EDITORIALS

THE MAURIAC SYNDROME
Dwarfism, hepatomegaly and obesity with juvenile diabetes mellitus

A triad of symptoms of varying degrees of dwarfism, hepatomegaly and obesity, developing slowly in diabetic children, has been commonly designated the Mauriac syndrome, after P. Mauriac's first descriptions published in 1930 and 1934[1, 2]. Mauriac wrote that with the discovery of insulin a new disease was born: juvenile diabetes, with curious troubles and manifestations of endocrine disturbances not previously seen because these patients formerly did not survive. Most cases of so-called diabetic dwarfism were reported during the first fifteen years or so after insulin became available. Mauriac at first suggested that long continued administration of insulin might be responsible for the syndrome. Subsequently there has been general agreement that the syndrome develops only among "badly managed" patients and is not seen in children who from the start of their diabetes are given good diets with daily insulin dosage adequately regulated.

The various symptoms associated with retarded growth in juvenile diabetes are now usually ascribed to nutritional deficiencies, and lack of insulin, rather than to metabolic derangements peculiar to the disease itself. But further questions arise with regard to predisposing factors that may lead to the development of this syndrome in some patients more easily than in others. Conceivably, each of the three major symptoms may be determined by independent factors that accompany the diabetic trait in an individual.

The patients who display this triad of symptoms are usually described as "brittle" diabetics, hard to manage. Thus the records of poor control may be explained, if not excused, by the fact that the adjustment of insulin dosage for proper control was much more difficult in these patients than in others of the same age whose physiologic adjustments were better, under approximately similar instructions with regard to diet and insulin dosage. While the complete syndrome occurs rarely, a recent article by Darnaud and others[3] on "les formes frustes" of the Mauriac syndrome (i.e. not fully developed and with mild manifestations) suggests that these derangements may exist more often than is generally recognized but follow an abortive course if appropriate therapy is offered. Granting this possibility, the physio-pathology of separate phases of the syndrome assumes greater interest in the absence of severe manifestations.

The salient features chosen for discussion here are: *Hepatomegaly,* characterized by surcharge of the liver with fat or glycogen or both; *dwarfism,* possibly conditioned by pituitary deficiency, but with nutritional factors playing a leading role; *obesity* with moon face, possibly associated with oversecretion of corticosteroid hormones; *hypersensitivity to quick-acting insulin and favorable responses to slow-acting insulin,* possibly related to both pituitary and hepatic factors.

Joslin states that prior to the introduction of protamine zinc insulin hepatomegaly was one of the outstanding complications of juvenile diabetes. Marble and others[4] reported 60 cases in 1938, representing approximately six per cent of the juvenile diabetics coming to their clinic. All of these had records of poor control, frequent occurrence of ketosis and of hypoglycemic reactions from regular insulin with dosage poorly regulated. Following treatment with slow-acting protamine zinc insulin the liver decreased in size in 79 per cent of these cases.

Hepatomegaly in the diabetic was at first thought to be due to fatty infiltration; later, many large livers of diabetic patients have been found surcharged with glycogen, some with both glycogen and fat. Lack of insulin is the most likely primary cause of fatty infiltration, but numerous investigators suggest that it may be caused or aggravated by a deficiency of lipotropic factors. While a nutritional deficiency seemed unlikely,

when so many of the patients are obese, Freudenberg[5] made the interesting suggestion that frequent bouts of ketosis might lead to wastage of nitrogen (well known) with losses of essential amino acids such as methionine, which the body cannot synthesize, and that such losses can lead to a deficiency of the lipotropic factor choline. A number of writers claim dramatic beneficial effects from the administration of methionine, choline and inositol[3, 6]. Such results are difficult to evaluate accurately because similar results are obtained in nearly all cases merely with a good diet and correct regulation of insulin dosage to avoid the occurrence of ketosis and to avoid abrupt, wide fluctuations in blood-sugar levels with attendant reactions.

Many writers point to similarities in the symptomatology of diabetic dwarfism and glycogen storage disease (Van Creveld-Von Gierke disease), namely, dwarfism, obesity, large liver, hypersensitivity to insulin and the frequent development of ketosis. Debré[7] and others suggest the possibility that the two metabolic disorders might coexist in the same individual, and that in the large liver of the diabetic there might exist a metabolic fault of glycogen-turnover similar to that found in the glycogen storage disease. Such a possibility is made plausible by reports of the occurrence of glycogen storage disease and of diabetes mellitus in separate members of one family and by the fact that patients with glycogen storage disease have developed diabetes mellitus later in life. Although this possibility is so far not supported by chemical studies that have been done on liver glycogen or by adrenalin tolerance tests (both found normal in patients with the Mauriac syndrome) the possibility of a partial fault in liver glycogen metabolism in these diabetic patients merits further study.

