BOOK REVIEW

GLUCAGON: MOLECULAR PHYSIOLOGY, CLINICAL AND THERAPEUTIC IMPLICATIONS, *edited by Pierre J. Lefebvre, M.D., and Roger H. Unger, M.D. $37.50, 370 pages. Oxford, Pergamon, 1972.*

The discovery of glucagon dates almost as far back as that of insulin. The molecular structure of glucagon has been identified; glucagon has been synthesized; and glucagon has served admirably as a model for the study of mechanisms of action of peptide hormones. And yet, the physiologic significance of the hormone, particularly in mammals, had not been clarified and defined with certainty. This book constitutes an all-out effort to present compiled evidence that glucagon does indeed participate in the physiologic regulation of nutrient utilization. Twenty-seven authors have contributed to this complete and up-to-date review of the structure of the pancreatic islet alpha cells, the chemical and physical properties of glucagon, the synthesis, release and metabolism of glucagon, biologic effects of glucagon, and methods of measurement and the blood levels of glucagon under physiologic and pathologic conditions.

A number of contrasting properties can be ascribed to this work: (1) Some topics have been discussed at great length while others of equal or greater importance have been covered very briefly. The chapter on phylogeny and ontogeny of glucagon production could be cited as an example of the former and that on the chemical and physical properties of pancreatic glucagon of the latter situation. (2) Some subjects have been covered in depth in a well organized, precise manner (e.g. glucagon receptors) while others have been presented in a superficial, not well organized fashion (e.g. in vivo metabolism of glucagon). (3) The information given in certain chapters (glucagon receptors, glucagon and the metabolism of glucose) is precise and well documented, while anecdotal in others (pancreatic alpha-cell function in miscellaneous clinical disorders, pharmacology and clinical use of glucagon).

Repetitiousness is quite bothersome throughout the entire book. In certain sections speculation is generously sprinkled among factual information; it is not always clear which is fact and which conjecture. Although the issue of the specificity of the radioimmunoassay of glucagon is dealt with appropriately, some information on plasma levels of glucagon derived from nonspecific assays has been presented without due caution. Certain abstract concepts, such as "glucose blindness" and the "insulin-glucagon ratio," have been somewhat overemphasized.

Some of the shortcomings are not unique to this volume: multiple authorship frequently brings such inconsistencies. Lack of sufficient factual information in certain areas is another contributing factor. An adequate number of references is given at the end of each chapter. It is a handy and useful reference book for the reader who is familiar with the subject. On the other hand, the reader who is not so familiar faces the risk of not recognizing with ease the speculative information from hard factual documentation.

SUMER PEK, M.D.

ABSTRACTS

Dunbar, J. C.; and Foa, P. P. (Department of Research, Sinai Hospital of Detroit, Detroit, Michigan): AN INHIBITORY EFFECT OF TOLBUTAMIDE AND GLIBENCLAMIDE (GLYBURIDE) ON THE PANCREATIC ISLETS OF NORMAL ANIMALS. Diabetologia *10*:27-35, 1974.

Verbatim summary. Tolbutamide and glibenclamide (glyburide) were administered to normal hamsters, mice or rats in daily doses proportional to their body weight and equivalent to those used in human therapy. The animals were sacrificed after six to eight weeks of treatment. Pieces of pancreas or isolated pancreatic islets were incubated or perifused in a medium containing glucose or tolbutamide, with or without leucine-1-^{14}C or glucose-U-^{14}C. The results indicate that the B cells of sulfonylurea-treated animals synthesized and released less insulin and oxidized less glucose than those of insulin- or saline-treated controls. Accordingly, at least in the glibenclamide-treated animals, the tolerance for glucose and the insulinogenic response to a glucose load *in vivo* were suppressed. Although insular function tended to return to normal after treatment was discontinued, the results reported in this paper do not support the generally accepted view that the lasting therapeutic effectiveness of the sulfonylureas is due to a beta-cytotrophic action.

