechanical device is described for measurement of energy expenditure in calories. The device was constructed on the basis of the observed linear correlation between oxygen consumption and the volume of expired air. The measurement of direct oxygen consumption correlated well with the results obtained by this portable calorimeter using a large

number of subjects performing a variety of physical activities. Multiple studies on a single subject at increasing levels of energy expenditure showed a maximum difference in any set of 7.8 per cent. The only limitation of the device is related to normal pulmonary function. Its value for education of physician and patient in matters of energy balance is emphasized. C.R.S.

Cahill, George F., Jr. (Elliott P. Joslin Res. Lab., Dept. of Med., Harvard Med. Sch., and Diabetes Found. Inc., Boston, Mass.): PATHOPHYSIOLOGY OF DIABETES. Med. Clin. N. Amer. *49*:881-92, July, 1965.

Diabetes is characterized by a pathophysiological state in which insulin effect is altered. The actions of insulin are: (1) to activate a glucose "carrier" system in muscle and adipose tissue so that glucose enters the cell from the extracellular fluid, (2) to increase the uptake of amino acids by muscle cells, (3) to inhibit neutral fat breakdown to free fatty acids, and (4) to stimulate the transformation of glucose to glycogen by the liver reducing hepatic glucose output. Insulin is released from the beta cells of the pancreas by an unknown mechanism sensitive to a rising blood glucose concentration. Insulin rapidly leaves the intravascular space and is rapidly inactivated by the liver. With a slight malfunction of this system, a time delay in clearance of glucose occurs and mild diabetes may be diagnosed. With more severe malfunction, decreased muscle and fat glucose uptake and increased hepatic glucose production result and hyperglycemia, glycosuria and ketonemia follow. An analogy of diabetes to the normal physiology of fasting may be made. The principal storage form of calories is fat. In starvation, the body's fuel needs, except for those of the nervous system, may be met by increasing fat breakdown. The CNS needs glucose which must be derived from gluconeogenesis. Thus, both in fasting and diabetes, the body behaves as if minimal insulin effect were exercised. Concepts of the pathophysiology of diabetes are thus keyed to a physiologic decrease in insulin effect. The reason is not clear; synalbumin antagonism, insulin complexing, inability of peripheral cells to respond to insulin, excessive insulin destruction and inability of insulin to leave the vascular space are possible factors. None has been demonstrated to be the sole etiologic factor. T.G.S.

Camerini-Dávalos, Rafael A. (N.Y. Medical College, New York, N.Y.): PREVENTION OF DIABETES. Med. Clin. N. Amer. *49*:865-79, July, 1965.

If diabetes is to be prevented, the details of its pathogenesis must be worked out. A first step appears to be the acquisition of complete knowledge of the natural history of the disease. There are three stages: *prediabetes* (the period of life from conception until an abnormality in carbohydrate metabolism is demonstrable), *chemical diabetes* (the period during which no symptoms are present but tolerance to glucose is impaired), and *clinical diabetes* (the characteristic symptoms are present and random blood glucose values are abnormal). A state of prediabetes is relatively insured in the identical twin of a diabetic and in the subject whose parents are both diabetic. Such individuals may have normal glucose tolerance even after cortisone administration but higher levels of free fatty acid, glycoproteins, insulin-like activity, immuno-reactive insulin, "complexed" insulin, and synalbumin antagonist may be found in their plasma. In addition, abnormalities in the finger pulse wave, microcirculation of the bulbar conjuntivae, and histology of the gingivae, skin and glomeruli may also be demonstrated in prediabetes. Although the causes of these changes are unknown, it is possible that management of the prediabetic with measures known to influence diabetes favorably may be effective. Early studies with both the sulfonylureas and phenformin suggest that this concept may be correct. If so, a means of preventing diabetes may be at hand. T.G.S.

Cohen, Geoffrey F. (Royal Free Hospital, London, England): EARLY DIAGNOSIS OF PANCREATIC NEOPLASMS IN DIABETICS. Lancet *2*:267-69, Aug. 7, 1965.

In the general population, carcinoma of the pancreas accounts for about 4 per cent of all malignancies. In diabetics, carcinoma of the pancreas accounts for 5 to 60 per cent of all malignancies. A means of earlier diagnosis of this lesion would be of value to the clinician caring for diabetics. The author suggests that the combination of unexplained weight loss and deterioration of diabetes control may suggest the presence of pancreatic cancer. Four case illustrations are presented. T.G.S.

