The Effect of Hypophyseal Stalk Section on Insulin Resistance

Richard A. Field, M.D., William A. Hall, M.D., William H. Baker, M.D., and Dagoberta Sosa, M.D., Boston

Four types of insulin antagonists have been described in the plasma of diabetic animals. One appears to be a beta lipoprotein which may be formed from, or under the influence of, somatotropin and an adrenal steroid.[1] Another, thought to be an alpha globulin, is present in the serum of insulin resistant patients during severe keto-acidosis, whether or not they had had prior treatment with heterologous insulin.[2] There is evidence that this factor may also be formed from, or under the influence of, somatotropin and adrenal steroid.[3] Vallance-Owen and Lilley have described an insulin antagonist residing in the albumin fraction from both uncontrolled insulin-requiring diabetics and normal human subjects, the activity of which is also dependent on the intact pituitary.[4] Lastly, Berson and Yalow have demonstrated an insulin-binding gamma globulin in the serum of all patients, diabetic or otherwise, after several months of heterologous insulin therapy.[5,6] The following case report is that of a patient who was suffering intractable pain from metastatic breast carcinoma and was subjected to hypophyseal stalk section in an effort to relieve her pain. Studies of the effect of this pituitary operation on her diabetes suggest that the latter immunologically stimulated antagonist may also be pituitary dependent.

CASE REPORT

(E.N. MGH #84898). This sixty-four-year-old housewife and mother entered the hospital in June 1959 because of severe pain from metastatic breast carcinoma. The patient had been massively obese for many years. In 1940, she underwent an uneventful menopause. In 1942, she had a subtotal thyroidectomy for a nodular goiter which had been present for many years. In 1943, a combined abdominal-perineal resection was performed for carcinoma of the rectum. No recurrence of this tumor has been found to date. In 1947, she developed diabetes mellitus, and in the following four years was well managed on diet alone, although she did not lose weight. Insulin was started in 1951, and for the following six years she was easily managed on 25 units of NPH insulin daily. In 1955, adenocarcinoma of the breast was discovered and she underwent left radical mastectomy. Early in 1957, insulin resistance appeared. At that time, there was no clinical evidence of tumor recurrence. She was found to be euthyroid and there was no evidence of a metabolic abnormality other than diabetes. In the ensuing twelve months, the dose of Crystalline Zinc Insulin was progressively increased to more than 300 units daily in order to free her from symptoms of florid diabetes. Late in 1957 she developed severe pain in the anterior chest. X rays of the chest and rib cage were unremarkable, but a biopsy of sternal marrow revealed metastatic carcinoma histologically consistent with origin from the breast lesion. A course of X-ray treatment to the involved ribs and sternum afforded no relief from the pain and had no effect on her insulin requirement.

In July 1959, the pituitary stalk was divided and a rubber diaphragm placed over the sella. During the operation and immediately afterward, several hundred milligrams of hydrocortisone were administered and, subsequently, she was given maintenance doses of 25 mg. daily. Postoperatively, there was complete relief of pain and to date there has been no recurrence of pain.

Pituitary gonadotropins, 17-ketosteroid and 17-hydroxysteroid excretion, protein-bound iodine levels and radioactive iodine uptake (performed at intervals after the operation) had declined, but remained within normal limits. Preoperative assay of insulin-antagonistic alpha globulins revealed measurable levels, but there were no significant or consistent changes postoperatively.

Assays of the patient's serum for insulin-binding gamma globulins were carried out just before operation and at intervals after operation. The patient's insulin:insulin-binding gamma globulin complex was of a very low energy of association. Most of Berson's insulin resistant patients have insulin antibodies which form two types of complexes, one of higher energy (12-13 kilocal./mol.), and one of lower energy (9-10 kilocal./mol.). This patient's serum showed complexes of binding energy which were below 9-10 kilocal./mol. This peculiarity of binding energy is unique in the extensive experience of Berson and Yalow, and tends to make precise quantitation of the insulin-binding gamma globulins somewhat difficult. However, the changes observed in this patient were of such a magnitude as to make this difficulty inconsequential.

Before operation, the insulin-binding gamma globulin level was more than 150 units/liter (figure 2). Ten days after

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From the Departments of Medicine and Neurosurgery, Harvard Medical School, and Massachusetts General Hospital, Boston, Massachusetts.