Federspil, G.; Casara, D.; Pedrazzoli, S.; Sicolo, N.; and Scandellari, C. (Institute of Semeiotica Medica, and Institute of Clinica Chirurgica, Padua University, Padua, Italy): IN VIVO STUDIES ON 5-HYDROXYTRYPTAMINE AND INSULIN SECRETION IN DOGS AND IN MAN. Diabetologia *10*:13-17, 1974.

Verbatim summary. 5-Hydroxytryptamine (5-HT) effects on the insulin secretion of anesthetized dogs and of humans were studied. From our investigations the following conclusions can be drawn: 5-HT when injected at a dose of 4.30 mg. into the pancreatic artery, elicits a sharp rise of insulin concentration in pancreaticoduodenal vein; on the contrary, 21.50 mg. of 5-HT is unable to modify insulin release. The infusion in fasting man of small amounts of 5-HT (∞ 0.50 μg/kg./min.) during 1 h, does not alter blood glucose nor plasma insulin levels; a similar infusion, however, increases insulin response after oral glucose load. The results obtained in dogs are in agreement with the idea that 5-HT may modulate insulin release from the pancreas. The results in man suggest that enteramine released by the intestine may increase insulin secretion induced by the ingestion of glucose, through a fine interplay with other gut-factors.

Freychet, P.; Brandenburg, D.; and Wollmer, A. (Unité de Re-

cherche de Diabétologie et d'Etudes radio-immunologiques des Hormones protéiques U.55 (INSERM), Hôpital Saint-Antoine, 184 Rue du Faubourg Saint-Antoine, 75012 Paris, France, Deutsches Wollforschungsinstitut, and Abteilung Physiologische Chemie, Technische Hochschule, Aachen, Free Republic of Germany): RECEPTOR-BINDING ASSAY OF CHEMICALLY MODIFIED INSULINS. COMPARISON WITH IN VITRO AND IN VIVO BIOASSAYS. Diabetologia *10*:1-5, 1974.

Verbatim summary. The binding affinity for the insulin receptor was determined with a variety of insulin derivatives and compared to the biological activity *in vitro* and *in vivo* and to the physical properties of the derivatives. The relative binding affinity of each derivative was measured in a specific insulin-receptor binding system using mono ^{125}I-insulin and purified plasma membranes of rat liver. Twenty-one chemically modified insulins were investigated, including acetylinsulins, crosslinked insulin dimer and insulin trimer, and insulins with an A_1—B_1 or A_1—B_{29} intramolecular crosslink. The relative binding affinity corresponded to the relative biological potency *in vitro* for all of the derivatives studied. There was a good agreement between the activity *in vitro* and the physical properties as measured by circular dichroism spectroscopy with the acetylinsulins and with the crosslinked insulin monomer, dimer and trimer. In contrast, with most of the derivatives possessing an intramolecular crosslink, the very reduced binding affinity (0.2-5.9 per cent) and the comparably reduced biological potency *in vitro* opposed the moderate changes in physical properties. Biological activity was consistently higher *in vivo* than *in vitro*.

Fulop, M.; Tannenbaum, H.; and Dreyer, N. (Dept. of Med., Albert Einstein Col. of Med., and Bronx Municipal Hosp. Center, Bronx, N.Y.): KETOTIC HYPEROSMOLAR COMA. Lancet *2*:635-39, September 1973.

Because previous studies have failed to certify that the cause of mental obtundancy and coma in diabetic ketoacidosis is not specifically the degree of acidemia, hypotension, dehydration, cerebral glucose utilization, or low oxygen consumption, the authors studied seventy episodes of acidosis in fifty two of their own patients. They graded the state of consciousness on a one (awake) to five (coma) scale and measured blood pH, serum glucose, sodium, potassium and urea, and calculated osmolarity. They found that the state of consciousness failed to correlate with blood pH but did parallel blood glucose and calculated osmolarity. The authors conclude that the main cause of ketoacidotic stupor is hyperosmolarity, which can be caused by hyperglycemia and hypernatremia. They further hypothesize that hyperosmolarity may cause mental impairment through the mechanism of cerebral dehydration and this in turn is related to duration of cerebral dehydration. They recommend routine measurement of plasma osmolarity in patients with severely uncontrolled diabetes. T.G.S.

