Comparative Evaluation of Glucose Stimulated Insulin Secretion in Nondiabetic, Diabetic, and Prediabetic Chinese Hamsters

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COMPARATIVE EVALUATION OF GLUCOSE STIMULATED INSULIN SECRETION IN NONDIABETIC, DIABETIC, AND PREDIABETIC CHINESE HAMSTERS

by

Ronald Neil Prange

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
April 1976

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Ronald Neil Prange
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Physiology

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SURVEY OF THE LITERATURE

Genetic and Environmental Factors Influencing
the Development of Diabetes in Man

Diabetes mellitus is commonly defined as a metabolic disorder frequently associated with a relative or absolute insulin deficiency. This results in symptoms of hyperglycemia, glycosuria, impaired lipid metabolism, lipemia, ketonuria, and finally death due to ketoacidosis or complications.

Although progress has been made in understanding the pathogenesis of diabetes mellitus in the past decade, the primary lesion(s) responsible for the disease remain(s) obscure. Data in the literature suggest environmental and genetic factors are primarily responsible for the etiology of diabetes. Since Pincus and White, (1933), first recognized that the incidence of diabetes within families was greater than could be accounted for by chance, studies on monozygotic and dizygotic twin pairs have revealed a strong likelihood of genetic transmission. Gottlieb et al., (1968), examined 104 sets of twins and found a high coordination of diabetes in monozygotic twins, but no such relationship among dizygotic twin pairs having one diabetic member. Tattersall and Pyke, (1972), also found a greater frequency of diabetes in both members of monozygotic twin pairs when a family history of diabetes prevailed than when familial diabetes did not predominate. Cerasi and Luft, (1967), studied insulin responses to glucose infusion challenges given to monozygotic and di-
zygotic twin pairs having one diabetic member. Their results show that non diabetic, dizygotic twin members respond normally, but non-diabetic monozygotic twin members have decreased insulin responses similar to their diabetic siblings. This suggested that depressed glucose stimulated insulin secretion may be a characteristic for the development of diabetes, and that the type of response may be genetically determined.

Although the primary lesion(s) remain(s) obscure, it may be possible to determine a mode of inheritance based on familial studies. For example, albinism was known to result from a recessive gene before the basic enzyme defect was established (Neel, 1970). However, a number of complications such as environmental factors, difficulties in distinguishing normality from abnormality, differences in definitions of diabetes and methodology employed, and the varying age of onset have led to various proposed genetic modes of inheritance of diabetes in man. Different opinions by a number of authors regarding this subject are summarized in Table I. A multifactorial or polygenic mode of inheritance appears to be the hypothesis receiving the most support.

To date, no single hypothesis for the genetic inheritance of diabetes mellitus explains all of the observed data for a number of reasons. Since the primary lesion is unknown, it is difficult to establish abnormalities resulting directly from this lesion and separate them from abnormalities which are secondary to the basic defect. Second, blood sugar is not a good physiological parameter for genetic studies because of the high degree of variability even within "normal"
populations. Blood sugar levels are influenced by nutrition, liver metabolism, hormones, etc. Yet, many of the hypotheses for the genetic inheritance of diabetes are derived from blood sugar analyses.

