RESISTANCE TO SMALL DOSES OF INSULIN IN VARIOUS CLINICAL CONDITIONS [1]

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In a number of clinical conditions the response of the level of blood sugar to a given dosage of insulin is less than that obtained in normal individuals. This phenomenon is commonly termed insulin resistance. Soon after the discovery of insulin numerous investigators described resistance in certain cases of diabetes mellitus. Radoslav (1) in 1924 administered known amounts of insulin to fasting individuals suffering from diabetes mellitus and pointed out that diabetics, without known complications, might be insulin resistant, insulin sensitive, or insulin hypersensitive. The early investigations on this subject were comprehensively reviewed in 1933 (2); since that time, there have been numerous reports describing insulin resistance in diabetes. Although the resistance has usually been attributed to various disorders complicating the diabetic state, certain cases exhibiting this phenomenon in marked degree have been unexplained (3). In 1941 Fraser, Albright, and Smith (4) demonstrated variations in response to the intravenous administration of 1/10 of a unit of insulin per kg. of body weight in a number of endocrine disorders. The dosage recommended by these authors has been employed by other investigators to show insulin resistance in schizophrenics (5), pellagrins (6), and in a small group of hypertensives (7). Kronenberg and McCulloch (8), employing a much smaller dose, 1/40 unit per kg., demonstrated increased tolerance to insulin in oneirophrenics and in several cases of acromegaly and malignant hypertension. The present investigation explored this phenomenon in 99 patients suffering from hypertension and from other disease conditions, and in 25 normal subjects. The smaller dose of Kronenberg and McCulloch was used in an attempt to increase the sensitivity of the test, and make possible the identification of submaximal responses that may have been masked by the larger doses recommended by previous workers.

METHOD

All subjects, except controls, were hospitalized and were receiving a normal hospital diet of high carbohydrate content. In no case was there a recent episode of anorexia or voluntary starvation, although some patients with neoplastic diseases had lost considerable weight. Subjects were fasted for 12 hours preceding the test. After collection of a sample of venous blood, 1/40 unit per kg. of body weight of crystalline insulin (Lilly) was injected intravenously, dosage being calculated on the basis of actual rather than ideal weight. The same lot of insulin was used throughout the series. To avoid small errors in dosage the insulin was diluted with physiological saline so that 1 ml. contained 1 unit. Venous blood was obtained at exactly 15, 30 and 60 minutes following injection. All blood samples were refrigerated until completion of the test and then were immediately analyzed for glucose by the microcolorimetric method of Nelson (9).

RESULTS

The effect of various dietary regimens on the response to the test dose of insulin has been investigated.[2] Three diets have been studied in the same normal subjects: a normal or hospital diet of high carbohydrate content, a low carbohydrate diet, and a low caloric diet. Table I shows the dietary composition, the mean fasting value of blood sugar and the mean per cent fall from the fasting level at the various time intervals. The mean per cent fall has been used, rather than the actual blood sugar value, in order to nullify variations in fasting values. Seven normal subjects were used for this study. In order to determine the reliability of single tests, three separate experi-

TABLE I

Effect of diet on response to intravenous insulin

Diet					Mean fasting value of blood sugar	Mean % fall from fasting value		
Type	Total calories	Protein	Fat	CHO		15 min.	30 min.	60 min.
		gm.	gm.	gm.	mg. %	%	%	%
Normal—Hospital	2030	70	100	250	80.1	34.6	43.9	10.7
Low CHO	1520	120	80	30	76.3	28.1	42.7	10.6
Low Calorie	750	50	60	40	75.0	29.4	43.9	11.3
					"F" Value*	2.87	0.22	0.08

* On applying the analysis of variance to the data the following "F" values must be equalled or exceeded to show significant variation between diets: 1% significance "F" = 6.93; 5% significance "F" = 3.58.

ments on a normal diet were run on each subject. No significant variation in the response to the intravenous injection of 1/40 unit of insulin per kg. body weight was found in any of the subjects. Therefore only one test was subsequently run on each of the other two diets. The subjects were placed on the separate diets for a period of three days and the test performed on the following day. Using analysis of variance (10) it was found that there was no variation in the response to the test dose of insulin in subjects on the three diets up to the 5 per cent level of significance.

In Table II are shown the results obtained on normal and hospitalized subjects. Twenty-five normal subjects were selected from the laboratory personnel and used as a control "no-disease" group; the mean per cent fall was 34.5 per cent in 15 minutes, 39.0 per cent in 30 minutes, and 10.1 per cent in 60 minutes. Considerable variation was found, the maximum fall from the basal level varying between 24 and 56 per cent. In no case was this fall less than 24 per cent. When tests were repeated two or three times on each of eight normal subjects a marked consistency of response for each individual was found. Results on 99 hospital patients have been divided into distinct groups according to type of disease. Using Fisher's method for small samples (11), analysis re-

TABLE II

The response of blood glucose to intravenous insulin
(1/40 unit per kg.)

