THE YEAR BOOK *of* ENDOCRINOLOGY

(1962-1963 YEAR BOOK Series)

EDITED BY

GILBERT S. GORDAN, M.D., Ph.D., F.A.C.P.

Professor of Medicine and
Chief of Endocrine Clinics, Department of Medicine,
University of California School of Medicine;
Attending Physician, University of California Hospitals,
San Francisco General Hospital, and Veterans Administration Hospital,
San Francisco, California

YEAR BOOK MEDICAL PUBLISHERS

INCORPORATED

35 EAST WACKER DRIVE CHICAGO 1

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INTRODUCTION

For endocrinology, 1962 was more a year of re-evaluation than of new concepts. Of particular concern are the interpretations to be placed on the contributions of immunology to hormone assay and to the etiology of certain possibly autoimmune endocrinopathies. It seems reasonably certain that immunoassay of insulin detects the insulin protein molecule more or less quantitatively. Certain discrepancies with biologic activity, however, suggest that the assay does not distinguish molecules with insulin's hormonal activity from those with attenuated or lost function. The question is not merely whether bioassay is inferior to immunoassay but rather what each measures. Similarly, the specificity and sensitivity of immunoassays for growth hormone are undergoing renewed question and scrutiny. It now appears that human growth hormone either shares or simulates the actions and immune characteristics of lactogenic hormone. The possibility that they are identical has, in fact, been raised, but the lack of acromegalic features in the Chiari-Frommel syndrome, in which the blood contains a substance immunologically undistinguishable from human growth hormone, speaks against their identity. The even more controversial problem of the significance of thyroid antibodies in chronic thyroiditis and in the etiology of "idiopathic" myxedema poses a more difficult problem. Despite the contrary opinions of some notable contributors to this field, I have become increasingly impressed by the thesis originally advanced by Roitt and Doniach and subsequently so carefully documented by them and their associates, indicating that the thyroid cytotoxic antibody has the physical and biologic properties to do the job. In their studies, it also occurs in adequate concentrations in the right conditions for their thesis. We have far less information about the nature and quantities of antibodies as the potential causes of Addison's disease, idiopathic hypoparathyroidism, possibly postsurgical hypoparathyroidism and hypothyroidism, and diabetes mellitus. Their role in causing some forms of insulin resistance seems on firmer ground. Since antibodies to damaged organs appear in the serum of patients with conditions in which the cause for the fundamental damage is not auto-

immune, e.g., myocardial infarction, it is clear that the presence of antibodies by itself does not prove causality. For example, antithyroid antibodies might be mere by-products, while delayed hypersensitivity could be causing thyroiditis and myxedema. An excellent review, "Antibodies and Autoimmune Diseases," by Milgrom and Witebsky (J.A.M.A. 181:706, Aug. 25, 1962) reiterates Witebsky's criteria for autoimmune disorders. I believe chronic lymphocytic thyroiditis (Hashimoto's disease) and postthyroiditis myxedema meet these requirements.

The most important problems in carbohydrate metabolism just now are the specificity of the various assays for insulin or "insulin-like activity" and the still completely unidentified cause(s) of degenerative complications in diabetes mellitus. The latter problem is currently under intensive study by the Diabetes Cooperative Group supported by the National Institutes of Health. Islet cell tumors manifested clinically by hyperinsulinism, the Zollinger-Ellison syndrome of intractable ulcer, or by watery diarrhea, malabsorption and hypokalemia are now tied in with the endocrine enigma of multiple ductless gland tumors, not all of which are adenomas, since carcinoma of the thyroid and pheochromocytoma appear to be parts of the syndrome. Catecholamines and other aromatic amines may be implicated in some of the symptoms of hyperthyroidism. The source of the long-acting stimulator of thyroid function found in the serum of patients with Graves' disease remains unestablished. Now that some investigators have reported finding a thyrotrophin-releasing substance in the hypothalamus, the thyrostat concontinues its cephalad progress. Of particular interest is the demonstration of the antithyroid activity of the thyroxin analogue diiodothyroacetic acid. Studies of thyroid hormone binding by serum proteins have confirmed the biologic importance of prealbumin and have resulted in direct measurement of the free, biologically active fraction.

