ABSTRACTS

A symposium on the new oral hypoglycemic agent glybenclamide (HB 419), was held in Rottach-Egern on the Tegernsee from January 27 to 29, 1969, under the auspices of Farbwerke Hoechst and Bohringer Mannheim. A selection of eighteen papers presented at this symposium has been published as the first supplement issue of the new journal *Hormone and Metabolic Research*. These papers are all written in English and were assembled under the joint editorship of Rachmiel Levine and E. F. Pfeiffer (HB 419, Supplement Vol. 1/69, Georg Thieme -Verlag, Stuttgart 1969).

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Glybenclamide has been under intensive laboratory and clinical study in Germany and France and to a lesser extent in North America, and in this symposium R. Müller et al. were able to report on 5,053 patients who were treated with this drug. On a weight basis glybenclamide is 250 times more potent a hypoglycemic agent than tolbutamide, 100 times more potent than carbutamide and fifty times more potent than chlorpropamide. If its clinical advantage is simply a matter of relative potency, with no qualitative difference in action, the drug would not be of unique interest. Some reports have suggested, however, a qualitative rather than quantitative difference from existing sulfonylureas. As glybenclamide is now undergoing clinical trials in the United States some highlights of the symposium are abstracted to familiarize American clinicians with this agent.

H. Weber et al. reported on molecular alterations around the sulfonylurea nucleus that cause a striking increase in potency in compounds such as glybenclamide. G. Hebold et al. described the results of extensive chronic and acute animal toxicity studies. They found no evidence of organ alterations in either dogs or rats that could be attributed to glybenclamide. There was no fertility impairment in rats or mice, and no teratologic effects in rats, mice or rabbits. At very high doses there was an increase in intrauterine fetal deaths in rabbits which they attributed to hypoglycemia. There was also a temporary retardation of development in newborn mice and rats when they were delivered by cesarean section, but not in offspring born spontaneously. This was interpreted as indicating a temporary delay in maturation.

Four interesting pharmacological studies on glybenclamide in which this agent is compared with the prototype sulfonylurea, tolbutamide, were presented (A. Loubatieres et al., F. H. Schmidt et al., R. D. Fussganger et al. and E. Aquilar-Parada et al.). Glybenclamide appears to be qualitatively similar to tolbutamide in the following respects:

(1) Acute administration of glybenclamide causes an increase in immunoassayable insulin in peripheral and pancreatic vein blood (A. Loubatieres et al.).

(2) Neither sulfonylurea will produce hypoglycemia in severely insulin deficient animals. This was demonstrated in depancreatized dogs (Loubatieres et al.), and in rats rendered diabetic with streptozotocin or alloxan (F. H. Schmidt et al.).

(3) Glybenclamide can potentiate the hypoglycemic effect of exogenous insulin in a severely diabetic animal (Loubatieres et al.). This raises the question of an extrapancreatic action in addition to its effects on the β cell.

(4) One of these extrapancreatic effects may be on adipose tissues lipolysis, for glybenclamide may have an inhibitory effect on adipose tissue lipase (F. H. Schmidt et al.) such as has been described for tolbutamide.

(5) Glybenclamide counteracts diazoxide inhibition of insulin secretion in both intact animals (Loubatieres et al.), and in vitro pancreas studies (Loubatieres et al. and G. Loffler et al.).

(6) Glybenclamide counteracts mannoheptulose and glucosamine-induced hyperglycemia (F. H. Schmidt et al.). Insulin measurements to ascertain if glybenclamide prevents the suppression of insulin secretion by these sugars were not reported, however.

(7) Pancreatic glucagon is released after glybenclamide-induced hypoglycemia (E. Aquilar-Parada et al.).

