ABSTRACTS

An International Diabetes Symposium was held in Marbella, Spain, Oct. 23-26, 1968, under the auspices of the New York Medical College Diabetes Center and leadership of Dr. Rafael Camerini-Davalos. Although space is limited in these pages, it is hoped that the following review will give the reader a useful summarization of some of the lectures presented at the Symposium.

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Abstracts Editor

GENETICS OF DIABETES

James V. Neel of the University of Michigan and *Arthur Steinberg* of Case Western Reserve discussed the present status of knowledge and problems in the study of the genetics of diabetes. The principal difficulty in studying diabetes continues to be the lack of understanding of the primary defect in the disease. Collaborative studies comparing very large numbers of children of diabetic and nondiabetic parents from the day of birth might yield important clues to the nature and inheritance of diabetes.

INSULIN SECRETION

Using organ culture technics *Albert Renold* et al. studied factors that control differentiation and function of rat pancreatic islet cells. Differentiation becomes evident by the twelfth day of gestation, and by the fourteenth to sixteenth day synthesis and accumulation of tertiary proteins occur. By the eighteenth to the twenty-second day of gestation when spontaneous birth occurs, IRI content increases fivefold. At this point pancreatic IRI exceeds adult values. Pancreatic IRI content may be increased by feeding, oral feeding being a more potent enhancer of IRI increase than intravenous feeding. These workers reported also on cells they termed as "intermediate" or "mixed" exocrine-endocrine cells which they had first detected while studying spiny mice at the onset of diabetes. These cells, while having the appearance of exocrine structures, had demonstrated a characteristic unique to beta cells—deposition of glycogen.

William E. Dulin reported on insulin secretion in the early diabetic KK mouse, db mouse and Chinese hamster. Blood glucose in the fed and fasted state in the KK mice did not differ from the normal controls. In older but not younger mice plasma insulin levels were higher than in the control animals, and body weight was increased. The authors hypothesize that diabetes in this animal begins with increased food intake and peripheral insensitivity to insulin, but hyperglycemia is reduced by inhibition of hepatic glucose output. In the db mouse increased food intake leads to obesity and this is associated with an increased plasma insulin level, but the insulin fails to reduce the blood glucose and more marked hyperglycemia occurs than in the KK mouse. Dietary reduction results in decrease in the blood sugar. Enzyme studies indicate that the responsiveness of adipose tissue in these animals is normal but, unlike the KK mouse, the hepatic response to insulin is apparently reduced.

In the Chinese hamster obesity is not an early manifestation of diabetes and the plasma insulin tends to be normal or elevated. Although muscle and adipose responses to insulin are normal, the liver of these species fails to respond adequately. As the hyperglycemia continues, islet cell reserves decrease and ketosis may supervene.

Rosalyn S. Yalow working with *Solomon A. Berson* reported on their investigations of "big insulin" and growth hormone as factors in the diminished glycemic response to excessive plasma insulin levels which occur in maturity-onset diabetes. Using a radioimmunoassay with a crystalline human insulin standard, they found that the insulin content of eluates from Sephadex columns correspond to molecular weights of 6,000 (insulin, "little insulin") and 9,000 ("big insulin," proinsulin), "big insulin" accounting for only 10 to 12 per cent of the total. They conclude that the small portion of the total insulin measured immunologically indicates that "big insulin" does not contribute importantly to the elevated plasma insulin levels seen in maturity-onset diabetes and therefore does not account for the insulin insensitivity observed.

In order to study growth hormone the authors utilized the fact that this substance is increased in the blood in subjects of normal weight four to six hours after a glucose load. Thus, two six-hour glucose tolerance tests were given in succession. In all normal subjects with a good growth hormone response after the first glucose load, glucose intolerance occurred in the second test. In two obese subjects who were poor growth hormone responders there was no abnormality in the second glucose tolerance test. One lean and one obese diabetic showed glucose tolerance changes in the same direction as the normals. When glucose tolerance tests were done

in the afternoon following a fourteen-hour fast, values lower than those observed in the morning were found, thus discounting diurnal variation as a factor. Glucose tolerance tests carried out after growth hormone has been stimulated by insulin-hypoglycemia produced glucose intolerance as observed with glucose loading. The authors stressed that because growth hormone levels varied from subject to subject, and the number of subjects studied was small, the importance of growth hormone per se could not be stated. However, the correlation of glucose intolerance with growth hormone increases calls attention to the importance of factors other than delayed secretion of insulin as a cause of glucose intolerance.