The "moon face" with obesity so often noted in clinical descriptions of the diabetic dwarf suggests the possibility of excessive liberation of corticosteroid hormones by overstimulation of the adrenal glands, linked with states of poor control commonly reported in clinical histories of these patients. Such adrenal stimulation conceivably might occur during frequent episodes of hypoglycemia associated with hypersensitivity to quick-acting insulin and during periods of ketosis caused by insulin-lack, during hours when the insulin dosage was not well distributed for continuous effect. Pertinent observations on this phenomenon were reported by McArthur and others[8] from a careful metabolic study on the effects of variations in insulin dosage upon adrenal cortical activity in a nineteen-year-old diabetic male (Mongol, with diabetes of twelve-years duration). Doses of crystalline insulin that were planned to ensure normoglycemia, but entailed frequent insulin reactions, led to greatly increased corticosteroid excretion. Smaller doses of insulin, which just prevented ketonuria but allowed heavy glycosuria, had no effect on corticosteroid excretion or on eosinophil counts. On the other hand, the development of ketosis with insulin-lack is attended with increased corticosteroid excretion and fall in the eosinophil count. McArthur and co-authors[8] conclude with the comment, "—maintenance of a high concentration of adrenocortical hormones in the circulation of a diabetic patient almost certainly exerts widespread biological effects—." Perhaps the repeated adrenal stimulation of insulin reactions, even mild, alternating with periods of ketosis, which are reported frequently in the case histories of the diabetic dwarfs, may indeed have biological effects evidenced by disturbances of growth, deposition of fat, and the development of the "moon face."

Hypersensitivity to quick-acting insulin in these patients may also be associated with hepatic factors, not yet well understood. Studies done by an ingenious technic of hepatic vein catheterization led Sherlock and others[9] to classify diabetic patients as hepatic-insulin-sensitive and hepatic-insulin-insensitive. In the first group intravenous injection of insulin resulted in extremely rapid uptake of sugar from the blood, while the "insensitive" group showed a much slower uptake of sugar by the liver after the same dose of insulin. Avidity of glucose-uptake, rapid synthesis of glycogen and differences in speed of release of sugar from the liver might account for differences in tendencies of individual patients to develop hepatomegaly, with surcharge of glycogen, under uneven adjustments of insulin dosage.

Recent studies by Best and his co-workers[10, 11] on the growth-promoting action of slow-acting protamine zinc insulin in hypophysectomized rats may have an important meaning with regard to treatment of the diabetic dwarf and of milder manifestations of the metabolic derangements here grouped under the Mauriac syndrome. In hypophysectomized rats, which fail to grow and are extremely sensitive to quick-acting crystalline insulin, the administration of slow-acting protamine zinc insulin in dosage gradually increasing from 1 to 6 units per day was followed by a dramatic resumption of growth with increase in body weight, protein content and skeletal size. Best suggests that in hypophysectomized rats, a lack of insulin (ascribed to decreased liberation of endogenous insulin) may be a factor limiting growth. In the light of these new findings, it

seems probable that the beneficial effects of protamine zinc insulin in the diabetic dwarf, on which all workers agree, may be ascribed to the growth-promoting and protein anabolic action of the slow-acting insulin. Presumably, this action of the slow-acting insulin is better than that of regular insulin merely because its effects are much more gradual and more prolonged.

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RETIREMENT OF DOCTOR WILDER

On July 1, 1953, Dr. Russell M. Wilder retired as Director of the National Institute of Arthritis and Metabolic Diseases, a position which he had held since January 1951. He was the first Director of the Institute, which is the newest of seven National Institutes of Health, and he played a leading role in the development of its resources and activities in the fields of research, support of research and training of specialists in rheumatology and metabolic diseases. Particularly, he was a leader in the formulation of the policies and program of the recently dedicated Clinical Center of the National Institutes at Bethesda, Md.

Russell M. Wilder, M.D.

Prior to accepting the post of Director of the Institute of Arthritis and Metabolic Diseases, Dr. Wilder had achieved a place of international distinction in the field of diabetes, metabolic diseases and nutrition. From 1915 to 1917, he participated with Dr. Rollin T. Woodyatt at the Presbyterian Hospital and Rush Medical College, Chicago, in important metabolic studies related to diabetes, particularly investigations of the rate of utilization of glucose and of ketone acids. He long will be remembered as one of the pioneers in the clinical use of insulin. He was the author of more than 200 scientific papers, many of them dealing with diabetes, co-author of several medical textbooks and author of two books about diabetes, *Clinical Diabetes Mellitus and Hyperinsulinism;* and *A Primer for Diabetic Patients.* In addition, he contributed much to the betterment of medical literature in the course of long service as Associate Editor of the *Archives of Internal Medicine;* he also was Associate Editor of the *American Journal of*