Cornblath, Marvin; and Reisner, Salomon H. (Dept. of Pediat., Univ. of Illinois, Coll. of Med., Chicago, Ill.): BLOOD GLUCOSE IN THE NEONATE AND ITS CLINICAL SIGNIFICANCE. New Eng. J. Med. *273*:378-81, Aug. 12, 1965.

Hypoglycemia is judged significant in the neonatal period when it is less than 20 mg. per 100 ml., when the true blood sugar is less than 20 mg. per 100 ml., in the low birthweight neonate, and less than 30 mg. per 100 ml. in the full-sized infant. Symptoms of hypoglycemia in this period consist of flushing, pallor, rolling up of the eyes, sweating, "wilting spells," lethargy, absence of Moro reflex, limpness, cyanosis, apnea, unusual irritability, convulsions and coma. Hypoglycemia in the infant, however, is not always symptomatic. Causes of low blood glucose in the neonate include familial neonatal, idiopathic spontaneous recurrent with or without leucine sensitivity, and lack of epinephrine response, islet cell adenoma, central nervous system abnormalities, congenital malformations and infections, adrenal hemorrhage, inborn errors of metabolism such as glycogen storage disease, glycogen synthetase deficiency, hereditary fructose and galactose intolerances and diabetes in the mother. Hypoglycemia should be treated with 2 or 3 ml. of 50 per cent dextrose per kilogram of body weight intravenously, followed by a continuous infusion of 15 per cent dextrose in water at a rate of 75 to 100 ml. per kilogram per twenty-four hours during the first forty-eight hours of life. After forty-eight hours of age, a total volume of 100 to 110 ml. per kilogram per twenty-four hours as 15 per cent dextrose in one-quarter strength saline solution should be given to avoid iatrogenic hyponatremia. If the levels of sugar do not remain above 30 mg. per 100 ml., either hydrocortisone (5 mg. twice per day by mouth) or ACTH (4 U. twice a day intramuscularly) should be given. The intravenous glucose should be discontinued slowly rather than stopped abruptly in order to prevent reactive hypoglycemia. B.R.B.

Devlin, James G.; and Brien, T. G. (Dept. of Med., and Therapeutics, Univ. Coll., "Woodview," Dublin, Ireland): RELATIONSHIP BETWEEN DIFFERENTIAL ANTIBODY BINDING CAPACITY AND CLINICAL REQUIREMENTS OF BEEF AND PORK INSULIN. Metabolism *14*:1034-36, September 1965.

A test to determine whether insulin-dependent patients may benefit by alteration of species source of insulin is described. Incubation mixtures containing diluted plasma, insulin (crystalline bovine, pork, dalanated pork and human insulin) and Insulin-I-131 were subjected to paper chromatography for separation of free and antibody bound insulin and the percentage of tracer I-131 bound by antibody determined. The effectiveness of pork insulins in replacing bovine insulin was readily determined. There was a close correlation between clinically determined insulin responsiveness and the relative beef/pork desalanated pork insulin binding capacity found by this technic. C.R.S.

Doisy, Richard J. (Dept. of Biochem., State Univ. of New York, Upstate Medical Center, Syracuse, N.Y.): EFFECT OF DIET ON HEPATIC AND SERUM INACTIVATION OF INSULIN. Endocrinology 77:49-53, July 1965.

Rats fed diets containing Torula yeast and low in sulfur amino acids manifest an insulin-inactivating system in their sera not demonstrated in rats receiving a normal diet. The supernatant fractions of livers obtained from rats fed these diets were unable to inactivate added insulin unless small amounts of glutathione were added in vitro. Depletion of hepatic glutathione was demonstrated in these animals and was considered responsible for the loss of the hepatic glutathione-insulin transhydrogenase system which inactivates insulin. Cystine added to the diet restores the ability of liver supernatant fractions to inactivate insulin. C.R.S.

Ernest, Ingrid; Linner, Erik; and Svanborg, Alvar (Med. Clinic II & Depts. of Ophth., U. of Gothenburg, Gothenburg, Sweden): CARBOHYDRATE-RICH, FAT-POOR DIET IN DIABETES. Amer. J. Med. 39:594-600, October 1965.