Tracer studies of bone mineral metabolism have added to information about the pathogenesis of certain types of osteoporosis and the mechanism of action of steroid hormones in their treatment. Numerous reports of the use of calcium in some kinds of osteoporosis, notably the idiopathic type in men, have appeared. The mechanism of action is completely unknown; bone accretion is not increased. It is with con-

siderable personal regret that I must record the death in 1962 of a valiant worker in this field, André Lichtwitz, age 62.

Pathways of adrenocortical steroidogenesis continue to unfold, and a newly recognized defect of 3β-ol dehydrogenase has been described in a rare form of congenital virilizing hyperplasia. Unhappily, triparanol, which last year appeared promising as a nonsurgical way of curing Cushing's disease, has proved ineffective, the fall in urinary corticosteroid excretion resulting from altered metabolism rather than decreased secretion. On the other hand, two groups have confirmed earlier reports that autotransplantation of hyperactive adrenal glands may prevent postoperative Addison's disease and, hopefully, postoperative growth of pituitary tumors. Abnormal steroidogenesis in the ovaries of patients with the Stein-Leventhal syndrome appears to be responsible for their hirsutism and other androgenic phenomena. Human pituitary gonadotrophin has proved effective in producing ovulation and even superovulation with twin pregnancies. (Perhaps the dose should be reduced!) A synthetic compound, clomiphene, is reported similarly effective in producing ovulation. Fears that progestational agents used in fertility control might damage the ovary have been dispelled by the observation of rebound superfertility on their withdrawal. Anabolic and antitumor compounds without androgenic activity have been described. The otherwise inert compound Δ^1-testololactone is reported effective in the treatment of advanced breast cancer.

Before closing the introduction to this, the last of a baker's dozen volumes I have enjoyed preparing with Year Book Medical Publishers, I wish to express a personal sentiment. Endocrinology has changed considerably, mostly for the better, in a very short time. Improved chemical methods, notably chromatography and isotopic analysis, have made possible the recognition of biologically important micrograms, nanograms or even picograms, in a field where "milligram amounts" once meant very tiny quantities. Perhaps the most worrisome impression gathered in years of facing thousands of papers is that precision of thought, as indicated by use of words, is steadily declining. An example is the current tendency to put in quotation marks precise terms for imprecisely measured substances, or to add "-like," but then to deal with the resulting estimates as if they indeed re-

ferred to specific or accurately measured entities. These are matters for medical teachers and editors of journals to handle. In lighter vein, I note that the designation "-trophic" (on which I have insisted in the volumes I edited) has been scrutinized rather closely in an exchange of letters in Science (137:336, 1962 and 138:723, 1962). I am delighted to find myself in the same camp with the distinguished biochemists, Jane A. Russell and Alfred E. Wilhelmi, who point out that these agents produce hypertrophy (not, I shudder to suggest, hypertropy) and their absence, atrophy (not atopy, a different condition). For having put up with this and others of my preferences these many years, I wish to thank Year Book Medical Publishers. Part of this volume was prepared during a profitable and pleasant sabbatical leave at Columbia University where I had the good fortune to have sections of this YEAR BOOK criticized by Doctors Jane H. Morse, David Schachter and Sidney Werner, to whom I am greatly indebted.