Glybenclamide seemed to differ qualitatively from tolbutamide in certain respects:

(1) In studies carried out with pancreas segments, isolated islets and perfused pancreas preparations, R. D. Fussganger et al. demonstrated that repeated exposure to tolbutamide resulted in a refractory state in which the tissue would no longer release insulin in response to this sulfonylurea. In contrast, repeated glybenclamide administration resulted in a continuing insulin release.

(2) Although the initial insulin peak after tolbutamide was greater than that after glybenclamide, the later agent caused a more persistent release as compared to the transitory insulin release following tolbutamide.

(3) Under certain experimental conditions, tolbutamide could be shown to interfere with glucose-induced insulin secretion from the perfused pancreas whereas glybenclamide potentiated this insulin release.

The above in vitro studies seemed to be confirmed in clinical studies reported by Raptis et al. They noted that the insulin secretion due to glybenclamide was characterized by a

delayed climb, a clearly lower, plateau-like maximum and a delayed decline, while tolbutamide manifested the well known abrupt insulin rise and decline. These investigators also noted similar insulin secretion dynamics in both normal and diabetic patients receiving glybenclamide.

Several reports dealt with the interaction of glybenclamide with the β cell and its insulin granules. In a paper presenting electron photomicrographs of the β cell, Kern et al. demonstrated that β-cell degranulation followed glybenclamide administration, the degranulation lagged six hours behind acute elevation of plasma insulin. Other investigators had previously demonstrated this type of lag in β-cell degranulation after tolbutamide administration. Kern et al. also tried to correlate the morphological picture observed using the electron microscope with the "two compartmental model" of insulin release previously proposed by G. Grodsky and his collaborators.

To investigate the hypothesis that the mechanism of action of sulfonylureas is to induce solubilization of the insulin granules within the β cell, Howell and Lacy incubated isolated insulin granules in the presence of a concentration of glybenclamide that stimulated insulin release from isolated islets. Glybenclamide did not affect granule stability, for these studies did not demonstrate an effect of glybenclamide on the solubility of the insulin granules.

The low therapeutic dose range of glybenclamide (1.25 to 20 mg./day) makes it difficult to trace the metabolic fate of this drug by conventional chemical technics. Therefore, O. E. Christ et al. carried out a radioisotope study by administering C-14-labeled glybenclamide to volunteers. They demonstrated that:

(1) The steady state biological half life of this agent is 6.6 hours.
(2) The drug is eliminated both in the urine (54 $\pm$ 10 per cent) and in the feces (45 $\pm$ 9 per cent) with no accumulation of the drug in the body.
(3) Glybenclamide is converted into two predominant metabolites by hydroxylation reactions. At the concentrations present in the blood, these metabolites have no hypoglycemic effect and they are rapidly excreted.

There were six reports of the clinical results obtained with glybenclamide. The investigators concerned all seemed to agree that glybenclamide was both a potent and a relatively nontoxic agent. As with other sulfonylureas, it should be used by maturity-onset diabetic patients, and not by those patients whose diabetes is of juvenile onset, or who are prone to ketosis. Retiene et al. noted that many patients classified as secondary failures when receiving other oral hypoglycemic agents could be adequately controlled by glybenclamide.

To evaluate the effect of glybenclamide on β-cell responsiveness, Chandalea et al. carried out oral and intravenous glucose tolerance tests prior to administration of this agent, and again after four weeks and four months of therapy. They noted increased insulin levels during both intravenous and oral tolerance tests after four weeks of therapy, as compared to the pretherapy insulin levels. The elevated insulin levels were accompanied by an improvement in glucose tolerance. Although the increased insulin levels following oral glucose persisted after four months of therapy, the insulin levels provoked by intravenous glucose diminished despite continuing evidence of improved glucose tolerance. The characteristic lag in insulin secretion frequently found in diabetes persisted during glybenclamide therapy.