The authors studied the effect of high carbohydrate, low fat diets on the retinopathy of nine patients with diabetic retinopathy and other clinical features, including blood lipids. The diet was free of egg, meat, fish and cheese, with carbohydrate mainly from fruits and starch-rich vegetables but not pure sugars. The carbohydrate was around 70 per cent of the day's total calories with 351 to 428 gm. per day. The fat intake was 16.7 to 19.1 gm., 7 to 8 per cent of the day's fat, a reduction of over 10 gm. per day from that of their previous studies of low fat diets.

There was little effect on microaneurysms, a definite effect in some patients upon resolution and disappearance of exudates but progressiveness or appearance of proliferative lesions. There were no effects on cardiovascular or renal functional tests. The levels of blood lipid fractions (cholesterol, phospholipid and glycerides) decreased after a period of approximately six months. S.B.B.

Fine, J. (Dept. of Chem. Path., Royal Gwent Hosp., Newport, Mon., Wales): GLUCOSE CONTENT OF NORMAL URINE. (FROM CORRESPONDENCE). Brit. Med. J. 1:1614, June 19, 1965.

In this correspondence Fine further discusses the technic for the glucose oxidase estimation of glucose in the urine and stresses the following: (1) Charcoal is effective in the removal of anti-enzyme substances, and the persistence of a small amount of anti-enzyme action has a negligible effect upon accuracy and subsequent quantitation of the urine glucose. (2) Deproteinizing, necessary for blood, has no advantage in urine. (3) Dilution of urine with a high glucose content is necessary, the final standard ideally to be obtained in the range of 10 mg. per 100 ml.

Thus weakly positive Clinistix urines need only be diluted 1 in 2 to 1 in 5, strongly positive specimens requiring dilution up to several hundred times. A preliminary Benedict test carried out by a modified method used by the author (Fine, J.: Brit. Med. J. 2:167, 1934) will yield an approximate result in the range of 0 to 10 gm. per cent and can serve as a guide to the amount of dilution required. R.F.B.

Ford, Henry C.; and Bailey, Richard E. (Div. of Diabetes and Metab., Dept. of Med. Univ., Oregon Med. Sch., Portland, Ore.): TOLBUTAMIDE TEST: A MISLEADING RESPONSE Brit. Med. J. 2:343-44, Aug. 7, 1965.

A fifty-year-old white woman with significant hypoglycemia was studied by the intravenous tolbutamide test with results indicating organic hyperinsulinism, but abdominal exploration did not reveal pancreatic nodules or aberrant pancreatic tissue. In subsequent necropsy no pancreatic adenomata or aberrant pancreatic tissue were found, and serial pancreatic sections showed normal structure except for minimal focal atrophy and fibrosis of exocrine tissue. No more than a few alpha cells were found due to technical difficulty, but the possibility of diminished numbers of alpha cells could not be ruled out. Glucagon levels were not measured.

The patient had none of the conditions reported by others to yield a blood glucose response following intravenous tolbutamide similar to that found in patients with insulinoma. It is suggested that specificity of intravenous tolbutamide test can be improved and its greatest current usefulness may be as an aid in excluding rather than establishing the diagnosis of insulinoma. R.F.B.

Genuth, Saul; Frohman, Lawrence A.; and Lebovitz, Harold E. (Dept. of Med. and Div. of Endocr., Duke Univ. Med. Center, Durham, N.C.): A RADIOIMMUNOLOGICAL ASSAY METHOD FOR INSULIN USING INSULIN-125-I AND GEL FILTRATION. J. Clin. Endocr. 25:1043-49, August 1965.

Verbatim summary: A radioimmunological assay for insulin is described using insulin-125-I as a tracer and gel filtration on Sephadex G75 to effect the separation of bound from free insulin. The relatively long half-life (sixty days) and the absence of β radiation by this isotope decreases the radiation hazard encountered during iodination procedures. As little as 0.25 μU. of insulin can be reliably measured by a single tracer for six months. O.V.S.