## TABLE I

Postulated Mechanisms of Genetic Transmission of Diabetes Mellitus in Man*

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<th>Mode of Inheritance</th>
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<tr>
<td>Autosomal Recessive</td>
<td>Pincus and White, (1933)</td>
</tr>
<tr>
<td></td>
<td>Hanhart, (1951)</td>
</tr>
<tr>
<td></td>
<td>Post, (1962)</td>
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<td></td>
<td>Nilsson, (1964)</td>
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<td></td>
<td>Steinberg, (1965)</td>
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<tr>
<td></td>
<td>Barrai and Cann, (1965)</td>
</tr>
<tr>
<td>Autosomal Dominant</td>
<td>Levit and Pessikova, (1934)</td>
</tr>
<tr>
<td></td>
<td>von Kries, (1953)</td>
</tr>
<tr>
<td></td>
<td>Vallance-Owen, (1963)</td>
</tr>
<tr>
<td>Juvenile-homozygous;</td>
<td>Cammidge, (1934)</td>
</tr>
<tr>
<td>adult-heterozygous</td>
<td>Harris, (1950)</td>
</tr>
<tr>
<td>Sex-linked</td>
<td>Penrose and Watson, (1945)</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>Lamy, Frezal, and Rey, (1961)</td>
</tr>
<tr>
<td></td>
<td>Simpson, (1962)</td>
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<tr>
<td></td>
<td>Neel et al., (1965)</td>
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*Taken from Ellenberg and Rifkin, 1970*
Third, different types of diabetes such as maturity onset or juvenile diabetes probably result from different basic genetic lesions at or several different gene loci. The possibility that one type of diabetes may be genetically different from another type makes interpretations both difficult and misleading since different symptoms with varying degrees of severity may result from different basic genetic lesions. Finally, environmental factors are believed to be important in the etiology of diabetes. This being the case, no definite conclusions regarding the mode of inheritance of diabetes can be made until the major environmental factors are identified.

Obesity is a common physical characteristic of diabetic patients (Williams, 1974). Obesity has been shown to effect carbohydrate metabolism by reducing the peripheral tissue sensitivity to insulin (Williams, 1974). This may stress insulin synthesizing mechanisms of the pancreas. Coupled with genetically controlled insulin secretion deficiencies, obesity may increase an individual's susceptibility to carbohydrate intolerance and eventually clinical diagnosis of diabetes (Williams, 1974).

Pregnancy and illness have been shown to stress the insulinogenic mechanisms of the pancreas by causing increased secretion of four glucose regulatory hormones: glucocorticoids, glucagon, catecholamines, and somatrophin (Williams, 1974). All of these agents act to increase blood sugar levels thus creating a need for more insulin for efficient metabolism (Ellenberg, 1970; and Williams, 1974).

Dietary factors, primarily over consumption of refined carbohydrates (sugar), have been suggested to be associated with the higher incidence of diabetes in some populations (Cleave and Campbell,
1973). The rise in sugar consumption by westernized civilizations over the past one hundred and fifty years has been dramatic (Figure I). Equally as dramatic has been the increase in the incidence of diabetes among populations consuming more sugar; a few examples will be mentioned presently.

Results of a study relating diabetic mortality indices in England and Wales to the consumption of refined carbohydrates can be seen in Figure II. These findings clearly indicate a direct relationship between the incidence of diabetes and sugar consumption. It is of interest to note that sugar intake as well as diabetic mortality declined during the war years when refined carbohydrates were not as readily available. Total caloric intake was decreased during this time also. The lack of continuity evidenced around 1945 may result from the introduction of improved insulins and penicillin (Cleave and Campbell, 1973).

Epidemiological studies comparing the incidence of diabetes in Indians of Natal to that of natives of India reflect the importance of refined carbohydrate consumption on diabetes (Cleave and Campbell, 1973). The national incidence of diabetes in native Indians is roughly 1%. In addition, the consumption of refined carbohydrates is rare. In contrast, Indians of the same ethnic group as those mentioned above brought to Natal, Africa, as indentured labourers for sugar plantations showed an incidence of diabetes of approximately 8%, one of the highest in the world. The sugar consumption of the Natal Indians was found to be nine times that of the native Indians. This striking difference in sugar consumption was suggested to be the cause of the equally striking difference in the incidence of dia-
Figure I*

Rise in Sugar Consumption in the United Kingdom

*Taken from Cleave and Campbell, 1973.
Figure II*

Diabetic Mortality Indices in England and Wales

*Taken from Cleave and Campbell, 1973.

--- sugar consumption

--- mortality index
betes. Is is of interest that the incidence of diabetes within Natal Indians alone shows a direct relationship with sugar consumption. Natal Indians having a low sugar intake have a reported incidence of diabetes of 2.3% while those consuming larger quantities of sugar show a 5.5% incidence.