GILBERT S. GORDAN

CARBOHYDRATE METABOLISM

► A few great discoveries can be singled out as outstanding contributions of endocrinology to medicine, health and human welfare. One thinks, of course, of such important examples as the use of iodine in prophylaxis of endemic goiter and hypothyroidism, thyroid replacement therapy in myxedema, abolishing surgical mortality in Graves' disease by preoperative administration of iodine, and the synthesis of gonadal and adrenocortical steroids for use as replacement therapy. But for sheer numbers of people whose lives have been saved, as well as for early initiation of important biochemical research, the discovery of insulin towers above all these. *The Canadian Medical Association Journal* in 1962 commemorated this, the greatest discovery in the history of endocrinology, on the occasion of its fortieth anniversary by reproducing the original preliminary report of Banting, Best, Collip, Campbell and Fletcher, which is presented as the lead-off article in this volume. I wish that space permitted inclusion of W. R. Campbell's delightful account of the Toronto School of those stirring times, a paper I heartily recommend to all who enjoy good reading (Canad. M. A. J. 87:1055, Nov. 17, 1962).

Despite the numerous assays for "insulin-like activity" or for proteins with the immunologic characteristics of insulin, I am not sure just how much reliance can be placed on quantitation of blood insulin levels at this time. Whether any method actually measures biologically active insulin can still be queried. The persistence after pancreatectomy of insulin-like activity measured by the epididymal fat pad casts serious doubt on the specificity of this assay. Despite the limitations of available methods, other data are in harmony with the results of blood assays indicating that sulfonylureas exert their hypoglycemic effects by releasing insulin from the pancreas. Whether the hypoglycemia associated with extrapancreatic tumors is due to an insulin-like or islet cell-stimulating humor from the tumor or, more likely, to excessive utilization of glucose by these usually enormous tumors is not established.

Decreased glucose tolerance has been demonstrated in renal failure and after the administration of thiazide diuretics to patients with mild diabetes mellitus. Despite considerable investigation, the factors responsible for the late degenerative complications of diabetes mellitus remain obscure. (The fact that diabetics now live long enough to develop these complications is itself a tribute to insulin.) Solution of these problems would be on a par with the discovery of insulin itself.

Islet cell tumors as part of the syndrome of endocrine adenomatosis are included in the chapter on Parathyroid Glands, and with acromegaly in the chapter on the Adenohypophysis. Also under the Adenohypophysis are reports of the effects of growth hormone in hypophysectomized, diabetic women; a case of diabetes mellitus plus primary failure of the thyroid, ovaries and adrenal cortex; and the repair of defective lipogenesis from glucose in the hypophysectomized rat by ACTH, growth hormone and thyroxin. Abnormal thyroxin metabolism in diabetes mellitus is described in the chapter on the Thyroid Gland. Abnormal conjugation of 17-hydroxycorticosteroids in diabetes mellitus is reported in the chapter on the Adrenal Cortex. The effect of growth hormone on intestinal transport of calcium is discussed in the chapter on the Parathyroid Glands, Calcium and Phosphorus Metabolism and Metabolic Bone Diseases.—Ed.

Insulin

Pancreatic Extracts in Treatment of Diabetes Mellitus were investigated by F. G. Banting, C. H. Best, J. B. Collip, W. R. Campbell and A. A. Fletcher[1] (Univ. of Toronto). Since von Mering and Minkowski produced fatal diabetes in dogs by total pancreatectomy, many investigators have attempted to obtain some beneficial effect in diabetes mellitus from feeding of pancreas. Pancreatic extracts given intravenously are reported to reduce blood and urine sugar transiently. In the belief that extracts did not demonstrate presence of an internal secretion acting on carbohydrate metabolism because of destruction of the active principle by digestive enzymes, attempts were made to eliminate the latter by taking advantage of the fact that acinous tissue degenerates 7-10 weeks after ligation of the pancreatic ducts. Extracts made with ice-cold Ringer's solution at 10 weeks invariably markedly reduced blood sugar and glycosuria when injected intravenously or subcutaneously into diabetic dogs; liver and spleen extracts were not effective. The active principle was destroyed by boiling in neutral or acid solution or by incubation with pancreatic juice for 2 hours at body temperature.

