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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.

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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

factor; here according to current concepts the pituitary growth hormone may play an important part. In the case of the "pre-diabetic fathers," the factor of inheritance must be the determining factor.

Jackson contends that when a woman gives a history of having had several large babies, the diagnosis of a pre-diabetic state is justified to such an extent that treatment should be started before glycosuria or hyperglycemia are known to exist. He believes that a pre-diabetic state must be present from the first pregnancy resulting in the delivery of a baby over ten pounds in weight to the time at which active diabetes is demonstrable. Critical students of the problem will find it difficult to accept these ideas as completely valid.

The whole concept of the pre-diabetic state is an intriguing one and may well prove of importance in advancing the knowledge regarding the etiology of human diabetes. One might ask what must be the evidences of diabetes before the diagnosis can be made. We need not wait for cardinal symptoms before we are justified in considering diabetes to be present. Is the condition certain to be present if the blood sugar two or three hours after eating is abnormally high even to a slight degree? If this is true, then diabetes exists if the blood glucose is consistently elevated in the absence of unusual endocrine or hepatic disease. Taken in this light, diabetes then varies only in the degree of mildness or severity and pre-diabetes does not exist unless it can be predicted when no measurable evidence of it is present by available chemical means.

The practical importance of the problem is concerned with the advantage to the patient of knowing of the existence of mild diabetes or the pre-diabetic state. This is a matter which concerns all interested in diabetes detection. One can agree with Jackson that it is of value in that it at least gives the physician the opportunity of prescribing a diet limiting the carbohydrate, and, if necessary, the caloric intake. The benefit which may come from this policy over a long period of years will have to be evaluated by comparison of the experience of those who do not change in dietary habits.

A point of immediate and practical value, which is emphasized by the author, is that the birth of abnormally large children calls for a careful evaluation of carbohydrate tolerance in the mother. She should have attention to the matter at the time and at regular intervals for the rest of her life.

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GROWTH OF THE ISLETS OF LANGERHANS

Ever since diabetes was produced by pancreatectomy, efforts have been made to learn more of the behavior of the islets of Langerhans. At present the principal methods for studying the islets are: 1) Counting the islands in serial or frequent microscopic section; 2) the qualitative appraisal of their size and condition on microscopic examination; 3) estimation of the islet volume (or weight); 4) determination of the insulin content of the pancreas; 5) estimation of insulin secretion by grafting the pancreatic vein of a test animal to the circulation of a depancreatized animal. One of the most useful of these procedures has been the measurement of islet volume under various experimental conditions. The article by Kinash and others, published in this issue of DIABETES, is a valuable addition to their previous work. It will remind physicians of a number of facts which they cannot see in their patients but which they might like to know.

The capacity of the islet to grow differs greatly in different species and is less in adult than in young animals. In rats, which have a great capacity for islet growth, the metabolic load is an important influence. This is shown by the use of pair-fed controls and by the authors' critical discussion of the mechanisms by which pituitary extracts may act. Since the diabetic cannot respond to an ample food intake with the normal secretion of insulin, this modern study confirms the value of dietary restriction in diabetes mellitus. Finally, these methods have been applied to man. Thus, Ogilvie[1] and Wrenshall[2] have found that both the islet volume and the extractable insulin of the pancreas *per unit of body weight* decrease with age. It is more true than facetious to say that obesity is a weighty predisposing factor to diabetes, and one may suppose that this is in part due to the limited ability of the islets of the adult to grow adequately in response to this metabolic demand. In any case the information gained by these studies is not only of value at the moment but is an incentive to further clinical application of methods developed in the laboratory.

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