Henquin, J. C.; Malvaux, P.; and Lambert, A. E. (Unité de Diabète et Croissance, University Hospital St. Pierre, Louvain, Belgium): GLUCAGON IMMUNOASSAY USING POLYETHYLENE GLYCOL TO PRECIPITATE ANTIBODY-BOUND HORMONE. Diabetologia *10*:61-68, 1974.

Verbatim summary. The use of polyethylene glycol 6000 to separate free and antibody-bound ligand has been applied to the radioimmunoassay of glucagon. Equalization of protein content in all tubes before precipitation of the glucagon-antibody complex was required. Time between addition of the polymer and centrifugation had no detectable effect. Degradation of ^{131}I-glucagon during incubation was best prevented by a combination of benzamidine (5 mM) and Trasylol (500 KIE/tube). Sensitivity of the assay permitted discrimination of buffer or plasma samples (100 μl) whose glucagon contents differed from 25 pg/ml., under 100 pg/ml., and 35 pg/ml., under 200 pg/ml. Reproducibility was 9.5 per cent (coefficient of variation) for plasmas with glucagon concentrations ranging from 100 to 300 pg/ml. Recovery of exogenous glucagon added to plasma was satisfactory. Measurement of glucagon was possible in fasting plasma samples diluted up to 1/8. The separation method described appears to be easy and reliable, especially when large numbers of samples are routinely handled.

Isenberg, J. I.; Walsh, J. H.; and Grossman, M. I. (Med. Service, VA Wadsworth Hospital Center, and Dept. of Med., UCLA Sch. of Med., Los Angeles, California): ZOLLINGER-ELLISON SYNDROME. Gastroenterology 65:140-65, July 1973.

This is a long (and unsummarized) selective review article on the Zollinger-Ellison syndrome. The article is quite extensive in its scope with a heavy emphasis on more recent developments in both the clinical and diagnostic (including the research aspects) areas of this interesting disease. This article appears to be of equal interest to both the gastroenterologist as well as the endocrinologist. F.G.B.

Kissebah, A. H.; Tulloch, B. R.; and Fraser, T. R. (Endocrine Unit, Department of Medicine, Royal Postgraduate Medical School, Ducane Road, London W 12 OHS): INTERRELATIONSHIP BETWEEN GLUCOSE AND ACETOACETATE METABOLISM IN HUMAN ADIPOSE TISSUE. Diabetologia *10*:69-75, 1974.

Verbatim summary. We have examined the utilization of glucose and ketone bodies in normal adipose tissue in response to insulin and some drugs used in diabetic therapy. Under basal conditions ^{14}C from acetoacetate was incorporated into long chain fatty acids, while ^{14}C from glucose was found principally in the glyceride glycerol fraction of tissue lipids. Fatty acid synthesis from acetoacetate was stimulated tenfold by glucose addition up to 20 mM and conversely, acetoacetate enhanced the incorporation of glucose ^{14}C into lipids. The stimulatory effect of glucose was independent of its transport, since it is not reproduced by 2-deoxy-glucose. Insulin further stimulated fatty acid synthesis from acetoacetate, an effect abolished in the absence of glucose. Phenethyl-biguanide (Phenformin) increased tissue glucose uptake, although it decreased glucose ^{14}C and acetoacetate ^{14}C incorporation into triglyceride. Free fatty acids (FFA) and very low density lipoproteins (VLDL) addition at concentrations observed in diabetic ketosis resulted in inhibition of acetoacetate utilization. We conclude that ketone bodies do not block glucose utilization in normal human adipose tissue in vitro. The apparent reduction in ketone body metabolism during diabetic ketosis may be related to the high FFA and VLDL levels observed.

Loten, E. G.; Rabinovitch, A.; and Jeanrenaud, B. (Laboratoires de Recherches Médicales, Division de Diabétologie et de Biochimie clinique, Département de Médecine, Geneva University Medical School, Geneva, Switzerland): IN VIVO STUDIES ON LIPOGENESIS IN OBESE HYPERGLYCAEMIC (ob/ob) MICE; POSSIBLE ROLE OF HYPERINSULINAEMIA. Diabetologia *10*:45-52, 1974.