Holbrooke S. Seltzer presented data to support the thesis that the primary lesion in hereditary diabetes is defective response of the beta cell to glucose. Using an "insulinogenic index," absolute relationships between insulin and glucose were sought. (This index is a ratio of insulin to glucose derived from measurements of the areas under the curves of these parameters during the glucose tolerance test.) Diabetics secrete greater amounts of insulin than normals, but their insulin output for the blood glucose in relation to their own (diabetic) glucose levels was reduced. In proportion to the severity of the diabetes, similar degrees of hyperglycemia result in more insulin being released from the normal subjects. In paired oral and intravenous glucose tolerance tests there was a sluggish and subnormal response to glucose in comparison with normals, and these abnormalities correlated with the clinical severity of the diabetes, as determined by the fasting blood glucose. The author used these and other data to support his view that beta cell dysfunction is the primary defect in diabetes.

INSULIN SECRETION AND METABOLISM

In the session devoted to insulin secretion and metabolism, *Roger H. Unger* and *J. Dupré* reviewed the effects of glucagon, secretin, and pancreozymin on insulin secretion and *Donald Steiner* reviewed proinsulin and its relationship to human diabetes.

L. Stimmler compared the metabolism of insulin in normal and diabetic subjects by intravenously injecting porcine insulin and measuring the disappearance rate by immunoassay. A slower disappearance was noted in diabetics (no previous insulin treatment) and in the healthy relatives of diabetic patients. This was associated with a slower and more prolonged hypoglycemic effect. The existence of an inhibitor of insulin metabolism was postulated.

David M. Kipnis reviewed the insulin and glucose data of others and his own to unravel the relative importances of insulin resistance and deficient insulin secretion in early stages of nonketotic diabetes. In prediabetic subjects insulin secretion is usually normal or slightly depressed, although occasionally a patient has excessive insulin. Of greater surprise in prediabetes is the occasional finding of increased sensitivity. In frank maturity-onset diabetes the insulin secretion pattern is characterized by a delay in onset, higher peak than normal and excessive total insulin output. Obesity in mild diabetes is usually associated with higher insulin levels. However, these responses must be evaluated on the basis of the insulinogenic stimulus (enteric factors plus the amount of glucose escaping to the peripheral circulation), the latter being far greater in the diabetic subject. Although impairment in insulin secretion is a sine qua non for hereditary diabetes, factors which alter the sensitivity of the organism to insulin (stress, obesity, hypo- hyperendocrine states) may accelerate or delay the onset of clinical diabetes in a genetically predisposed individual.

Sheldon Berger used intravenous insulin tolerance tests (0.1 U./kg.) to determine whether the decreased glucose tolerance observed following cortisone was due to insulin resistance. In both the patients with normal and abnormal cortisone glucose tolerance tests, pretreatment with cortisone failed to decrease insulin sensitivity as indicated by the insulin tolerance test.

MATERNAL-PLACENTAL-FETAL RELATIONSHIP

Norbert Freinkel and his colleagues reviewed the metabolic alterations of late pregnancy, reported on studies in pregnant rats, and proposed a biochemical hypothesis to explain the diabetogenic effects of the gravid state. Although maternal insulin does not cross the placental barrier, the fetus and placenta contain proteolytic enzymes which do and these degrade maternal insulin. In late pregnancy fasting insulin levels are increased, the fasting blood sugar is decreased, and free fatty acids are increased over those found in normal subjects. During pregnancy intravenous glucose produces greater rises in plasma insulin with less effect on the blood sugar than seen in postpartum, suggesting the sparing of maternal glucose for uterine consumption, possibly by the action of steroid and peptide hormones elaborated by the placenta (e.g., estrogens, progesterone, chorionic gonadotropin, and placental lactogen), which are not subject to negative feedback in the mother, e.g., whether she is fasting or fed. This point was supported by the fact that rat fetuses weigh the same when sacrificed at nineteen days whether the mothers were fasted or fed. The principal substances crossing the placental barrier are amino acids, which are also needed to provide glucose for maternal cerebral demands.

