EDITORIALS

STEROID DIABETES

The term "steroid diabetes" has come into such wide use in recent years that it merits editorial comment and definition. Properly the term is applied in clinical medicine to a diabetic state resulting from an excess of adrenal steroids which have a high degree of carbohydrate activity. Such steroids interfere with the action of insulin, impair carbohydrate utilization and augment the formation of sugar from protein. The most potent are cortisone and hydrocortisone, the latter being slightly more active than the former, according to assays on animals.

Steroid diabetes was first produced experimentally in the normal rat by Ingle who in 1941 administered large doses of cortisone.[1] The condition has certain features, first described by Ingle and associates in the rat, which distinguish it from pancreatic diabetes.[2] In steroid diabetes there is a relative insensitivity to insulin. Since the condition is attributable in part to excessive gluconeogenesis from protein under the catabolic influence of adrenal steroids, it is associated with a negative nitrogen balance which is not corrected by administration of insulin. In addition, steroid diabetes, in contrast to pancreatic diabetes, is temporary, subsiding when the source of excess adrenal steroids is removed.

The occurrence of steroid diabetes in man is limited principally to patients with spontaneous adrenal cortical hyperfunction of the type which produces Cushing's syndrome[3] and to some patients who are receiving cortisone, hydrocortisone or corticotropin in large doses for therapeutic purposes. It is thus apparent that steroid diabetes is relatively rare, and that large amounts of carbohydrate-active steroids are necessary for its production. In cases of "ordinary" diabetes there is no convincing evidence of hyperfunction of the adrenal cortex, except transiently during severe diabetic acidosis.[4] Insufficiency of the islet tissue increases the likelihood that diabetes will result from the presence of excessive amounts of adrenal steroids.[5]

While the term "steroid diabetes" should be limited to those diabetic states which result from an excess of adrenal steroids, it should be recognized that the presence of some adrenal steroids is necessary for the maintenance of the ordinary diabetic state. Many of the features of diabetes disappear if the adrenals of the diabetic are destroyed or removed,[6] and the diabetic state is restored if cortisone or hydrocortisone is administered. It appears that the adrenal hormones play what Ingle has called a "permissive" role in ordinary diabetes; they do not cause the diabetes but their presence is necessary for its maintenance.

The paper in this issue of DIABETES by Bookman[7] and associates describes steroid diabetes in the human being resulting from administration of large doses of corticotropin or cortisone. Conn and associates[8] previously have described the production of steroid diabetes by corticotropin, and some of its characteristics. The capacity of corticotropin, as well as of cortisone and hydrocortisone, to induce diabetes in man, shows that the secretory capacity of the adrenal glands, in some individuals at least, is great enough during stimulation to reproduce the diabetogenic effects of large doses of the carbohydrate-active adrenal steroids.

RANDALL G. SPRAGUE, M.D.

---

[1] Ingle, D. J.: The Production of glycosuria in the normal rat by means of 17-Hydroxy-11-dehydrocorticosterone. Endocrinology. 29:649-652, Oct. 1941.

[2] Ingle, D. J.; Sheppard, Ruth; Evans, J. S., and Kuizenga, M. H.: A comparison of adrenal steroid diabetes and pancreatic diabetes in the rat. Endocrinology. 37:341-356, Nov. 1945.

[3] Sprague, R. G.; Hayles, A. B.; Power, M. H.; Mason, H. L., and Bennett, W. A.: "Steroid Diabetes" and alkalosis associated with Cushing's syndrome: Report of case, isolation of 17-Hydroxycorticosterone (Compound F) from urine, and metabolic studies. J. Clin. Endocrinol. 10:289-306, Mar. 1950.

[4] McArthur, Janet W.; Sprague, R. G., and Mason, H. L.: The urinary excretion of corticosteroids in diabetic acidosis. J. Clin. Endocrinol. 10:307-312, Mar. 1950.

[5] Sprague, R. G.; Mason, H. L., and Power, M. H. Studies of the effects of adrenal cortical hormones on carbohydrate metabolism in human subjects. Proc. Am. Diabetes Assoc. 9:149-166, 1949.

[6] Long, C. N. H., and Lukens, F. D. W.: Observations on adrenalectomized, depancreatized cats. Science. 79:569-571, June 22, 1934.

[7] Bookman, J. J.; Drachman, S. R.; Schaefer, L. E.; and Adlersberg, D.: Steroid diabetes in man. The development of diabetes during treatment with cortisone and certicotropin. Diabetes. 2:100-11, Mar.-Apr., 1953.