Verbatim summary. C57BL/6J *ob/ob* mice are obese, hyperglycemic and hyperinsulinemic, and are relatively insensitive to the action of exogenously administered insulin. These animals convert more of an intravenous dose of radioactive glucose to lipids

in both adipose tissue and liver than do control mice. The lipogenic capacities of the intestine, skin and remaining carcass, however, are not greatly different from those of lean mice. While lean mice respond to intravenous insulin with a marked increase in incorporation of labelled glucose into lipids in adipose tissue, obese mice do not.

Both lean and obese mice made diabetic with streptozotocin have a decreased plasma insulin and convert less glucose to fatty acids than do nontreated mice. This is particularly marked in the case of the adipose tissue of obese mice. Similarly, reduction of insulin levels by the injection of anti-insulin serum also caused a decreased lipogenesis which was particularly marked in the case of obese mice.

It is postulated that part of the increased lipogenesis seen in *ob/ob* mice may be due to the abnormally high circulating insulin levels in these mice.

MacDermott, R. P.; and Kramer, P. (Dept. of Medicine, Boston Univ. School of Med., Boston, Mass.): ADENOCARCINOMA OF THE PANCREAS IN FOUR SIBLINGS. Gastroenterology *65*:137-39, July 1973.

Verbatim summary. Pancreatic adenocarcinoma in four siblings is reported. In two brothers and one sister, there is autopsy or surgical biopsy proof of adenocarcinoma of the pancreas. In another brother, carcinoma of the pancreas was found at surgical exploration, but no biopsy or autopsy was obtained. There is no clinical evidence of hereditary pancreatitis in the family.

Morgner, D. K. (Abteilung fur klinische Endokrinologie, Dept. Innere Medizin, Med. Hochschule, Hanover): BEHAVIOR OF FREE FATTY ACIDS UNDER THYREOSTATIC THERAPY. Med. Klin. *68*:310, 1973.

Serum FFA levels were significantly higher in twenty three hyperthyroid patients than in controls (means: 1,100 μEq/L. versus 572 μEq/L. in healthy persons). After fourteen days of effective antithyroid treatment (2 gm. Natrium perchlorate or 80 mg. methylmercaptoimidazol daily), serum FFA were normalized (mean: 641 μEq/L.). This observation confirms the significance of thyroid function in lipolysis and indicates that serum FFA might be an additional laboratory aid in the supervision of thyrostatic therapy. N.K.

Olefsky, J.; Batchelder, T.; Farquhar, J. W.; and Reaven G. M. (Department of Medicine, Stanford Univ., Sch. of Med., and Palo Alto Vet. Adm. Hosp., Palo Alto, California): DISASSOCIATION OF THE PLASMA INSULIN RESPONSE FROM THE BLOOD GLUCOSE CONCENTRATION DURING GLUCOSE INFUSIONS IN NORMAL DOGS. Metabolism *22*:1277-86, October 1973.

Constant glucose infusions were given to anesthetized dogs during which plasma insulin concentrations were measured serially. Blood glucose levels peaked at sixty minutes and then fell steadily while plasma insulin rose continuously suggesting that the concentration of blood glucose was not the primary stimulus for insulin secretion. Reinfusion with a larger glucose load, regulated by constant monitoring to reproduce the glycemic response obtained with the first infusion, resulted in significantly higher plasma insulin concentrations than during low load infusions. These techniques have demonstrated that plasma insulin levels can be dissociated from coexisting blood glucose concentrations. The amount of glucose utilized by the beta cell may explain the ability of increased glucose loads to augment insulin secretion since the level of blood glucose does not appear to be the primary determinant of the insulin response to glucose. C.R.S.