Haro, Expedito N.; Blum, Stuart F.; and Faloon, William W. (Dept. of Med., and the Sarah Taylor Metabolic Unit, University Hosp., State Univ. of New York, Upstate Med. Center, Syracuse, N.Y.): THE GLUCAGON RESPONSE OF FASTING OBESE SUBJECTS. Metabolism 14:976-84, September 1965.

Liver glycogen stores were assessed by observing the effects of intravenous glucagon upon the peripheral blood glucose in seven obese fasting subjects. Three subjects receiving liberal diets before the study manifested a subnormal response within the first four days of food deprivation. However, as the fast continued the glucose response returned to normal. During a second fast, the same subjects maintained a normal blood sugar response to glucagon. Another group of patients

on restricted diets maintained their blood sugar response to glucagon. Another group of patients on restricted diets maintained their blood sugar response to glucagon during a similar fast. These observations indicate that glycogen formation and gluconeogenesis are enhanced following a period of glycogen depletion produced by restricted dietary intake. C.R.S.

Kaufman, Mildred (U.S. Dept. Health, Education and Welfare, P.H.S., Div. of Chronic Diseases, Washington, D.C.): THE MANY DIMENSIONS OF DIET COUNSELING FOR DIABETES. Amer. J. Clin. Nutr. *15*:45-49, July 1964.

There are approximately 1.7 million people in the United States concerned with controlling their diabetes. This number has increased each year by 150,000 to 200,000 and it is likely that the numbers added per year will continue to increase. A recent survey has indicated that of 160 patients with diabetes, 126 were poorly regulated primarily because the patient failed to adhere to the prescribed diet. This was due to a lack of knowledge, as well as to social and emotional problems. Current practices of prescribing diabetic diets are reviewed. The shortcoming in failing to tailor the diets to fit the patient is pointed out. The need for diet counselors and new educational technics are discussed. Group education both for in- and out-patients and the use of teaching machines are suggested. B.R.B.

Leading Articles. VASCULAR LESIONS OF DIABETES MELLITUS. Brit. Med. J. *2*:603-04, Sept. 11, 1965.

Data are briefly summarized suggesting the participation of diabetic microangiopathy in the lesions of diabetic retinopathy, nephropathy, neuropathy, and also in the peripheral vascular lesions of the diabetic patient. R.F.B.

MacKay, N.; Gordon, A.; and Neilson, J. McE. (Stobhill Gen. Hosp., Glasgow, Scotland): OBSERVER ERROR IN DEXTROSTIX ESTIMATIONS OF BLOOD-SUGAR. Lancet 2:269-70, Aug. 7, 1965.

Three observers independently used Dextrostix to assess blood glucose values of 267 venous samples obtained from patients attending a diabetic clinic. They compared their results with a standard reducing method. For laboratory values below 90 mg. per 100 ml., the Dextrostix method agreed within ±10 per cent in over 80 per cent of the samples in this range. For values between 90 and 200 mg. per 100 ml., this precision of agreement was found in less than two thirds of the samples. A tendency for Dextrostix to underestimate blood sugar was noted. The use of Dextrostix to diagnose hypo- and hyperglycemia was recommended but their use to supplant routine laboratory methods was not endorsed. T.G.S.

Maqueo, Manuel; Azuela, Jose Chavez; Karchmer, Samuel; and Arenas, Jorge Cinco (Depts. of Path. & Obstet., Hospital de Gineco-Obstetricia Número Uno, I.M.S.S., Mexico City, D.F., Mexico): PLACENTAL MORPHOLOGY IN PATHOLOGIC GESTATIONS WITH OR WITHOUT TOXEMIA. OBSERVATIONS IN CASES OF DIABETES MELLITUS, HYDROPS FETALIS, TWIN PREGNANCY, PLACENTA PREVIA, AND HYDATIDIFORM MOLE. Obstet. & Gynec. *26*:184-91, August 1965.

Verbatim summary: One hundred and forty-nine placentas from women with uncontrolled diabetes mellitus, hydrops fetalis, twin pregnancy, placenta previa (with or without toxemia), and hydatidiform moles associated with toxemia were compared with fifty-five placentas from women with normal gestation. Many histologic similarities in appearance were found in placentas from women with uncontrolled diabetes and hydrops fetalis. There were also similarities in the frequency of toxemia.