[8] Conn, J. W.; Louis, L. H., and Wheeler, C. E.: Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone; relation to uric acid metabolism. J. Lab. & Clin. Med. 33:651-661, 1948.

INSULIN RESISTANCE

Insulin resistance may or may not be associated with the visible manifestations of allergy to insulin. Although the majority of patients with minor, transitory, allergic reactions to insulin are not noticeably resistant to insulin, one rightly looks for allergy to insulin as a possible cause of sever insulin resistance. In the last decade, the study of insulin resistance has been advanced by the application of several new methods. Lerman[1] and Lowell,[2,3] selecting patients because they were insulin resistant (with or without associated local allergy) have presented strong evidence for an immunologic mechanism. The same immunologic methods have indicated that antibodies to administered insulin may be produced in rabbits.[4] Insulin recrystallized six times is much less antigenic than commercial insulin[5] and the use of insulin prepared from human pancreas may be normally effective in the presence of resistance to the usual commercial insulin.[3] Such results indicate that the allergy to administered insulin is due either to some contamination of the protein hormone, or to differences in the actual structure of insulin from different sources, to which these few patients are susceptible.

Further evidence of the part which allergy may play in insulin resistance has appeared since the control of allergic reactions by corticotropin (ACTH) has been possible. Howard[6] treated a patient, who had marked resistance and allergy to insulin, with corticotropin and was able to restore the patient to a stage of mild diabetes for which no insulin was needed. Sera of this and of other insulin resistant patients were examined for their effect on the action of insulin on the isolated rat diaphram.[7] There was striking inhibition of the effect of insulin in vitro by the sera of patients requiring 300 units of insulin per day or more. In the patient who had been treated with corticotropin, this inhibitory action of the serum was no longer present. Finally, Marsh and Haugaard[7] have shown that the serum of insulin resistant patients behaves differently from the hormones which inhibit the action of insulin in vitro. Thus in the presence of antibodies, less insulin is bound to the rat diaphragm: antagonistic hormones appear not to prevent this binding of insulin to tissue but to inhibit its subsequent metabolic action. These results emphasize the importance of immune reactions in insulin resistance. The preliminary differentiation of immunological and hormonal types of insulin resistance by new methods suggests that this obscure corner of diabetes may be considerably enlightened in the future.

F. D. W. LUKENS, M.D.

[1] Lerman, J.: Insulin resistance. The role of immunity in its production. Am J. Med. Sci. 207:354-360, 1944.

[2] Lowell, F. C.: Immunologic studies in insulin resistance. I. Report of a case exhibiting variations in resistance and allergy to insulin. J. Clin. Invest. 23:225-31, 1944.

[3] Lowell, F. C.: Immunologic studies in insulin resistance. II. The presence of a neutralizing factor in the blood exhibiting some characteristics of an antibody. J. Clin. Invest. 23:233-240, 1944.

[4] Franklin, W.; and Lowell, F. C.: Experimentally induced insulin resistance and allergy in the rabbit. J. Allergy 20:400-403, 1949.

[5] Paley, R. G.; and Tunbridge, R. E.: Dermal reactions to insulin therapy. Diabetes 1:22-27,1952.

[6] Howard, J. E.: Proceedings of the Second Clinical ACTH Conference, edited by Mote, J. R., New York, The Blakiston Co., 1951, Vol. I, p. 318.

[7] Marsh, J. B.; and Haugaard, N.: The effect of serum from insulin-resistant cases on the combination of insulin with the rat diaphragm. J. Clin. Invest. 31:107-110, 1952.

A PRE-DIABETIC STATE IN PARENTS OF OVERWEIGHT BABIES

It is widely recognized that maternal diabetes bears a close relationship to production of abnormally large babies as well as to hydramnios, a high fetal mortality and perhaps toxemia. It has been clearly shown by Miller, Kriss and Futcher and others, that abnormally large children may be born to mothers who have no evidence of diabetes at the time of birth (as judged by existing methods) and who later develop diabetes.

W. P. U. Jackson,[1] in his recent article in the British Medical Journal, offered fresh, carefully studied and convincing evidence along these lines. He found that 62 per cent of women who developed overt diabetes after childbearing claimed to have had before becoming diabetic at least one baby over 10 pounds in weight at birth; 31 per cent of the babies of these women were over 10 pounds as compared with 4.6 per cent of the babies of women in the control group. One of the most internal maternal environment must be the dominant engaging parts of Jackson's studies and one which appears to be a new contribution to the knowledge of