The importance of maternal gluconeogenesis was investigated by administering pyruvate-3-C-14 intravenously to nineteen-day-old pregnant and matched virgin rats. Although in the pregnant fed animals production of glucose-C-14 was not appreciably increased, in pregnant animals starved for twenty-four to forty-eight hours there was a marked increase in glucose-C-14 levels within five to ten minutes after infusion of pyruvate-C-14. Furthermore, after forty-eight hours of fasting, urinary nitrogen rose, indicating renal gluconeogenesis.

Lipid metabolism was examined by measuring the FFA and glycerol content of fat from fed and forty-eight-hour fasted nineteen-day-old pregnant rats and virgin females. The fat of the pregnant animals was found to contain more FFA in both conditions. When lumbar fat from these animals is incubated in media containing fat-free albumin, or the same with glucose, or glucose and insulin, fatty acid turnover rates are markedly increased during late pregnancy.

The authors propose that the phenomena associated with pregnancy constitute "accelerated starvation" for the mother which results in conservation of maternal glucose and materials for gluconeogenesis and assures continuous supply of nutrients for the fetus. When the mother cannot produce the addi-

tional insulin needed when she eats, diabetes occurs.

Virgilio G. Foglia reported on experiments to evaluate the evidence of infertility and outcome of pregnancy in prediabetic and diabetic rats. Cesarean sections were carried out in the last four days of pregnancy. In 95 per cent of pancreatectomized rats the blood sugar levels were lower than 180 mg. per 100 ml.; 55 per cent of the pancreatectomized rats had an empty uterus despite the presence of sperm in the vaginal smear. Fetal mortality was present in a high percentage of the cases, 41 per cent against 6.9 of the controls. Fetal mortality was higher in hyperglycemic rats but also occurred in normal rats. Giant fetuses occurred after the eighteenth day of pregnancy and were independent of either size or sex. Giant placenta was also seen from the eighteenth day of pregnancy so that fetal:placental weight ratio was normal.

Marvin Cornblath compared the clinical course and laboratory findings of infants of thirty-one gestational diabetic mothers (IGDM) and nineteen insulin-dependent mothers (IDM) with a view to determining the reasons for the high morbidity and mortality of these offspring. The mean birth weight of the IGDM was greater than IDM (42 per cent over the ninetieth percentile for the former, 32 per cent for the latter). It was noted that the same problems that afflict the IDM were present in the IGDM but with reduced frequency and severity. The response of IGDM in comparison with normal controls to oral glucose loading during the first twenty-four hours of life indicates a greater ability by the IGDM to metabolize glucose. During fasting, plasma insulin was higher and free fatty acids lower in the IGDM than in normal infants, suggesting the insulin of the IGDM has a greater effect on lowering lipid than glucose. These types of responses support the hypothesis that in utero the beta cells of the IGDM have been conditioned to fluctuating glucose levels.

L. Molsted Pedersen et al. compared the glucose disposal rate and free fatty acid concentration in infants of diabetic mothers three hours after normal birth. In normal infants the K-value was low and the FFA concentration was elevated. During the first days the K-value increased and the FFA concentration decreased. In the diabetic group just the opposite occurs, namely, the K-value is high and the FFA concentration is low. On the fifth day the K-value decreases and the FFA value is increased so that no significant difference between the two groups of infants is demonstrated at this time.

PREDIABETES, AND CHEMICAL OR LATENT DIABETES

Marvin D. Siperstein et al., using electron microscopy, examined the normal capillary basement membranes of fifty normal, fifty diabetic, and thirty prediabetic subjects. Basement membrane hypertrophy was found in 98 per cent of overt diabetics and 50 per cent of prediabetics, but in only 8 per cent of normal subjects. Basement membrane thickness in diabetic subjects was unrelated to age, weight, severity or duration of the diabetes. Subjects with severe hyperglycemia due to causes other than genetic diabetes only infrequently showed basement membrane hypertrophy. When a cotton sponge was implanted under the fascia lata of a patient with juvenile diabetes serial biopsies revealed that basement membrane width of newly formed capillaries was not increased until about twenty months.

John T. Ireland addressed himself to the question of whether significant basement membrane thickening occurs in early diabetes mellitus by studying not just peripheral capillaries but the mesangial region and other cellular details. In nine healthy normal and four newly diagnosed diabetic subjects there were no significant differences between the control and diabetic groups in the over-all mean basement thickness of the central mesangial zone. No abnormality in the epithelial, endothelial, or mesangial cell structure in the diabetic group was found.