A highly potent extract was prepared from the pancreas of the fetal calf under age 5 months, and an active extract which retained potency for at least 1 month eventually was obtained from normal adult ox pancreas. Daily injections of these extracts prolonged the life of a completely diabetic dog to 70 days, at which time the animal was killed. When carbohydrate was given, the extract increased the respiratory quotient from about 0.7 to nearly 1.0.

Preparation of a highly potent, sterile extract allowed administration to human diabetic subjects after a week of a constant diet. Blood sugar was estimated by the revised Folin-Wu method, urinary sugar by Benedict's method, acetone bodies by Van Slyke's method and respiratory quotient by the Tissot-Haldane and Douglas-Haldane methods. In 7 cases of diabetes mellitus, the effects of subcutaneous administration paralleled those in depancreatized animals. Fall in blood sugar and, in 2 cases, rise in respiratory quotient

(1) Canad. M. A. J. 87:1062-1067, Nov. 17, 1962; reprinted from March, 1922, issue.

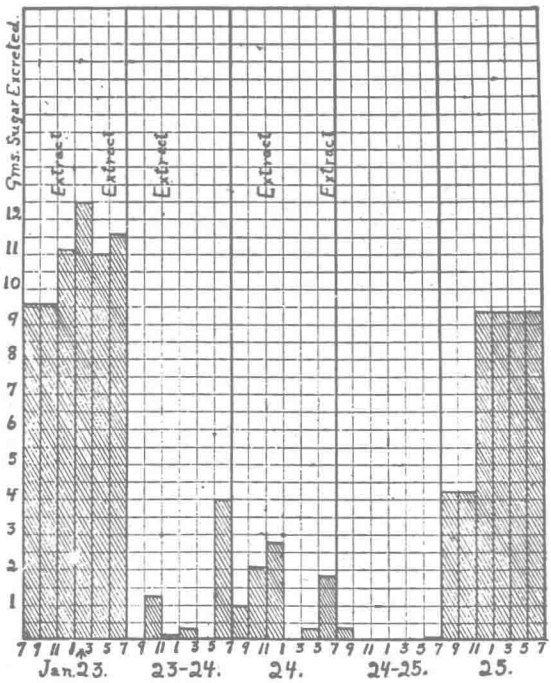

Fig. 1.—Curve of glucose excretion during extract administration. Large dots indicate blood sugar. (Courtesy of Banting, F. G., *et al.*: Canad. M. A. J. 87:1062-1067, Nov. 17, 1962.)

were more or less coincident with attainment of a normal blood sugar level. Subjective symptoms were completely relieved in all patients. Sugar excretion showed marked decrease or, if dosage was adequate, disappeared; ketonuria was abolished. Without careful control, severe toxic reactions may occur.

Boy, 14, had enuresis and excessive appetite 2 years previously; sugar was found in the urine. Despite adherence to diet and even fasting, glycosuria persisted, he began to lose weight, and urinary frequency was noted. He had always been fond of sweet food. There was no family history of diabetes. He was poorly nourished and pale, his hair was falling out, there was an acetone odor on his breath, and he was listless. The urine was strongly acid, and tests for sugar and ketones were strongly positive; blood sugar level was 5.8 mg./cc. Despite maintenance on a 100-Gm. carbohydrate diet, he became worse clinically. The first, less concentrated extracts given brought about a 25% fall in blood sugar level and a slightly lowered sugar

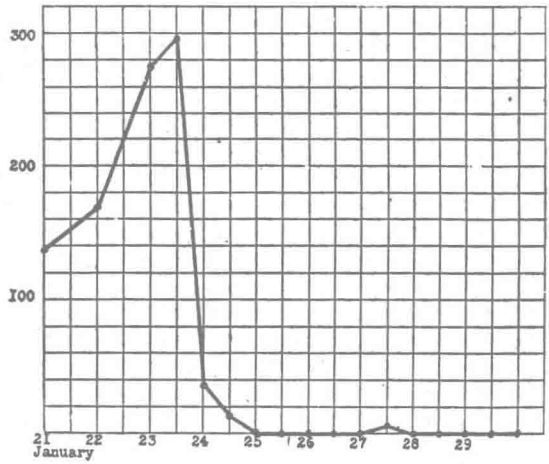

Fig. 2.—Cessation of ketonuria after administration of extract. (Courtesy of Banting, F. G., *et al.*: Canad. M. A. J. 87:1062-1067, Nov. 17, 1962.)