Changes in the cellular constituents of the trophoblast, degenerative changes in the decidual vessels, and acute infarcts are more frequent in toxemia than in normal pregnancy. Thus these placental lesions will be seen more often in toxemia, regardless of the factor or factors predisposing to its development. There are widely differing morphologic pictures associated with toxemia, suggesting that this is not a single clinico-pathologic entity. E.A.W.

Melin, Hans (Dept. of Med., Umea University, Umea, Sweden): AN ATROPHIC CIRCUMSCRIBED SKIN LESION IN THE LOWER EXTREMITIES OF DIABETICS. Acta Med. Scand. Suppl. 423, 1964.

Author's abstract: A previously unknown skin lesion in diabetics is described that occurs isolated, or in groups as small, rounded, atrophic brown spots in the lower parts of the legs. The lesions disappear after a year or two, but in the meanwhile new lesions may appear and the picture as a whole remains unchanged. The patients are often unaware of the lesions.

Of 277 diabetics (120 men and 157 women) the atrophic skin lesion occurred in 65 per cent of the men and in 29 per cent of the women. The lesions were correlated to the duration of diabetes. In the maturity-onset diabetics the lesions appeared earlier than in the juvenile ones. The lesions were correlated to the presence of retinopathy, nephropathy, and neuropathy, but not to the incidence of high blood pressure. The occurrence of the skin lesion in nondiabetics was found to be very rare.

The histological picture showed atrophy of the epidermis and sometimes slight fibrosis of the dermis. The melanin content was definitely increased and hemosiderin was sometimes found in small amounts. PAS-positive vascular changes, especially in the capillaries in the superficial dermis, were found about as often in the lesions as in the intact skin.

A micro-angiographic study, performed on autopsy material, revealed a greater abundance of small vessels within the lesion than in the nearby intact skin. The vessels within the lesions often radiated to the skin surface in a divergent fanwise manner. Accordingly, the disappearance of a locally injected isotope (I-131 and Na-24) was quicker in the lesion than in the adjacent normal skin. In diabetics with traumatic scars on their legs of about the same age as the atrophic lesions the disappearance was significantly slower in the scars than in the atrophic lesions, suggesting a spontaneous origin of the lesions.

A fluorescence-microscopic study of the atrophic skin lesion with antihuman gamma globulin revealed the presence of gamma globulin in the capillary walls immediately under the epidermis and also in the basal cell layer of the epidermis. The possibility of the lesions being the result of changed immunological conditions is discussed.

The atrophic skin lesion described represents a common and typical complication of long-term diabetes which, due to its localization, is easily accessible for studies. W.R.K.

Parrish, J. A. (St. Bartholomew's Hosp., London, England): URINARY INFECTION IN DIABETIC OUTPATIENTS. Lancet 2: 414-15, Aug. 28, 1965.

In the past, some authors have presented evidence that a greater incidence of urinary tract infection was present in diabetics than in the general population. Others have not confirmed this contention. The author surveyed 342 male and 177 female diabetic patients by culturing mid-stream voided urine. Only seven men had bacteriological evidence of infection and five of these had had surgical operations on the lower GU tract. Of the women, twenty-five (or 14 per cent) had evidence of infection; 84 per cent of them had had previous catheterization. The data suggest that previous instrumentation rather than diabetes alone may be responsible for GU infection in the diabetic. T.G.S.

Shipp, Joseph C.; Cunningham, Richard W.; Russell, Richard O.; and Marble, Alexander (Dept. of Med., Univ. of Florida Coll. of Med., Gainesville, Fla., and the Joslin Clinic, Boston, Mass.): INSULIN RESISTANCE: CLINICAL FEATURES, NATURAL COURSE AND EFFECTS OF ADRENAL STEROID TREATMENT. Medicine (Baltimore) *44*:165-86, March 1965.