Assan, R.; Aubert, Ph.; Souchal, B.; Tchobroutsky, G.; and Derot, M. (Groupe U 55 de l'INSERM, et Chaire du Diabète et des Maladies Metaboliques, Hotel-Dieu, Paris, France): ANALYSIS OF 154 CASES OF SEVERE DIABETIC ACIDO-KETOSIS (1963-1967). THE EXPERIENCE OF AN URBAN CENTRE FOR THE EMERGENCY TREATMENT OF DIABETIC COMA. La Presse Medicale 77:423-26, March 8, 1969.

The authors reviewed their experience in 154 cases of diabetic ketoacidosis seen in the last five years. The cause of the coma was infection in one third of the cases, whereas in a larger number the coma was due to interruption of insulin treatment and/or unusual food intake or psychiatric reasons, hence these latter causes were preventable. Hypokalemia and iatrogenic alkalosis and hyperosmolarity were among the problems encountered. Aggressive insulin therapy was justified. M.C.B.

Bjorntorp, Per; Bergman, Halvar; Varnauskas, Edvardas; and Lindholm, Bjorn (First Med. Serv., and the Metabolic Lab., Sahlgrenska Sjukhuset, Univ. of Goteborg, Goteborg, Sweden): LIPID MOBILIZATION IN RELATION TO BODY COMPOSITION IN MAN. Metabolism 18:840-51, October 1969.

Labeled palmitate and glycerol were used to measure the turnover rates of free fatty acids (FFA) and glycerol in patients with simultaneously determined adipose tissue mass and other body compartments. FFA concentration and turnover rate correlated strongly as did glycerol concentration and turnover. FFA and glycerol concentrations showed positive correlations with body fat and the fat/cell mass ratio. Serum immunoreactive-insulin levels were correlated positively with body fat. The results show that with increasing body fat lipid mobilization and lipolysis are increased. No correlation between body cell mass and lipid mobilization or lipolysis was observed. It appears likely that some factor in adipose tissue is responsible for increased lipid mobilization and lipolysis in obesity. C.R.S.

Elkeles, R. S.; Wright, A. D.; Lowy, C.; and Fraser, T. R. (Dept. of Med., Royal Postgraduate Med. Sch., Hammersmith Hosp., London, England): SERUM-INSULIN IN ACROMEGALY. Lancet 2:615-18, Sept. 20, 1969.

The authors studied forty-three acromegalic patients with an oral glucose tolerance test using sequential serum insulin measurements. In thirty-eight acromegalics who did not have diabetes, the mean post-glucose levels were raised by 50 per cent compared to controls. However, the mean values were high because a group of 30 per cent of the acromegalics exceeded normal levels (15 per cent had below normal levels and 55 per cent were normal). A possible correlation between HGH levels and insulin levels ($r = 0.27$; p 0.04) was suggested.

Treatment of acromegaly with Y-90 lowered HGH 58 per cent and insulin response index 21 per cent. In three diabetics studied before and after treatment, a reduction in both blood sugar and IRI was noted. Evidently other factors than growth hormone activity seem to be the main determinants of variations in serum insulin levels in acromegaly. T.G.S.

Flock, Eunice V.; Tyce, Gertrude M.; and Owen, Charles A. (Mayo Clin., and Mayo Foundation, Sect. of Biochem., Rochester, Minn.): GLUCOSE METABOLISM IN BRAINS OF DIABETIC RATS. Endocrinology *85*:428-37, September 1969.

Metabolism of glucose by brain tissue of rats rendered hyperglycemic (1) by alloxan treatment, (2) by mannoheptulose injection or (3) following evisceration (including pancreatectomy) was studied using glucose-U-C-14 given after elevation of the blood sugar by infusion of glucose. In 1 and 2, the uptake of radioactive glucose was higher than in normal rats but conversion of glucose to glutamate, other amino acids and lactate was similar to that of normal rats. In 3, although the uptake of glucose in the brain was elevated, conversion of glucose to its metabolites was greatly reduced. In groups 1 and 2, the liver not only increases blood glucose through gluconeogenesis but also in some way aids glucose uptake in brain. In group 3, impairment in glucose metabolism in the brain appears to be due to the absence of the liver. C. R. S.