Genuth et al., (1967), and Pyke, (1969), observed the incidence of diabetes in the Pima Indians of North America to be related to diet and physical exercise. They found that 50% of the elderly people had abnormal glucose tolerance. It was of interest that this population transferred during its last two generations to an American-type diet containing more refined carbohydrates. In addition, the degree of physical activity required for survival declined from that of their old culture. Similar observations prevailed when studies of this type were done on South African and New Zealand Indian populations by Campbell, (1963), and Prior et al., (1966). Populations who labor to survive and that nourish themselves with high protein, low carbohydrate-fat foodstuffs (Alaskan Eskimos and Athabaskan Indians) do not show this high prevalence of diabetes (Renold et al., 1972).

Cohen et al., (1961), observed that the diet of Yemen Jews contained no sucrose while that of the same ethnic group living in Israel was high in this refined carbohydrate. It was suggested that this difference might be one reason for the rarity of diabetes in Yemen compared to its higher prevalence in Yemenite Jews living in Israel.

In summary, diabetes mellitus has a definite genetic component, but the mode of inheritance is not completely understood. Environmental factors appear to effect the penetrance of the genetic abnorm-
ality, the degree to which is also a cloudy issue. Until these environmental contributions and the primary lesion(s) are defined, little information can be granted to explain the mode of inheritance and the etiology of diabetes mellitus.

Prediabetes in Man

Since it is generally accepted that diabetes mellitus has a genetic component, any individual who has a diabetic genotype can be defined as a diabetic from the moment of conception. However, the clinical symptoms of the disease may never present themselves as a phenotypic expression. Therefore, prediabetes may be considered a theoretical category designating individuals which possess a genotype for diabetes but lack any symptoms associated with clinical diabetes. The term prediabetes covers the time span between conception and the first clinical observation of glucose intolerance demonstrating a positive diagnosis for diabetes. Prediabetes implies as yet unknown abnormalities which may act to precipitate the manifest disease. To date, the only accepted prediabetic with complete accordance is the asymptomatic identical twin of a diabetic patient unless the diabetic has the disease as a result of infection or accidental loss of his pancreas.

The prediabetic must be identified before one will be able to find the primary lesion(s) that are responsible for an individual's susceptibility to diabetes and explain its mode of inheritance. Some perceivable marker existing prior to glucose intolerance which distinguishes the prediabetic from the normal individual must be established. Knowledge of such a marker would allow an investigator to
compare metabolic pathways, intermediates, chromosomes, etc. of pre-diabetics to those of normal subjects with the goal of solving some of the mysteries associated with diabetes. Also, if the prediabetic can be recognized prior to actual onset, intervention therapy could be prescribed if appropriate therapy was available. A number of attempts aimed at identifying the prediabetic have been initiated.

Two drugs, diphenylhydantoin, an insulin secretion inhibitor, and tolbutamide, a potent insulin stimulatory compound, have been used in studies designed to identify prediabetics. Levin et al., (1973), observed a depressed insulin release in mildly glucose intolerant subjects treated with diphenylhydantoin in response to post-glucose administration of arginine. Insulin release was not depressed in control subjects that received the drug. It was suggested that the drug effect may be characteristic of early diabetes. Unger and Madison, (1958), administered tolbutamide to mild diabetics and normal subjects. Twenty and thirty minute blood sugar levels were then calculated as percent decrease from fasting values taken before drug treatment. Their results showed that mild diabetics had higher blood sugar levels at both time periods than nondiabetic controls. They proposed this method as being 95% effective in positively identifying mild diabetics.

Fajans and Conn, (1954), proposed a cortisone modified glucose tolerance test as a tool to separate prediabetics from normal subjects. Test subjects received two oral cortisone doses prior to a standard glucose tolerance test. Results showed that subjects having a family history of diabetes were glucose intolerant whereas subjects lacking this genetic background respond normally. Only very long
term studies will tell whether or not this will prove valuable in predicting the future diabetic population.