J. M. B. Bloodworth et al. measured basement membrane in normal dogs, alloxan-diabetic dogs, and metasomatotrophin-diabetic dogs, and muscles of prediabetic patients. In the small sample of humans studied there was no evidence of increase in capillary basement width in normal controls or prediabetics. In both caged and uncaged dogs there was a definite increase of basement membrane width of the muscle, kidney, and retinal capillaries in the diabetic group. These values were statistically significant after diabetes had been present for two to three years. Age was associated with increases in the basement membrane width of the capillaries in the retinal and renal glomerulae of the dog and rat but was not observed in the muscle and fat capillaries of the dog. The authors concluded that the limited data tend to show no effect of diabetic control on the muscle capillary membrane measurements in the dogs.

J. Stuart Soeldner et al. reported on the influence of weight on serum insulin and serum growth hormone responses in the male offspring of two diabetic parents. When glucose tolerance and insulin level results were sorted according to per cent of ideal weight of the test subjects using five equal subdivisions between 101 and 126 per cent, there were few significant differences. In thirteen instances the mean serum insulin levels in the heavier normal subgroups were significantly higher than in the leanest normals. On the other hand, this occurred in only six instances of the offspring of diabetic parents. In the diabetic offspring group the serum insulin: blood glucose relationship was lower in three of five instances and growth hormone levels were higher within the first hour following glucose loading in the diabetic offspring. The change in serum insulin:blood glucose ratio in diabetic offspring may suggest a diminished ability of the beta cell to respond to glucose. There was no explanation for the increased growth hormone levels in the offspring of diabetic patients.

Oscar Lozano-Castañeda et al. reported on metabolic and vascular studies in prediabetic subjects. The initial blood glucose tolerance test revealed a high prevalence of previously unknown asymptomatic diabetics (19.3 per cent) and a large number of undiagnosed abnormalities after oral glucose, such as reactive hypoglycemia (17.2 per cent) and transient hyperglycemia (31 per cent). As a result, only 32.4 per cent of the group studied had a truly normal glucose tolerance test. No differences were detected in the free fatty acid response to oral glucose. Venular dilatation and also abnormality in gingival biopsies were noted in this group but were thought to be nonspecific.

R. A. Camerini-Davalos and colleagues, looking for a genetic "marker" for diabetes, reported on their studies of

thirty-seven prediabetics (the offspring of two diabetic parents or the identical twin of a known diabetic) in whom historical, physical, and biochemical parameters, including insulin and glucose, were measured. In the larger number of different examinations performed, these investigators observed positive differences in the following tests: (1) elevation of mean blood glucose values during the oral glucose tolerance test in the prediabetics as a group at 60, 90, 120, and 180 minutes (however, these differences did not distinguish individual prediabetics); (2) lower glucose values were found during the cortisone glucose tolerance test; (3) higher mean K-value following intravenous administration of glucose, indicating slower glucose assimilation; (4) a significant difference in sialic acid between normals and prediabetics; (5) significant elevation of IRI at sixty minutes in about a third of fifty subjects. In addition, abnormal monocrotic pulse waves were found in about 65 per cent of prediabetics, but only 27 per cent of normal controls. Studies of the gingival vessels with the light microscope showed thickening of the vessel walls with a PAS+ material. These investigators concluded that detectable abnormalities in prediabetes exist, but the nature requires much better definition. A major problem in the interpretation of results is the wide variation of responses in the prediabetic group and a lack of consistency in responses. Thus, the "marker" has not yet been identified.

John B. O'Sullivan reported the significance of gestational diabetes as a precursor of frank diabetes and risk factor in fetal wastage. Because pregnancy affects the response of normal subjects to both the oral and intravenous glucose tolerance test, diagnostic criteria were proposed to predict what degrees of glucose intolerance were of clinical significance in terms of the eventual development of overt diabetes. Three test levels, consisting of the addition of one, two, and three standard deviations respectively to the mean glucose levels at each time interval for a population of over 700 were used. Application of these criteria to clinic patients indicated that over a follow-up period of up to twelve years, the incidence of diabetes increased in rough proportion to the degree of abnormality in the glucose tolerance tests. However, oral glucose tolerance did not necessarily get worse from pregnancy to pregnancy.