Insulin resistance is defined arbitrarily as the requirement of over 200 units of insulin daily for a period longer than forty-eight hours. Patients with known hemochromatosis, acute infections, endocrine abnormalities, and insulin resistance associated with ketoacidosis, have been excluded. The clinical features and natural course of thirty-four patients with diabetes mellitus and insulin resistance seen at the Joslin Clinic between 1940 and 1960 are described. Three-fourths of the patients were over forty years of age. There was no sex predilection. Over 50 per cent developed within five years after the diagnosis of diabetes, and two thirds became resistant within the first year of insulin treatment. The onset of resistance usually occurred over a period of several weeks. There was little correlation between previous insulin dosage and the severity of insulin resistance. The maximal twenty-four-hour insulin dosage was 5,700 units. Seventy per cent of the patients required less than 1,000, and 50 per cent less than 500 units daily. Allergy to insulin was manifested by local reactions at injection sites, urticaria, eosinophilia, or anaphylaxis in approximately 30 per cent. The duration of the resistant state was less than six months in half, and less than one year in three fourths of the patients. The longest duration was fourteen years.

A review of fifty-five patients with insulin resistance from the literature since 1948 is presented in table form. The clinical features and course were similar to those reported from the Joslin Clinic except for slight predominance of females and a considerably higher maximal twenty-four-hour insulin dosage of 38,000 units.

Four patients from the authors' series with insulin resistance are described in detail. They illustrate features of the resistant state including allergic reactions, ketoacidosis, and prolonged hypoglycemia. The patients received most of the proposed forms of treatment, which include the use of 2, 3 dimercaptopropanol nitrogen mustard, insulin derived from different animal species and particularly that of pork origin, tolbutamide, phenformin and adrenocortical steroids.

Different indications for adrenal steroid treatment were present. Each patient showed a decrease in insulin requirement during adrenal steroid treatment. A review of the literature of patients with insulin resistance treated with ACTH or adrenal steroids is presented. Insulin requirements decreased in 75 per cent of the twenty patients during twenty-six trials with ACTH or adrenal steroids. About half showed a marked decrease in insulin requirements during the first two weeks of treatment, and in several this occurred within the first three to five days.

Some possible mechanisms of insulin resistance are discussed. It is probable that most instances of insulin resistance, as defined in this report, have an immune basis. Although the mechanism of action of adrenal steroids in insulin resistance is incompletely understood, some indications for use in insulin resistance are suggested. In the absence of contraindications, this treatment may be beneficial in those patients who require high insulin dosages over a prolonged period or whose course is highly unstable with fluctuations between ketosis and hypoglycemia; also in those who have a history of allergy to insulin, especially when it might be necessary to give insulin intravenously, or those who develop frequent sterile abscesses or other reactions, at injection site. When steroids are used, it is advisable to begin at 60 to 80 mg. per day of prednisone (or glycocorticoid equivalent) in divided doses. Once a response has occurred the dose can be gradually reduced. A daily maintenance dose of 5 to 10 mg. of prednisone may be continued for long periods. Ultimately, a return of the insulin sensitive state will be indicated when the drug is stopped. B.F.K.

Spellacy, William N.; Goetz, Frederick C.; Greenberg, Beryl Z.; and Ells, Joyce (Depts. of Obstet. and Gynec., and Intern. Med., Univ. of Minnesota Med. Sch., Minneapolis, Minn.): PLASMA INSULIN IN NORMAL "EARLY" PREGNANCY. Amer. J. Obstet. Gynec. 25:862-65, June 1965.

Verbatim Summary: Plasma insulin and blood glucose were measured in normal "early" pregnancy and again late postpartum. There is a slight elevation in the amount of circulating insulin at this period of gestation. E.A.W.

Weil, Leopold; Seibles, Thomas S.; and Herskovits, Theodore T. (Eastern Reg. Res. Lab., Philadelphia, Pa.): PHOTO-OXIDATION OF BOVINE INSULIN SENSITIZED BY METHYLENE BLUE. Arch. Biochem. *111*:308-20, August 1965.

Photo-oxidation of bovine insulin at *p*H 7.0 and 10° C. affects only the histidine residues in the B chain, but, if the temperature is raised, oxidation of tyrosine residues occurs. Photo-oxidation is enhanced when carried out in 8 M urea, but that of histidine, tyrosine, methionine, and tryptophan is unaffected. As photo-oxidation of histidine in insulin is increased, biological activity (mouse convulsions) decreases and disappears when both histidine residues have been oxidized. Other physical changes induced by photo-oxidation suggest that inactivation of insulin is not due to changes in secondary or tertiary structure. Zinc insulin is oxidized more slowly than the zinc-free preparation and appears to have a somewhat more unfolded structure than the latter. P.H.W.