Having glucose intolerance does not necessarily mean a person either is or will become a diabetic by classical definitions. Many people who respond abnormally to glucose tolerance tests lack complications of diabetes (Cerasi, E.; and Luft, R., 1972). In addition, glucose intolerance lacks specificity, is not clearly defined, is not always reproducible, and is generally accepted as being a terminal phase rather than a basis for the disease. Therefore, any methodology using glucose intolerance alone as a predictive index for future diabetes has to be questioned. A considerable amount of evidence suggests that the lack of insulin synthesis and/or release may be the primary lesion responsible for abnormal carbohydrate balance and other manifestations associated with diabetes.

Seltzer, (1970), reported the beta cells of diabetics do not respond as well to a glycemic stimulus compared to those of normal subjects. Upon either intravenous or oral glucose administration, normal individuals demonstrate immediate and maximal insulin release. In mild diabetics, insulin release is blunted and delayed. This characteristic response was even more evident in a group of moderate diabetics. This inverse relationship between glucose levels in the blood and insulin secretion led Seltzer to propose that the primary lesion of familial diabetes was defective beta cell physiology.

Floyd et al., (1968 and 1970), reported that patients having maturity-onset diabetes release subnormal amounts of insulin in response to either oral glucose or intravenously administered amino
acids. Subnormal insulin secretion was also evident in nondiabetic relatives of diabetics. This may suggest that insulin secretion is deficient at an early stage of the disease even though glucose tolerance tests are normal.

Parker et al., (1968), detected diminished plasma insulin levels in newly diagnosed juvenile diabetics following oral glucose, intravenous tolbutamide, or arginine infusion tests. Pathologic examination of pancreata from juvenile diabetics that died due to ketoacidosis shows severe islet and beta cell deficiencies (Ogilvie, 1964). This information, coupled with postmortem pancreatic insulin levels (Wrenshall et al., 1952) clearly suggest abnormal insulin production in juvenile diabetics. It seems unlikely to assume that the pancreatic lesions responsible for inadequate insulin production are dormant prior to clinical diagnosis of diabetes.

Cerasi and Luft, (1972), observed a decreased insulin response to glucose infusions in diabetic and prediabetic patients (Figure III). The initial and late phases of insulin response to glucose stimulation were either absent or reduced and delayed in diabetics and prediabetics. Furthermore, insulin response to glucose infusions given to healthy members of monozygotic twin pairs having diabetic siblings were similar to those of their diabetic counterparts (Cerasi and Luft, 1967). The insulin response was delayed and suppressed, just as the type on response seen in overt diabetics. This led Cerasi and Luft to propose that the type of glucose stimulated insulin response may be genetically determined. They concluded that impaired insulin release may be a prerequisite for the development of diabetes and may be an expression or marker of a genetic trait.
Figure III*

Glucose Stimulated Insulin Response in Nondiabetic, Prediabetic, and Diabetic Patients

Early Response

Late Response

- Nondiabetic control
- Prediabetic
- Diabetic

*Taken from Cerasi et al., 1972.
for the disease.

An Animal Model

Man's relatively long life span and the varying age of onset of clinical signs of diabetes characteristic of man have made clinical studies similar to those mentioned above both difficult and impractical. It would require many years of continuous observations before any conclusions could be made. Man's long generation time and cultural background have also made controlled genetic and environmental studies impossible. A laboratory animal model having similar genetically inherited diabetic syndromes in addition to rapid progeny turnover is highly desirable. Such a model would allow for environmental control, dietary manipulation, selective inbreeding, intense pathological, and terminal investigations which are not feasible in man. Several reviews, (Sirek and Sirek, 1970); (Stauffacher and Renold, 1971); (Bray and York, 1971); and two symposiums, (Renold and Dulin, 1967); (Renold, 1970); concerning spontaneous diabetes in animals have appeared in the literature.

The Chinese hamster (Cricetulus griseus) may be the most suitable animal model available at this time. Hereditary carbohydrate abnormalities in the Chinese hamster were first described by Meier and Yerganian, (1959 and 1961). Further investigation has shown that diabetes in the Chinese hamster is quite similar to that in man. Both man and the Chinese hamster have a variable age of onset with a wide range of severity, (Joslin, 1959; and Gerritsen and Dulin, 1967), show characteristic deficiencies in plasma and pancreatic insulin
levels and secretion, (Gerritsen and Dulin, 1967; Seltzer, 1970; and Wrenshall et al., 1952), and respond similarly to sulfonylureas, (Fajans et al., 1956; and Gerritsen and Dulin, 1966). As in man, a polygenic mode of inheritance has been proposed for diabetes in the Chinese hamster by Butler, (1967).