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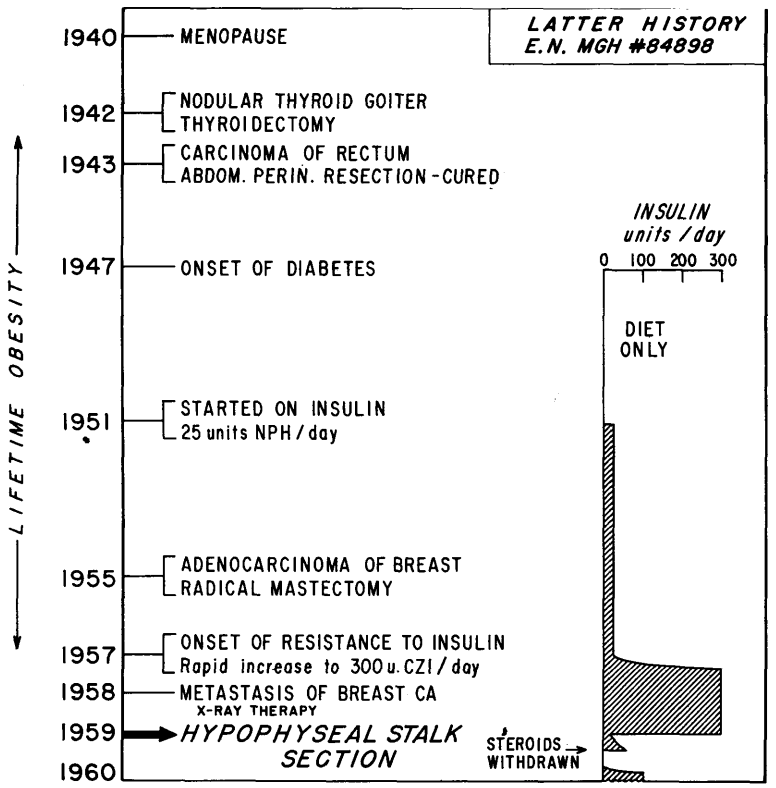

FIG. 1. Historical outline. Insulin requirement declined after operation and currently has stabilized at 27 per cent of the preoperative requirement.

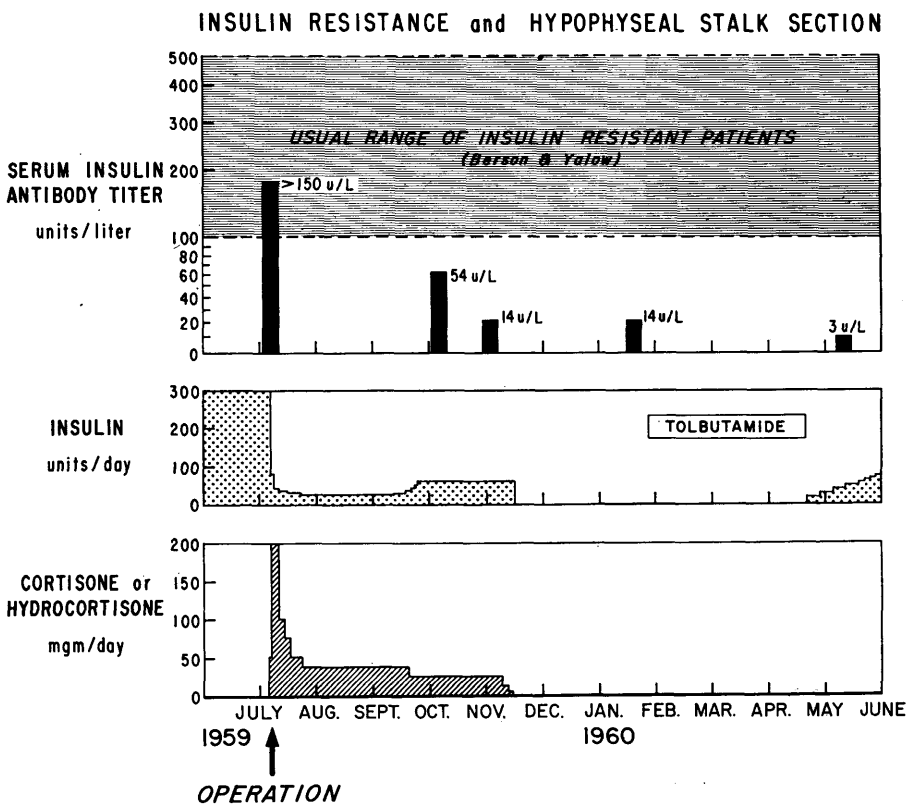

FIG. 2. Serum insulin-binding globulin level declines after operation, and is at lowest level eleven months postoperatively. Steroids were withdrawn 4½ months postoperatively.

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operation, the level had decreased to 54 units/liter. After withdrawal of steroids four months later, the level was still further reduced to 14 units/liter. Most significantly, ten months after operation, despite the reinstitution of insulin three weeks earlier, the anti-insulin gamma globulin level was at its lowest, a definitely but barely measurable 3 units/liter.

Coincident with the initial postoperative fall in insulin antibodies, there was a clinical remission of diabetes accompanied by a diminished insulin "requirement" to 25 units of NPH insulin daily. During the four months following operation, there was a gradual increase in insulin requirement to 60 units of NPH insulin daily.

In early November 1959, steroids were withdrawn completely and the patient's fasting blood sugars promptly fell to normal and glycosuria disappeared. Administration of insulin was discontinued. For two months, without any specific therapy, the patient was clinically free of diabetes, but in January 1960, glycosuria and hyperglycemia recurred and tolbutamide was started. After an initial favorable response to tolbutamide, the effect of this agent gradually diminished, and in late April 1960, insulin was again started. With progressive increases in insulin to a current level of 80 units daily, the patient's blood sugars have been brought into a more physiological range and the symptoms of florid diabetes have subsided. Her weight has not fallen from the preoperative level of 180 lb. and she has regained her sense of well-being. She is active about her home and carries on her usual social activities.