Prager, R.; Abramovici, A.; Liban, E.; and Laron, Z. (Institute of Pediatric and Adolescent Endocrinology and Laboratory of Developmental Pathology, Beilinson Medical Center, Petach Tikva and Departments of Pediatrics, Physiology and Pathology, Sackler Medical School of Tel-Aviv University): HISTOPATHOLOGICAL CHANGES IN THE PLACENTA OF STREPTOZOTOCIN INDUCED DIABETIC RATS. Diabetologia *10*:89-91, 1974.

Verbatim summary. Induction of diabetes by one intraperitoneal dose of streptozotocin (50 mg./kg.), eight to twelve days before mating, was found to produce severe degenerative cystic lesions in the spongiosa layer of the placenta. The administration of streptozotocin, sixteen to twenty-four days prior to mating, showed nonsignificant changes in the placenta. The morphologic changes observed might well explain the correlation between the bigger placentas and the smaller fetuses found in the streptozotocin-treated rats. STR administered before mating had no teratogenic effect on the fetuses.

Raskin, P.; and Siperstein, M. D. (Dept. of Intern. Med., Univ. of Texas Southwestern Med. Sch. at Dallas, Dallas, Texas, and the Vet. Admin. Hosp., Dallas, Texas): HYPERLIPIDEMIA AND DIABETES MELLITUS: CAN ELECTRON MICROSCOPY HELP IN THE DIAGNOSIS? J. Mount Sinai Hosp., N.Y. *40*:350-58, May-June 1973.

Elevations of plasma triglyceride and carbohydrate abnormalities of varying severity frequently accompany one another. Uncontrolled diabetes can result in severe hyperlipidemia. On the other hand hypertriglyceridemia may lead to glucose intolerance in the absence of genetic diabetes mellitus. In the authors' laboratory measurement of the width of the muscle capillary basement membrane establishes the differential diagnosis. A basement membrane width greater than 1,600 A strongly suggests the presence of genetic diabetes mellitus, while a value below 1,325 A makes this diagnosis highly unlikely. Once the primary diagnosis is established the appropriate treatment can be aimed at the primary abnormality. P.S.E.

Schauder, P.; and Frerichs, H. (Division of Gastroenterology and Metabolism, Department of Medicine, University of Göttingen, Federal Republic of Germany): CYTOCHALASIN B: INHIBITION OF GLUCOSE-INDUCED INSULIN RELEASE FROM ISOLATED RAT PANCREATIC ISLETS. Diabetologia *10*:85-87, 1974.

Verbatim summary. Cytochalasin B (200 μg/ml.) completely inhibited the glucose-induced insulin release from isolated rat islets. Basal release was unaffected. The cytochalasin-induced inhibition was rapidly reversible. Pretreatment with cytochalasin B seemed to increase the sensitivity of islets to a subsequent glucose stimulation.

Soler, N. G.; Bennett, M. A.; FitzGerald, M. G.; and Malins, J. M. (General Hospital, Birmingham B4 6NH England): INTENSIVE CARE IN THE MANAGEMENT OF DIABETIC KETOACIDOSIS. Lancet *1*:951-53, May 1973.

In this publication the authors review the mortality associated with diabetic ketoacidosis as seen in their hospital during three periods of time. During 1943-48, 18.8 per cent of 170 instances of ketoacidosis were fatal and of these 10.6 per cent of the total died of ketosis alone. During 1955-59 there was a 12 per cent over-all mortality among 160 admissions and 6.2 per cent died of ketosis. During 1968-72 an intensive care approach was emphasized in the management of 258 episodes of ketosis and the over-all mortality was reduced to 6.2 per cent while deaths at-

tributable to ketosis alone fell to 2.7 per cent. The chief causes of death among the sixteen who died during the 1968-72 period were hypokalemia, 4 and myocardial infarction, 3. There was a positive correlation between increased mortality, old age, severity of bicarbonate reduction and elevation of blood glucose. Aggressive potassium replacement, electrocardiographic monitoring, frequent serum potassium measurements, continuous aspiration of gastric contents, use of frusemide in cases of reduced urine flow after rehydration and a team approach with constant observation are given as reasons for improved salvage. T.G.S.