Statement of the Problem

Standard glucose tolerance tests used for clinical diagnosis of diabetes are of little value in recognizing the prediabetic for a number of reasons mentioned earlier. Glucose stimulated insulin secretion studies in healthy members of monozygotic twin pairs with diabetic siblings suggest subnormal insulin response may be indicative of prediabetics. Only very long term studies will afford conclusive information regarding insulin secretion as a predictive index of diabetes in man. However, insulin secretion studies using the Chinese hamster as an animal model may offer decisive conclusions regarding this hypothesis. The investigations described in this thesis were conducted to evaluate glucose stimulated insulin secretion as a marker for future diabetes and to further characterize the diabetic syndrome in the Chinese hamster.
MATERIALS AND METHODS

Selection and Maintenance of Animals

The Chinese hamsters were selected from a highly inbred colony at The Upjohn Company in Kalamazoo, Michigan. Hamsters from inbred lines (brother to sister matings for at least nine generations) producing 60% to 80% diabetics by five months of age were designated as experimental animals. Animals were selected from AC, AH, X, and L inbred sublines. Hamsters from inbred lines (nine or ten generations) which have never produced diabetics in the past (M and AA lines) were used as controls. All of the hamsters were classified as being diabetic or nondiabetic on the basis of urine glucose levels determined by Tes-Tape® procedures. Gerritsen and Dulin, (1967), have shown that Chinese hamsters showing consistent Tes-Tape values of 4+ have fasting and nonfasting blood sugar levels greater than 200 mg/dl. and 300 mg/dl., respectively. Once any given hamster showed consistent 4+ Tes-Tape values on urine glucose analyses, it was considered to be phenotypically diabetic. A phenotypic diabetic hamster is defined here as one having the genetic components for the development of diabetes in addition to consistent glucosuria. Prior to the demonstration of consistent 4+ Tes-Tape values (in retrospect), the hamster was considered to be prediabetic. All hamsters chosen from the diabetic producing lines mentioned previously which did not show consistent 4+ values on Tes-Tape analyses during the experiment were designated as genotypic diabetics. A genotypic diabetic hamster is

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defined here as one having the genetic components for the develop­
ment of diabetes, but lacking glucosuria. All animals were allowed
food (Purina Mouse Breeder Chow) and water ad libitum and individ­
ually housed in stainless steel cages kept in a controlled environ­
ment of 76°F for the duration of the experiment. The animals were
given one week to acclimate to these conditions prior to commence­
ment of the experiment.

Blood Sugar Measurement

Blood samples were prepared by transferring 0.05 ml. of whole
blood from each 0.15 ml. sample taken into Technicon AutoAnalyzer
vials containing 1.95 mls. of 2.5% sodium fluoride. Quantitation
was determined with a Technicon AutoAnalyzer (Technicon Instruments
Company, Chauncey, New York) using a modified ferricyanide oxidation­
reduction procedure described by Hoffman, (1937).

Plasma Insulin Measurement

Following the removal of 0.05 ml. aliquots for blood sugar
analysis, plasma was separated from the remaining blood sample by
centrifugation. Plasma insulin concentrations were determined
from 0.01 ml. of plasma using an ultra-micro radioimmunoassay des­