Goodman, Stephen I.; Pollak, Shlomo; Miles, Barbara; and O'Brien, Donough (Univ. of Colorado Med. Center, Denver, Colo.): THE TREATMENT OF MAPLE SYRUP URINE DISEASE. J. Pediat. *75*:485-88, September 1969.

Verbatim summary. The early management of three infants with maple syrup urine disease is described with particular reference to variations in daily requirements for branched-chain amino acids. The use of a new dry base mix consisting of a dextrimaltose-corn oil-mineral mix, an iron-vitamin mix, and an amino acid mix as a formula base has facilitated earlier home management of these patients.

Hellman, Bo; and Lernmark, Ake (Dept. of Histology, Univ. of Umea, Umea, Sweden): INHIBITION OF THE IN VITRO SECRETION OF INSULIN BY AN EXTRACT OF PANCREATIC ALPHA$_1$ CELLS. Endocrinology *84*:1484-88, June 1969.

A water extract prepared from alpha$_1$ cells of pigeon pancreas significantly inhibited the secretion of insulin from the microdissected pancreatic islets of obese-hyperglycemic mice. This observation is consistent with the hypothesis of a local regulation of endocrine activity in B cells from adjacent alpha$_1$ cells. While the identity of the inhibitor of insulin release remains to be determined the possibility of gastrin or catecholamines derived from the alpha$_1$ cells is suggested for this role. C.R.S.

Manigand, G.; Auzepy, Ph.; Jan, F.; Leguillant, F.; and Deparis, M. (Clinique medicale de Hopital de Bicetre, Paris, France): DEATH DUE TO CEREBRAL EDEMA DURING SEVERE DIABETIC COMA. La Presse Medicale 77:790-92, April 26, 1969.

A sixteen-year-old boy was admitted to the hospital in severe diabetic ketoacidosis. Nine hours after treatment was started, the patient became deeply comatose and died thirty-six hours later. Postmortem examination showed cerebral edema and medullary compression. The authors reviewed seven other similar reported cases. M.C.B.

Plager, John E.; Matsui, Nobuo; and Ariyoshi, Yutaka (Div. of Med., Roswell Park Memorial Inst., New York State Dept. of Health, and The Med. Foundation of Buffalo, Buffalo, N.Y.): "ANTI-INSULIN" ACTION OF CORTISOL. 2. COMPARISON OF THE INFLUENCE OF CORTISOL ON THE METABOLISM OF GLUCOSE, FRUCTOSE, MANNOSE AND GALACTOSE. Endocrinology *84*:1450-55, June 1969.

Rates of metabolism for glucose, mannose, fructose and galactose in decreasing order were shown using the mouse ear strip in the conversion of these sugars to CO_2, fatty acid and glycogen. Addition of cortisol was demonstrated to inhibit metabolism of each of these sugars but was greatest for the more actively utilized sugars and least for the poorly utilized galactose. The demonstration of cortisol inhibition of fructose, mannose and galactose metabolism is consistent with the action of cortisol in preventing passage of these sugars into the cell. Inhibition of phosphorylation of the sugars by cortisol is an unlikely site of action. The penetration of three nonmetabolizable sugars, xylose, arabinose and mannitol, was not inhibited by cortisol, suggesting a different mechanism for uptake of these sugars. The observations on inhibition of penetration of metabolizable sugars by cortisol indicates an action on the cell membrane. C.R.S.

Rosenlund, Mary Loretta; Crean, Gerard P.; Johnson, Dale G.; Holtzapple, Philip G.; and Brooks, Frank (Children's Hosp. of Philadelphia, and The Hosp. of the Univ. of Pennsylvania, Philadelphia, Pa.; The Southern Gen. Hosp., Glasgow, Scotland): THE ZOLLINGER-ELLISON SYNDROME IN A TEN-YEAR-OLD BOY. J. Pediat. *75*:443-48, September 1969.