ORGANIZATION SECTION

ALLIED HEALTH COURSE ATTENDANCE SURPASSES PREVIOUS RECORDS

Attendance at the Sixth Allied Health Postgraduate Course in Diabetes, held in Atlanta April 22-24, totaled 387 registrants including dietitians, nutritionists, nurses, social workers, program directors and administrators from forty states, Washington, D.C., and Canada, which constitutes the largest registration for the Course since its inception. John K. Davidson, M.D., Ph.D., was Director of the Course, and Maria T. Alogna, R.N., Mary Goldsmith, R.D., and Tevora S. Riley, R.N., were Co-directors. The Course was presented under the auspices of the Committee on Professional Education of the American Diabetes Association, Karl E. Sussman, M.D., Denver, Chairman, and was held in cooperation with the Georgia Diabetes Association and Emory University School of Medicine.

THIRTY-FOURTH ANNUAL MEETING

A complete account of the Thirty-fourth Annual Meeting of the American Diabetes Association, which was held in Atlanta, Georgia, June 14-16, will be published in a coming issue of this Journal. Comparative attendance at this and previous meetings will be reported, as will the roster of Officers and Directors for the 1974-75 organizational year.

TWELFTH RESEARCH SYMPOSIUM

The American Diabetes Association will present its Twelfth Research Symposium entitled "Transplantation of Pancreatic Islets and the Histocompatibility of Endocrine Tissues" on October 25-26 at the Hotel Radisson Downtown in Minneapolis. The Symposium is a project of the Committee on Research, of which Edward R. Arquilla, M.D., Ph.D., Irvine, California, is Chairman. Frederick C. Goetz, M.D., Minneapolis, is Director of the Symposium. Co-directors are Walter Ballinger, M.D., and Paul E. Lacy, M.D., Ph.D., St. Louis; and Arnold Lazarow, M.D., Ph.D., Minneapolis.

The program, which includes a registration form, will be sent to all members of the Professional Section. The Symposium is open to the aforementioned members and to others by invitation.

Fee for the Symposium is $50.00. Fellows, residents and interns in a training status who have not completed five years of formal training may register for a fee of $25.00.

CHICAGO IS SITE OF 1975 POSTGRADUATE COURSE

"Diabetes in Review: Clinical Conference 1975," the Twenty-second Postgraduate Course of the American Diabetes Association, will be held at The Drake in Chicago, January 28-31.

NEW PROGRAM FOR ESTABLISHED INVESTIGATORS

The Board of Directors of the American Diabetes Association, on the recommendation of the Committee on Research, has approved a program of five-year Established Investigatorships, to be initiated by the selection of two Investigators in the spring of 1975 for funding as of July 1. Additional Investigators will be selected each year until a total of fifteen per annum are supported.

The Investigatorships will provide financial support for established scientists whose work is relevant to the general area of diabetes research. The Established Investigatorships will foster maximal research productivity for highly qualified individuals by providing the means to relieve them of excessive service, teaching or administrative responsibilities. The recipients of these awards are to be individuals of unusual research ability and originality who have made major contributions to the field of diabetes research regardless of age or present position. However, it is stipulated that at the time the award is made, the candidate must be actively engaged in research related directly or indirectly to diabetes. Individuals approaching retirement age will ordinarily not be considered as reasonable candidates except in cases of truly exceptional merit.

Terms of Award: The maximum contribution from the American Diabetes Association to the salary support of an Established Investigator is $25,000 per year. Institutions remain responsible for fringe benefits and overhead. Institutions may supplement the salary of an awardee compatible with the institutional salary scale.

A grant of $10,000 per annum is to be made available to each Established Investigator for laboratory and travel support. In addition, the Investigator may apply for other grants-in-aid from any organization, including the Association. The department and the institution in which the Investigator works will each receive $1,000 annually.

Awardees are expected to devote a majority of effort to the achievement of the objectives of the Established Investigatorship. Their principal involvement must be with the actual conduct of research. They may, however, receive or provide research training and participate in teaching and other appropriate functions of their institutions. Awardees may not undertake substantial administrative responsibilities during the tenure period. Awardees may not engage in clinical practice, professional consultation, or