Insulin Radioimmunoassay

All reagents used in the insulin assay were diluted with 1%
bovine serum albumin (Nutritional Biochemicals, Cleveland, Ohio) in
0.01M sodium borate (pH 7.0), hereafter, referred to as 1% BSA. Glucagon free beef insulin (Lot #PJ4609, Eli Lilly, Indianapolis, Indiana) was used in preparation of insulin standard solutions containing 512, 256, 128, 64, 32, 16, 8, 4, 2, and 1 uU/ml. A 0.01 ml. aliquot of insulin standard, unknown plasma sample, or 1% BSA for blanks was transferred to disposable test tubes. In addition, 0.02 ml. of guinea pig anti-insulin serum (1:128,000 dilution) prepared as described by Morgan and Lazarow, (1963), and 0.02 ml. of $^{125}$I-insulin containing 10 uU/ml. (Abbott, Chicago, Illinois) with specific activity greater than 50 mc/mg. were added to each test tube. The contents were thoroughly mixed on a Vortex mixer, covered with Saran Wrap, and placed in a refrigerator for 36 to 48 hours. Following this incubation, 0.02 ml. of normal guinea pig serum (1:100 dilution) and 0.02 ml. of undiluted anti-guinea pig serum obtained by the method of Morgan and Lazarow, (1963), were added to the reaction mixture. The contents were mixed as before, covered with Saran Wrap, and again stored in a refrigerator for 4 hours. At the end of this incubation, the tubes were centrifuged for 3 minutes at 1500 rpm. The supernatant fraction was transferred by dropping pipette to clean disposable test tubes suitable for a Packard Auto-Gamma Spectrometer. The precipitate was washed by adding 0.3 ml. of 1% BSA to each centrifuge tube and thoroughly mixed as before. These tubes were centrifuged again for 3 minutes at 1500 rpm. After removing the supernatant, tubes containing the washed precipitate and those containing the supernatant fraction were placed in a Packard Auto-Gamma Spectrometer. Radioactivity was measured for 10 minutes.

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per sample.

Urine Glucose Tes-Tape

Animals were designated as being diabetic on the basis of consistent Tes-Tape values of 4+. These analyses were performed by expressing urine from the hamster directly on a small strip of Tes-Tape. A positive response was evidenced by a color change from yellow to dark green. Tes-Tape procedures were repeated on all animals at 4 or 5 day intervals for the duration of the experiment.

Statistical Procedures

Comparisons were made by using a one way variance analysis employing a Dunnett multiple comparison procedure.

Preliminary Investigation

A preliminary investigation was done with the Chinese hamster in order to establish a glucose dose that would serve as a maximal stimulus to the insulin producing tissue of the pancreas. Malaisse et al., (1967), showed data which suggests that a glucose stimulus of 300 mg/dl. results in maximal insulin secretion by pancreatic tissue. Thus, an orally administered glucose load that would elevate blood glucose levels to 300 mg/dl. was desired. After several attempts using single doses of glucose at concentrations up to 4.0 g/kg body weight failed to produce the desired result, multiple doses of glucose were given. Three sequential, oral glucose loads of 7.5 g/kg, 4.0 g/kg, and 3.0 g/kg. body weight were administered to each
animal at 0, 4, and 8 minutes respectively. This procedure increased
the blood sugar levels to at least 300 mg/dl. in both control and ex-
perimental animals 30 minutes after the initial dose was given.
Blood sugar levels were still elevated 60 minutes after the primary
dose (Figure IV).

Plasma insulin levels in hamsters subjected to the glucose
loading procedure described above are shown in Figure IV also. The
peak insulin response in nondiabetic controls and in hamsters selec-
ted from diabetic producing lines appeared to be 30 minutes after the
initial glucose dose; plasma insulin levels declined 60 minutes after
the initial dose. In addition, the greatest statistical difference
between plasma insulin levels of control and experimental animals
appeared to be 30 minutes after the initial glucose dose. Results
of this preliminary investigation were used in establishing the glu-
cose loading procedure described below.