Group	No. patients	Mean fasting value of blood sugar*	Mean % fall from fasting value		
			15 min.	30 min.	60 min.
		mg. %	%	%	%
No disease	25	84.6	34.5(1.9)	39.0(2.9)	10.1(1.6)
Essential hypertension	38	84.1	29.7(2.4)	41.6(2.3)	11.9(1.1)
Neurogenic	20	83.2	30.3(4.0)	41.5(3.2)	12.3(2.2)
Endocrine	10	85.5	34.9(3.8)	47.0(4.1)	13.7(2.7)
Vascular	8	84.0	22.0(3.7)	35.1(4.1)	9.0(3.8)
Malignant hypertension	11	86.9	10.0(2.2)	15.9(2.3)	4.9(2.7)
Collagen	10	82.1	15.7(2.8)	22.4(3.1)	2.3(3.9)
Neoplastic	15	84.9	8.5(3.0)	13.8(3.7)	3.4(2.4)
Hepatic	6	84.3	8.0(2.0)	13.7(2.1)	0.0(2.7)
Infection					
Severe	8	95.8	8.8(2.1)	12.3(3.7)	6.5(2.5)
Low grade	11	84.1	26.7(2.8)	32.5(2.4)	10.5(2.7)

* After a 12 hour fast a sample of venous blood was obtained from the patient. Samples of venous blood were withdrawn 15, 30, 60 minutes after intravenous injection of 1/40 unit of insulin per kg. Blood sugar was determined in the aliquots by the micro-method of Nelson (9). The numbers in parentheses following the mean per cent falls are the standard errors. The probability that the difference of the underscored values from normal is due to chance is less than one-tenth of 1 per cent.

vealed that the probability of the difference in the underscored values from the normal being due to chance was less than one-tenth of 1 per cent.

1. Hypertension. Patients were classified as having "essential" or malignant hypertension. The latter group was characterized on the basis of a rapidly progressive course, grade four retinopathy, evidence of renal damage, and a markedly elevated diastolic blood pressure. No significant difference in response to insulin was found to exist between "essential" hypertension and the normal group. However, malignant hypertensive patients were all definitely insulin resistant, and, in general, the degree paralleled the severity of the disease. A few individuals in the "essential" hypertensive group were also resistant, but in all of them there existed either severe psychoneuroses or other complications such as apoplectic stroke, heart failure, or pulmonary embolism.

Since it is generally recognized that essential hypertension probably includes a number of subgroups which may differ in regard to etiology and response to treatment, patients were further classified according to the types suggested by Schroeder and Steele (12). The "endocrine" type was made up for the most part of obese females with "pseudo-Cushing's" syndrome (13). Among other findings sweat sodium was low, fat distribution was central, white striae were present over the abdomen, thighs, and breasts, and the elevated blood pressures usually responded well to salt restriction. The neurogenic type comprised the majority and were characterized by the presence of a labile blood pressure, minimal vascular disease, a benign course, and associated emotional disturbances. These patients were usually found to give a positive response to the intradermal histamine test (14). The vascular group was composed of patients whose elevation of blood pressure was associated with arteriosclerosis; they tended to have wide pulse pressures and were in an older age group. Patients in the three aforementioned categories showed slight but statistically insignificant variations from normal in their responses to insulin. Patients with chronic glomerulonephritis and hypertension varied in their responses but seemed to be insulin resistant only during the active phase of their nephritis; there were, however, too few (six) for definite conclusions to be made.

2. Other diseases. A group of *collagen* disease was made up of patients with rheumatic fever, rheumatoid arthritis, scleroderma and acute disseminated lupus erythematosus. Other groups included *neoplastic* diseases (carcinoma, Hodgkin's disease, and lymphosarcoma), *hepatic* and *infectious* diseases. In each of these groups significant resistance to the action of insulin was found. Patients with severe infections, hepatic and neoplastic diseases were the most resistant. Only in low-grade infections was there no significant change, and only in severe infections was the fasting value of blood sugar appreciably elevated (mean value, 95.8 mg. per cent compared to 84.6 mg. per cent in normal individuals).

In general patients showed increasing resistance with increasing severity of disease (Table III).

TABLE III

Comparison of severity of disease state and response to intravenous insulin*

Disease state	No. patients	Mean fasting value of blood sugar	Mean % fall from fasting value		
			15 min.	30 min.	60 min.
		mg. %	*%*	*%*	*%*
No disease	25	84.6	34.5(1.9)	39.0(2.9)	10.1(1.6)
Acute					
Severe	8	95.8	8.8(2.1)	12.3(3.7)	6.5(2.5)
Mild	11	84.1	26.7(2.8)	32.5(2.4)	10.5(2.7)
Chronic					
Severe	23	85.5	9.2(1.7)	17.4(2.4)	4.3(1.3)
Moderate	28	86.4	16.7(1.9)	21.1(2.0)	5.1(1.9)
Mild	29	83.9	19.8(2.4)	30.8(2.3)	6.6(1.7)

* Notations same as in Table II.