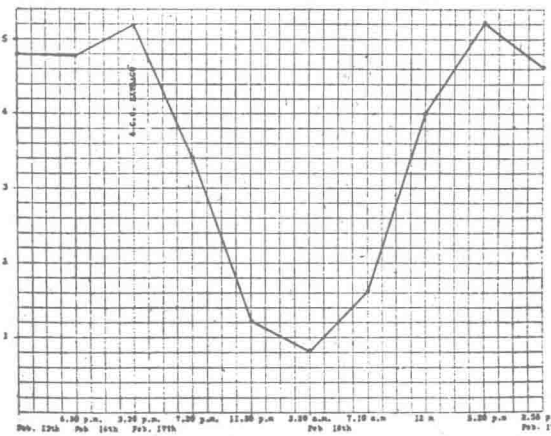

Fig. 3.—Effect of one injection of extract on blood sugar (mg. per c.c. = 0.1%). (Courtesy of Banting, F. G., *et al.*: Canad. M. A. J. 87:1062-1067, Nov. 17, 1962.)

excretion. Later, daily injections resulted in decreased sugar excretion (Fig. 1), from over 100 to 7.5-45.1 Gm. per day; acetone bodies disappeared from the urine (Fig. 2); and the boy became brighter and more active and said he felt stronger. When no extract was given for 10 days, sugar and acetone reappeared in the urine; administration of extract again lowered sugar and caused acetone to disappear. A 4-hour record of blood sugar after administration of a single dose of 6 cc. of extract is seen in Figure 3.

Another patient with severe diabetes, who had been excreting 20-Gm. glucose on a 10-Gm. carbohydrate diet, exhibited a sugar-free urine after injection of extract and obtained complete relief from severe depression and extreme lassitude. Respiratory quotients showed a definite rise after injection.

Although the improvement is temporary, it is believed that the hope of more permanent results after more adequate and carefully regulated dosage is justified. The results leave no doubt that these extracts represent a therapeutic measure of unquestionable value in treatment of certain phases of diabetes in man.

Lente Insulin Triad: With Emphasis on Use of "Lente Combinations" was reported by Fred W. Whitehouse, William L. Lowrie, Earl Redfern and John B. Bryan[2] (Detroit). The combination of insulin with zinc at different pH values in the presence of an acetate buffer yielded two physical fractions, an amorphous and a crystalline fraction. The amorphous fraction, named semilente, has a peak action in 2-4 hours with a duration of action of 10-12 hours. The crystalline fraction, named ultralente, has a peak action at 18-24 hours with a duration of over 36 hours. A combination of 70% ultralente and 30% semilente, called lente, has a peak action at 8-14 hours with a duration of 20-26 hours.

A combination of two of the three members of the lente insulin triad was given to 65 diabetic patients (29 men), aged 5-70 years; 36 were under 40. Most were normal in weight. Duration of diabetes was 1-30 years and was over 15 years in 24 patients. Follow-up ranged from 6 to 36 months.

A combination of lente and ultralente was given to 42 patients, semilente and lente to 18 and ultralente and semilente to 5. These combinations were given to patients whose diabetes was uncontrolled with a single daily injection of an intermediate insulin. Semilente was used with lente when greater hypoglycemic activity was needed during the day, ultralente with lente insulin when greater activity was needed during the night. This often obviated the need of an evening injection of intermediate insulin

Use of the lente triad gave satisfactory control of the diabetes in these patients. Disadvantages were minor and allergy was absent, as there is no added protein in lente insulin.

(2) Ann. Int. Med. 55:894-902, December, 1961.