INDIANA UNIVERSITY

GRADUATE SCHOOL

Department of Biochemistry

METABOLIC STUDIES IN ACUTE INSULIN DEFICIENCY

by

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The thesis of Milton Stern entitled "Metabolic Studies in Acute Insulin Deficiency" submitted to the Department of Biochemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Indiana University has been read and approved by the Committee.

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TABLE OF CONTENTS

CHAPTER		PAGE
I	INTRODUCTION	
	Historical Introduction	1
	Structural Studies of the Pancreas	3
	Biochemical Investigations	5
	Investigations Concerning the Treatment of Diabetes	7
	Chemistry of Insulin	10
	Experimental Diabetes	14
	History of Insulin Antiserum	27
II	INSULIN ANTISERUM	
	Preparation of Antigen	40
	Antigen Administration	40
	Collection of Antiserum	41
	Method of Assay	42
	EXPERIMENTAL	
	Animals	45
	Methods and Materials	47
	Blood Glucose	48
	Blood Radioactivity	51
	Blood Glucose Specific Activity	54
	Carbon Dioxide Production	60
	Radioactive Carbon Dioxide Production	60
III	DISCUSSION	71
IV	SUMMARY	83
	BIBLIOGRAPHY	86
	CURRICULUM VITAE	104

SUMMARY

These investigations are basically concerned with the pre-diabetic state and the time interval during which the animal experiences the withdrawal of the physiological effects of insulin from a normal or hormonal deficient state. The chronic diabetic, as represented by the alloxanized rat, was compared with the acute insulin deficient animal. The latter state was accomplished by the intraperitoneal injection of guinea pig anti-insulin serum (AIS) which had a titer of 2.5 units/ml.

Utilization of (U) C^{14} glucose, as evidenced in terms of expired radioactive carbon dioxide and specific activity of blood glucose, was observed in normal, adrenalectomized and hypophysectomized rats which has been treated with anti-insulin serum.

The following observations are reported:

<u>Blood Glucose</u> - Intact normal rats receiving insulin antiserum show a prompt increase in blood glucose, attaining an average level of 285mg% within two hours. The degree of hyperglycemia achieved was comparable to that found in the alloxan diabetic animals used in this study. Adrenalectomized and hypophysectomized rats attained much lower blood sugar levels (180mg%) following insulin antiserum injection, and these values were comparable to blood sugar levels obtained in diabetic-adrenalectomized rats.

<u>Specific Activity</u> - Changes in specific activity of blood glucose in insulin antiserum treated normal rats approximated values found

in alloxan diabetic animals during the first 1 1/2 hours of the experimental period. Beyond this point specific activity of blood glucose in antiserum treated animals paralleled normal values.

In normal rats 89% of the injected C^{14} was removed from the blood during the first two hours. An average removal of 51% was found in antiserum treated animals and 40% in alloxan-diabetic rats during the same period.

Glucose Oxidation - Antiserum treated normal, adrenalectomized or hypophysectomized rats produced only 61-70% the amount of $C^{14}O_2$ as controls. By comparison alloxan-diabetic rats produced only 21% and diabetic-adrenalectomized rats 33% of the $C^{14}O_2$ obtained in normal control rats.

Total Carbon Dioxide Production - Adrenalectomy or treatment of normal rats with insulin antiserum does not vary total carbon dioxide production from that of the control group. Administration of anti-insulin serum to the adrenalectomized animal lowers carbon dioxide production to 63%, a level which is comparable to the alloxan diabetic and the adrenalectomized-alloxan diabetic. The level exhibited by the hypophysectomized animal is reduced 50%.

Tissue Incorporation of C^{14} - The alloxan diabetic incorporates 33% as much C^{14} into liver glycogen as the control ($p < 0.01$). Normal rats treated with insulin antiserum increase incorporation into liver glycogen by 50% ($p < 0.01$). Both the acute and chronic deficient animals show no significant variation ($p > 0.05$) of incorporation of C^{14} into muscle glycogen. However, the means of 116 ± 48 and 108 ± 17, respectively, trend to decreased incorporation when compared to the normal 205±90.

The results obtained indicate that the elevation in blood glucose, produced by insulin antiserum administration, is due to insulin deficiency as well as adrenal and pituitary control. The acute insulin deficient animal expresses a decreased utilization and oxidation of radioactive blood glucose. Tissue incorporation studies of C^{14} glucose are suggestive of decrease peripheral utilization and increased hepatic production of glucose. Comparison of the acute and chronic insulin deficient animals indicates that decreased glucose utilization and oxidation to expired carbon dioxide are primary manifestations of insulin deficiency.