Glucose Loading Composit Procedure

Following an overnight fast, a 0.15 ml. blood sample was ob-
tained from the orbital sinus of each hamster by the method of Riley,
(1960). All blood samples were collected in 8 X 75 mm culture tubes
containing one drop of sodium heparin (Upjohn) and maintained in an
ice water bath until processed 3 to 4 hours later. Three sequential,
oral glucose loads of 7.5 g/kg., 4.0 g/kg., and 3.0 g/kg body weight
were then administered to each animal at 0, 4, and 8 minutes respec-
tively thus comprising a total glucose challenge of 14.5 g/kg. body
weight over an eight minute period. Glucose doses were given in 0.2
ml. of distilled water, and body weights ranged from 15 to 25 grams. A second blood sample was taken 30 minutes after the initial glucose load as described above. This test procedure was repeated once every four weeks until the hamsters reached five months of age. Epidemiological studies of the Chinese hamster, (Schmidt et al., 1970), have shown that most animals that eventually become diabetic develop glucosuria by this time.
Figure IV

Plasma Insulin and Blood Sugar Responses to Oral Glucose Administration in Chinese Hamsters Selected from Nondiabetic and Diabetic Producing Lines

Nondiabetic Lines

[16]

[ ] No. Animals
( ) Blood Sugar (mg %)
* P<0.05
** P<0.01

Diabetic Lines

[12]

Plasma Insulin (μU/mL)

Time (minutes)
RESULTS

A summary of the Tes-Tape results is shown in Table II. None of the hamsters selected from the nondiabetic producing sublines (designated as control) described earlier showed any positive Tes-Tape responses during the course of the experiment. Fourteen hamsters chosen from diabetic producing sublines described earlier showed consistent 4+ values on Tes-Tape analyses by the time they were three months of age. As soon as any given hamster showed this Tes-Tape pattern, it was considered to be phenotypically diabetic; prior to this time, it was considered to be prediabetic (in retrospect). As mentioned above, hamsters not showing consistent positive Tes-Tape values but selected from diabetic producing sublines were classified as genotypic diabetics.

Fasting plasma insulin and blood sugar levels of both genotypic diabetic and prediabetic hamsters were not significantly different from control (Table III and Figure V). Thirty minutes after a glucose challenge, plasma insulin values of genotypic diabetics and prediabetics were significantly lower than controls. In contrast, blood sugar values of genotypic diabetics and prediabetics were significantly greater than controls (Table III and Figure V). However, data from genotypic diabetics and prediabetics could not be distinguished (Table III). Increases in plasma insulin and blood sugar from fasting to 30 minute levels of both genotypic diabetic and prediabetics following glucose administration were again significantly lower and greater respectively than controls (Table IV). Genotypic
<table>
<thead>
<tr>
<th>Animal Classification</th>
<th>Age (months)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>N (20)</td>
<td>N (20)</td>
<td>N (19)</td>
<td>N (19)</td>
</tr>
<tr>
<td>Genotypic Diabetic</td>
<td></td>
<td>N (14)</td>
<td>N (12)</td>
<td>N (12)</td>
<td>N (12)</td>
</tr>
<tr>
<td>Prediabetic</td>
<td></td>
<td>N (14)</td>
<td>N (4 )</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Phenotypic Diabetic</td>
<td></td>
<td>---</td>
<td>P (10)</td>
<td>P (14)</td>
<td>P (14)</td>
</tr>
</tbody>
</table>

*N - Negative Response  
P - Positive Response; consistent 4+ values  
( ) - Number of Animals
## TABLE III

Fasting and 30 Minute Plasma Insulin and Blood Sugar Levels of Hamsters Tested at One Month of Age

<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting Plasma Insulin (uU/ml.± S.E.M.ª)</th>
<th>Fasting Blood Sugar (mg/dl.± S.E.M.)</th>
<th>30 Minutes Plasma Insulin (uU/ml.± S.E.M.)</th>
<th>30 Minutes Blood Sugar (mg/dl.± S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>55 ± 11</td>
<td>79 ± 5</td>
<td>395 ± 36</td>
<td>297 ± 16</td>
</tr>
<tr>
<td></td>
<td>(20)b</td>
<td>(20)</td>
<td>(20)</td>
<td>(20)</td>
</tr>
<tr>
<td>Genotypic Diabetic</td>
<td>48 ± 11</td>
<td>76 ± 5</td>
<td>190 ± 40d</td>
<td>398 ± 16d</td>
</tr>
<tr>
<td></td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
</tr>
<tr>
<td>Prediabetic</td>
<td>53 ± 17</td>
<td>93 ± 6c</td>
<td>156 ± 22d</td>
<td>402 ± 20d</td>
</tr>
<tr>
<td></td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
</tr>
</tbody>
</table>