Based on these and other data, test level II criteria, e.g., two or more values exceeding a fasting blood sugar of 90, one hour 165, two hour 145, and three hour 125, were found to identify best those patients with the highest risk of diabetes. For both oral and intravenous glucose tolerance tests, K-values greater than 1.34 during the third trimester were associated with increased fetal wastage.

EPIDEMIOLOGY OF EARLY DIABETES

Leon D. Ostrander, Jr. et al. reported on the experience of the U.S. Public Health Service prospective study in Tecumseh, Michigan, in which 9,000 persons in the community were checked in two series of examinations (1959-60) (1962-65). Forty-nine of eighty-seven who had been classified diabetics as a result of previous detection had some manifestation of cardiovascular disease, including coronary heart disease, peripheral vascular disease, cerebral vascular disease, T-wave inversion in their ECG, or hypertension. The prevalence of these abnormalities was higher than the expected frequency calculated from the total population and adjusted for age. Twenty-two per cent of 209 persons with diagnoses of probable coronary heart disease at the time of the first examination had died and most deaths were attributed to cardiovascular disease; in this group who died hyperglycemia was more frequent as an early finding than in the survivors. These findings indicate the importance of hyperglycemia in the outcome of coronary heart disease. In the Tecumseh study the most frequent finding associated with morbidity and mortality from cardiovascular disease is hyperglycemia.

Glen W. McDonald reported on a comparison of 50 and 100-gm. glucose loads in three-hour glucose tolerance tests of ninety-six prison volunteers. The only significant difference in the means of the two tests was at the two-hour level where the mean blood glucose level for the 100-gm. dose was 16.1 ± 3.36 greater than for the 50-gm. dose. This report indicates that if the two-hour value is omitted the results of glucose tolerance tests carried out with the different doses of glucose may be compared.

NATURAL HISTORY OF EARLY DIABETES

Stefan S. Fajans et al. studied the course of asymptomatic disease in thirty individuals (children, adolescents, and young adults) on whom the diagnosis of latent diabetes had been made. The group consisted of fifteen patients between nine and seventeen, and fifteen between eighteen and twenty-five years of age. Individual patients had been followed for periods of one to sixteen years. The following findings were reported: (1) in the majority of individuals the glucose intolerance did not progress; (2) a delayed and subnormal insulin response occurred in nonobese patients with mild diabetes; (3) in individual patients there may be considerable fluctuations in the insulin response to glucose and in glucose tolerance; and (4) the finding from time to time of improved glucose tolerance in the presence of decreased insulin levels and vice versa suggested that in addition to the pancreatic insulin response to glucose other factors may affect glucose tolerance. Because the disease is apparently slowly progressing in most patients studied, it is suggested that with early detection the use of prophylactic procedures such as diet, weight restrictions, and possibly oral antidiabetic agents is indicated.

TREATMENT OF EARLY DIABETES

Leo P. Krall reviewed his experience with dietary treatment of airline pilots with mild diabetes. This group of patients is highly motivated because excess weight and treatment with hypoglycemic agents will lead to grounding. Thus, in four out of five cases response to diet alone was satisfactory, and the fifth individual, who required insulin, had demonstrated a good response to diet alone for several years.

Robert L. Jackson proposed the use of glucagon as a means of increasing the sensitivity of detection methods for chemical diabetes in children. Forty-three of forty-eight children who were chemical diabetics as indicated by the oral glucose tolerance test had venous glucose clearance rates of 1.1 per cent per minute or greater during intravenous glucose tolerance tests. When glucagon was added to the intravenous glucose tolerance test, abnormal responses were elicited in about half of the children with chemical diabetes.

A. Loubatieres reviewed research in support of a positive beta-cytotropic effect of the hypoglycemic sulfonylureas and their use as a preventive measure in the treatment of early diabetes. These agents stimulate neogenesis of beta cells, increase the total mass of beta cells and augment the synthesis and release of endogenous insulin. Administration of the hypoglycemic sulfonylureas studied does not result in exhaustion of the beta cells. In fact, the development of diabetes is delayed in dogs with 90 per cent pancreatectomy.

Charles J. Goodner et al. reported on their studies of the effects of chlorpropamide in obese maturity-onset diabetes. Patients fed standard meals and followed on a metabolic ward showed an increase in plasma insulin and reduction of blood glucose over values which occurred during a similar period of observation without sulfonylurea treatment. In addition, in most patients studied sulfonylurea treatment corrected the pretreatment tendency toward a delay in output of insulin. Moreover, insulin increases occurred in association with blood glucose increases as with feeding, and were reduced during fasting. After five weeks of treatment the hypoglycemic effects persisted but plasma insulin levels were reduced. It was concluded that without changing the pattern of secretion of insulin by the beta cell, chlorpropramide improved the insulin response to "physiologic stimuli."