Verbatim summary. A ten-year-old boy with the Zollinger-Ellison syndrome is presented. Gastric secretory studies showed a twelve-hour basal output of over 2 L.; with Histalog stimulation the acid output was two times normal. At laparotomy he was found to have nonbeta islet cell tumor metastases in the liver. No primary tumor was found in the pancreas. An extract of the tumor demonstrated secretory activity, and immunoassay of the patient's blood revealed significant elevation of gastrin. Quantitative studies of the gastric mucosa showed an unusually large parietal cell mass. The boy is well and asymptomatic two years following total gastrectomy.

Sabeh, G.; Corredor, D. G.; Mendelsohn, L. V.; Morgan, C. R.; Sieracki, J. C.; Sunder, J. H.; Wingert, J. P.; and Danowski, T. S. (Depts. of Med. & Path., Univ. of Pittsburgh and Med. Center & Shadyside Hosps., Pittsburgh, Pa., Dept. of Anat., Univ. of Indiana, Bloomington, Ind.): GROWTH HORMONE AND INSULIN LEVELS IN NEWLY DISCOVERED GLUCOSE INTOLERANCE. Metabolism *18*:741-47, September 1969.

In nonobese and obese women with newly discovered but untreated glucose intolerance, the levels of growth hormone during glucose loading were lower than those observed in nonobese control subjects. The glucose-induced insulin responses in the diabetic groups were excessive but proved to be deficient when related to concomitant increases in blood sugar. The individual groups include some persons whose insulin responses relative to blood sugar levels equal or exceed those of healthy control subjects. The wide span of differences in the blood glucose/insulin ratios suggest that changes in insulin levels occur during the transition from a nondiabetic to a diabetic state. C.R.S.

Samaan, Naguib A.; and Craig, James W. (Dept. of Med., Case Western Reserve Univ. Sch. of Med., Cleveland, O.):

SERUM INSULIN AND GROWTH HORMONE IN LIPOATROPHIC DIABETES. Metabolism *18*:460-68, June 1969.

Three siblings with lipoatrophic diabetes were studied with observation on growth hormone and insulin responses to various stimuli. One subject with mildly abnormal glucose tolerance had abnormal elevations of serum insulin after an oral glucose load while the two patients with more severe diabetes had normal fasting insulin concentrations which failed to rise after glucose administration. Intravenous tolbutamide produced an abnormally slow decline in blood glucose in all three patients and a subnormal rise in serum insulin in the most severe diabetic patient. Resistance to intravenous insulin was manifested but insulin antibodies could not be demonstrated in the sera. The fasting serum concentrations of growth hormone were normal in all cases but showed little response to hypoglycemia. The fasting levels of free fatty acids were elevated and decreased after glucose administration. The serum insulin content in these patients appeared to decrease with greater clinical severity or duration of diabetes. Increased levels of growth hormone were not required for maintenance of lipoatrophy or severe insulin resistance. The relationship between failure to stimulate growth hormone secretion and pathogenesis of lipoatrophic diabetes is unclear. C.R.S.

Senior, Boris; and Loridan, Liliane (Dept. of Pediat., Tufts Univ. Sch. of Med., and Pediat. Endocr.-Metab. Serv. [Boston Floating Hosp. for Infants and Children], New England Med. Center Hosps., Boston, Mass.): FAT CELL FUNCTION AND INSULIN IN A PATIENT WITH GENERALIZED LIPODYSTROPHY. J. Pediat. *74*:972-75, June 1969.