DISCUSSION

The association of insulin resistance with insulin-binding gamma globulins has been clearly demonstrated by Berson and Yalow,[5,6] and others.[7,8] The potent effect of cortisone on reducing insulin resistance concomitant with reduction of insulin-binding antibodies has been noted by many workers, although Geller et al. have reported a case in which insulin resistance was precipitated by cortisone and reversed with nitrogen mustard.[9] BAL and ACTH are also known to suppress antibody formation, and Friedlander has successfully treated some insulin resistant patients with sulfonylurea agents.[7]

It is difficult to escape the conclusion that the reduction in insulin-binding globulin accompanying amelioration in diabetes in this patient had a cause-and-effect relationship. The following explanations are to be considered in accounting for the decline of antibody in this patient.

1. Cortisone replacement therapy in the postoperative period affected the antibody decline by suppressing its production at its source. This seems unlikely, since the insulin-binding globulin level continued to decline after steroids had been discontinued, reaching its lowest level six months later.

2. The pituitary body is the site of production of the antibody and its decline is secondary to hypopituitarism. This seems unlikely since the operation failed to result in detectable anterior pituitary insufficiency, but was followed by a marked decline in antibody level.

3. The metastatic tumor tissue elaborates the antibody under the influence of an intact hypothalamic pituitary axis. A careful search of the literature has not uncovered any report of tumor tissue producing insulin antibody.

4. The antibody is produced by the usual immune mechanism under the influence of an intact hypothalamic-pituitary axis. The failure of antibody to reappear at significant levels after the renewed insulin stimulus to the immune mechanism strongly suggests such a dependence.

It is possible to discount the nonspecific effects of advancing metastatic disease and cachexia in the initial decline of insulin resistance and its failure to recur in the months following the operation since the patient is thriving and more active than prior to pituitary stalk section. We currently favor the hypothesis that the intact hypothalamic-pituitary axis exerts some influence (possibly a permissive one on an immune mechanism) on the elaboration of insulin-binding globulins. This formulation is being tested in other diabetics who have undergone pituitary stalk section.

SUMMARY

A patient with insulin resistance which subsided after pituitary stalk section is described. The amelioration in diabetes was accompanied by a dramatic decline in the patient's production of an insulin-binding gamma globulin which possessed unusual immunochemical characteristics. A permissive role of the pituitary on elaboration of insulin-binding gamma globulins is suggested.

SUMMARIO IN INTERLINGUA

Le Effecto del Section del Pedunculo Hypophyseari Super le Resistentia a Insulina

Es describite le caso de un patiente con resistentia a insulina que subsideva post le dissection de su pedunculo pituitari. Le melioration del diabete esseva accompaniate de un declino dramatic in le production del insulino-ligante globulina gamma que possedeva inusual characteristicas immunochimic. Es proponite le these que le pituitario exerce un rolo permissive in le elaboration de globulinas gamma capace a ligar insulina.

ACKNOWLEDGMENT

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antibody assays reported here, and to Dr. J. B. Field of the National Institute of Arthritis and Metabolic Diseases for performing the insulin antagonist assays.

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Why Human Genetics?

One possible explanation of the wide variation in the organ weights, etc., of highly inbred animals lies in the complexities of the interaction between genes. While inbreeding tends to establish a definite gene pool which is passed on to the offspring, there appears to be no assurance that recombinations might not cause the animals to be heterogeneous because of differences in interactions between the existing genes. In other words, what determines the characters in an animal is not only "the genes with which they are born" but the important variations in the potential interactions of these genes.

Another possible explanation of the widely different patterns of organ weights possessed by inbred animals is somatic mutations. These mutations would have to be very common to produce the effects which have been observed, and for various reasons it seems that this explanation is only possible, but not probable.

Regardless of what interpretation we may accept with respect to the variability in "inbred" strains of animals, a consideration of the facts is highly pertinent in the realm of human genetics because so-called normal human beings exhibit similar enormous variability. Endocrine glands, for example, vary in size and activity over wide ranges—often tenfold or more. Wide variation is the general rule in the realm of composition, enzyme activities, excretion patterns, pharmacological reactions, and nutritional needs, as well as in miscellaneous physiological areas. Furthermore these diversities exist so far as we know within every ethnic group and hence are universal.

In the field of medicine I do not believe that genetic factors are considered as seriously as they should be, and that geneticists are partially to blame. One geneticist, for example, refers to "a patient with a genetic condition." Reference was probably to a patient with hemophilia or some well-established hereditary disease, but the phrase as used suggests that some diseases have no genetic roots. This, in my opinion, is clearly not the case. In the strict sense no patient ever went to see a physician who did not have to greater or lesser degree "a genetic condition." Ample evidence indicates that even susceptibilities to infectious diseases are inherited, though of course the exact modes of inheritance are not known.

By Roger Williams in
Journal of Heredity, Vol. 51,
No. 2, March-April 1960.

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