Harry Keen and *John Jarrett* reported on the coincidence of vascular disease and hyperglycemia and the effects of treatment of hyperglycemia on the course of the vascular disease. The sample studied was the group of patients found to have hyperglycemia in the survey of Bedford, England, in 1962. The two-hour blood sugar was used to differentiate the 503 patients into three test groups. Normal subjects had blood sugar levels up to 120 mg. per 100 ml. Those with blood sugars of 200 mg. per 100 ml. were classified as definitely diabetic and patients with blood sugars in the range of 120 to 200 mg. per 100 ml. were classified as borderline diabetics. The presence of arterial disease was assessed by an objective questionnaire which included historical data on angina pectoris, myocardial infarction, or the presence of intermittent claudication. The observed/expected incidence of cardiovascular disease was 79 per cent for normal subjects, 103 per cent for borderline diabetics, and 127 per cent for the diabetics.

In order to assess the effect of hypoglycemic therapy, half of 248 patients with borderline diabetes were treated with tolbutamide, 0.5 gm. b.i.d., and the other half with placebo. Both of these groups were further subdivided and one subgroup was asked to limit carbohydrate intake to 120 gm. daily and the other half to decrease the intake of table sugar. Although the number of patients in each individual group was small, after five years the incidence of worsening of cardiovascular disease (e.g., "probable" evidence such as myocardial infarction, onset of angina pectoris, onset of intermittent claudication, worsening of ECG, stroke, or cardiovascular death) was less in the tolbutamide-treated group (22 per cent) than in the other two groups (33 per cent). The data suggested, but did not prove, that subjects treated with tolbutamide and carbohydrate restriction had the least cardiovascular complications. Although there were no significant differences in blood glucose control when the two-hour postprandial levels in the various treatment groups were compared, examination of random blood sugar levels collected in the late afternoon showed the tolbutamide group to have sugars that were 8 mg. per 100 ml. less than the tolbutamide group.

On the basis of the data presented, the authors suggested that tolbutamide had effects which were independent of those exerted on two-hour postprandial blood sugars and raised the question that the two-hour postprandial blood sugar is not a satisfactory method of monitoring total carbohydrate metabolism. They concluded that the borderline diabetic has a higher than usual risk for arterial disease but this risk can be reduced by preventive treatment.

Robert Feldman and *Derek Crawford* reported on the prophylactic use of oral hypoglycemic drugs in asymptomatic diabetes in the Permanente Group. The study group consisted of 258 subjects (fifteen to fifty-nine years of age) who were followed from four to twenty-four months. Of the 258, 219 were definitely diabetic and thirty-nine were probable diabetics. All patients were treated with a diabetic diet and were assigned double blind and randomly to tolbutamide (50 per cent), phenformin (25 per cent), and placebo (25 per cent). Glucose tolerance was retested at four, eight, twelve, eighteen, and twenty-four months. Diabetic diets were prescribed for all subjects, reduction diets being recommended for patients who were overweight. Additional complications of diabetes were assessed by serial electrocardiograms, nerve conduction, and pulse wave velocities, but no results on these were presented.

The results included the finding that all patients lost weight during the first year. Weight loss was most consistent in the phenformin group but glucose tolerance improved least. Glucose tolerance improved most in the tolbutamide group but weight was regained after one year. Glucose tolerance also improved and weight was regained in the placebo group. There were wide variations in IRI with no significant differences in treatment groups. However, the mean decrease in IRI appeared to be least with tolbutamide. There was no correlation between improvement in glucose tolerance and change in IRI. Longer periods of observation were suggested to assess the significance of the changes in glucose and IRI at one and two years.

Bernard W. Knick reported on seven years of experience with oral hypoglycemic therapy in twenty-nine adult-type diabetics and seven juvenile-type diabetics. In the former group there were six spontaneous remissions, two who developed subclinical diabetes, and fourteen with clinical diabetes. In the juvenile type there were no spontaneous remissions, two who developed subclinical diabetes, and five who developed clinical diabetes.