Two children under two years of age presented with features suggestive of cerebral gigantism: increased height, acromegalic features with large hands and feet, large skulls with dolichocephaly, high arched palate, receding hairline, prognathism and clumsiness. Routine laboratory studies were normal. Endocrine evaluations revealed no abnormalities in thyroid or adrenal function. Fasting levels of immunoreactive growth hormone were normal and growth hormone responses following intravenous glucose or insulin-induced hypoglycemia were not excessive. Radiological assessments of the pituitary fossa and carpal bone age were normal but phalangeal development in one case was markedly advanced. Clinical and laboratory features of these two cases are included in a review of forty-one other cases reported in the literature. The etiology of this condition remains obscure. R.K.K.

Surmaczynska, Barbara; and Metz, Robert (Dept. of Med., Northwestern Univ. Sch. of Med., Chicago, Ill.): HORMONAL AND IMMUNOLOGICAL PROPERTIES OF INSULIN FRAGMENTS: 1. THE INDIVIDUAL PEPTIDE CHAINS. Endocrinology *85*:368-72, August 1969.

Hormonal and immunologic properties of the A and B chains of beef insulin were compared with those of the parent molecule. With insulin immunoassays and bioassays, the separated peptide chains of insulin appeared to be devoid of insulin-like hormonal properties except for a very weak insulin-like activity of the A chain (less than 1/1,000 that of insulin). Both peptide chains failed to interact with neutralizing or reaginic insulin antibodies. There was no evidence that B chain functioned as an antagonist to the action of insulin or muscle, either alone or in combination with albumin. C.R.S.

Sutton, P. M.; and Taghizadeh, A. (Dept. of Morbid Anat., Univ. Coll. Hosp. Med. Sch., London, England): A NEW PANCREATIC HORMONE AND THE ETIOLOGY OF DIABETES MELLITUS. Lancet *2*:935-37, Nov. 1, 1969.

Diabetes is not always the result of simple insulin deficiency. The obese maturity-onset diabetic may be resistant to insulin therapy and may display a high insulin concentration after oral glucose. Since the authors performed a study in rats in which they removed the entire pancreas and two thirds of the liver and found that the animals became profoundly hypoglycemic some hours later, they speculate that the pancreas may secrete a hormone which causes hepatic gluconeogenesis. They propose that maturity-onset diabetes may result from an initial overproduction of pancreatic gluconeogenic hormone. Earlier, the beta cells respond by increased insulin secretion. Later, a relative insulin deficiency but not ketosis occurs. In contrast, juvenile diabetes is caused by primary beta cell failure. T.G.S.

Whitcomb, Frederick F., Jr.; Lummis, Frederick R., Jr.; Mejia, Jamie A.; and Achkar, Edgar J. (Dept. of Gastroenterology, Lahey Clin. Foundation, Boston, Mass.): IDIOPATHIC HEMOCHROMATOSIS: CLINICAL AND LABORATORY FEATURES IN THIRTY-THREE PATIENTS. Lahey Clin. Bull. *18*:109-16, July-September 1969.

The authors reviewed the experience of the Lahey Clinic with idiopathic hemochromatosis from 1931 to 1962. A total of thirty-one men and two women were found with this disease, none of whom had a family history of hemochromatosis.

Diabetes mellitus was present in thirty patients (91 per cent) and it was the presenting symptom in ten of these. Diabetes was diagnosed before hemochromatosis in twenty-one patients. A family history of diabetes was present in seven patients. No information is given as to the presence or absence of microangiopathy.

Cardiac disease was found in fifteen patients (45 per cent). Postmortem examination in five patients with congestive heart failure showed infiltration with hemosiderin and absence of significant coronary artery disease. Hepatoma was found in four patients. Pigmentation of the skin was observed in twenty-six patients. Atrophic testes were found in six patients (18 per cent).

Sixteen patients were treated with mutliple venesections. The average period of follow up for all patients was thirty-five months. There were seventeen known deaths with an average duration of life after the diagnosis of hemochromatosis of twenty-nine months. The most frequent causes of death were cardiac failure in five and hepatic insufficiency in another five patients. M.C.B.