In a number of endocrine disturbances (four patients with thyrotoxicosis and one each with acromegaly, Cushing's syndrome, obesity and Albright's syndrome) the degree of resistance demonstrated was in good agreement with that previously reported using 1/10 of a unit per kg. of body weight.

DISCUSSION

To evaluate changes in the level of blood sugar produced by the intravenous administration of insulin three factors are of prime importance: the effect of the nutritional state, the quantity of insulin, and the time of blood sampling. The nutritional status of the subject is well known to have

a profound effect on the glucose tolerance test and some work has been done demonstrating its effect on the insulin tolerance when larger quantities of insulin have been given. In the present study no significant variation has been noted in cases of high and low carbohydrate, and low calorie diets in normal subjects. It is recognized, however, that the results may be open to question due to the short duration of the experimental periods and the utilization of only normal subjects. The use of minimal doses of insulin has a number of advantages. First, it is possible to apply a stress to the subject which is small enough to detect delicate variations in function which may be completely masked by larger doses. Second, the danger of severe hypoglycemia is avoided especially when patients with endocrine disorders are studied. It has been the practice in many clinics to use similar small quantities of insulin in patients suspected of Addison's disease and panhypopituitarism. Third, the small quantity of insulin produces a minimum of trauma and the effect is dissipated in a short time. The optimum time of blood sampling depends in part on the dosage. However, it is generally recognized that the nadir in the blood sugar is reached somewhere between 15 and 30 minutes after injection of moderate amounts of insulin. It was deemed satisfactory to withdraw venous blood exactly 15 and 30 minutes after injection rather than at more frequent or at varying time intervals. The blood sugar value of the 60-minute sample was considered to be the one approaching the fasting level.

Soskin and Levine (15) have outlined the disturbances which may diminish the normal action of insulin as follows:

"1. Poor absorption from subcutaneous tissues.

"2. Abnormally rapid destruction of insulin in skin, blood or other tissues.

"3. Overactivity of the physiological antagonists to insulin, particularly the hormones of the anterior pituitary, adrenal cortex and thyroid glands.

"4. Infections, toxemia, and liver disease, *i.e.,* conditions in which the liver does not respond normally to its endocrine regulators.

"5. Unusual antibody formation to insulin or to other proteins present in insulin preparations."

Insulin resistance in endocrine disorders, hepatic disease, and perhaps in infections, can be explained by one or several of these disturbances. Since, however, in every disease of the variety selected some significant degree of rsistance was found one is inclined to consider a single factor as responsible. The site and action of insulin in the body are still so little understood that many factors may play an important role. For example, recent interest has been focussed on a naturally occurring factor, similar to insulin, causing hyperglycemia which might well be said to have an "anti-insulin" action (16). *In vitro* inhibition of the hexokinase reaction, produced by adrenal cortical extract, has been shown to be reversed by the addition of insulin (17). Furthermore, adrenal corticoids have long been known to increase glyconeogenesis. In patients with Cushing's syndrome the urinary corticoids are elevated and there is an associated resistance to insulin (18). Most recently Conn, Louis, and Johnston (19) have administered adrenocorticotropic hormone to normal subjects and have observed the production of a diabetic state with an increased resistance to endogenous insulin. These results have been confirmed by other workers (20). Therefore, under certain conditions adrenal corticoids may produce resistance to the action of insulin. Selye (21), on the other hand, has pointed out that increased adrenal-cortical activity occurs during the "resistance" stage of the "general adaptation syndrome." It is beyond the scope of this paper to discuss this theory but there is good evidence that the adrenal cortex increases in size in response to stress and may secrete more hormones, as has been demonstrated after operations (22), pneumonia, cold and other stresses (18, 23). It is possible that the present findings are best explained on this basis. Thus, the disease states studied may be considered as non-specific stresses acting on the body to produce, among other things, increased adrenal cortical activity. In essential hypertension the stress may not be great enough to cause a degree of resistance measurable by these methods, or regulating mechanisms may compensate for this particular reaction until a malignant phase is reached.

SUMMARY

1. An intravenous insulin tolerance test employing 1/40 unit per kg. of body weight has been used in 25 normal subjects, 49 hypertensive patients, and in 50 patients suffering from other diseases.

2. The response of blood sugar to intravenous insulin in patients with essential hypertension is not significantly different from that in normal individuals, whereas those with malignant hypertension are resistant to a statistically significant degree.

3. Resistance to insulin was found in collagen, neoplastic, hepatic and infectious diseases as well as in certain endocrine disorders.

4. The hypothesis that insulin resistance may be due to increased adrenal cortical activity resulting from a reaction to stress is discussed.

ACKNOWLEDGMENTS

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