ª Standard error of the mean.

b ( ) Number of Animals.

c Significantly different from genotypic diabetics, P<0.05.

d Significantly different from control, P<0.01.
TABLE IV
Increase in Plasma Insulin and Blood Sugar from Fasting to 30 Minutes Following Glucose Administration in Hamsters Tested at One Month of Age

<table>
<thead>
<tr>
<th>Animal</th>
<th>Plasma Insulin (uU/ml.±S.E.M.)</th>
<th>Blood Sugar (mg/dl.±S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(uU/ml.±S.E.M.(^a))</td>
<td>(mg/dl.±S.E.M.)</td>
</tr>
<tr>
<td>Control</td>
<td>351 ± 29</td>
<td>217 ± 16</td>
</tr>
<tr>
<td></td>
<td>(20)(^b)</td>
<td>(20)</td>
</tr>
<tr>
<td>Genotypic</td>
<td>142 ± 34(^c)</td>
<td>325 ± 18(^c)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>(14)</td>
<td>(14)</td>
</tr>
<tr>
<td>Prediabetic</td>
<td>103 ± 19(^c)</td>
<td>310 ± 23(^c)</td>
</tr>
<tr>
<td></td>
<td>(14)</td>
<td>(14)</td>
</tr>
</tbody>
</table>

\(^a\) Standard error of the mean.
\(^b\) Number of animals.
\(^c\) Significantly different from control, P<0.01.
Figure V

Plasma Insulin and Blood Sugar Responses to Oral Glucose Administration in the Chinese Hamster

- Nondiabetic
  - [20]
  - (375)

- Prediabetic
  - [14]
  - (400)

[ ] No. Animals
( ) Blood sugar (mg %)
* P<0.01
diabetics and prediabetics were once again indistinguishable with regard to these parameters (Table IV).

Table V shows plasma insulin responses to oral glucose administration in two month old Chinese hamsters. Fasting plasma insulin levels of phenotypic diabetics were significantly greater than those of genotypic diabetics, but were not different from nondiabetic controls. Plasma insulin 30 minutes after glucose administration and the change from fasting to the 30 minute level were both significantly less in genotypic and phenotypic diabetics than in nondiabetic controls. The change from fasting to the 30 minute plasma insulin level in phenotypic diabetics was significantly less than that for genotypic diabetics.

Table VI shows blood sugar responses to oral glucose administration in two month old Chinese hamsters. Fasting blood sugar levels of phenotypic diabetics were significantly greater than those of both genotypic diabetics and nondiabetic controls. Blood sugar levels of genotypic and phenotypic diabetics 30 minutes after glucose administration were significantly greater than those of nondiabetic controls. The changes in blood sugar from fasting to 30 minute levels in both genotypic and phenotypic diabetics were significantly greater than those for nondiabetic controls.

Table VII shows plasma insulin responses to oral glucose administration in three month old Chinese hamsters. Fasting plasma insulin levels of genotypic and phenotypic diabetics were not significantly different from each other or from those of nondiabetic controls. Plasma insulin 30 minutes after glucose administration and the change
TABLE V
Plasma Insulin Levels of Two Month Old Chinese Hamsters<sup>a</sup>

<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting</th>
<th>30 minutes post-glucose administration</th>
<th>Change from fasting to 30 minute level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (10)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40 ± 7</td>
<td>269 ± 26</td>
<td>229 ± 22</td>
</tr>
<tr>
<td>Genotypic Diabetic (7)</td>
<td>25 ± 2</td>
<td>171 ± 26&lt;sup&gt;d&lt;/sup&gt;</td>
<td>146 ± 26&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phenotypic Diabetic (8)</td>
<td>56 ± 13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>139 ± 21&lt;sup&gt;e&lt;/sup&gt;</td>
<td>83 ± 14&lt;sup&gt;c,e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>All plasma insulin levels expressed in uU/ml. ± standard error of the mean.
<sup>b</sup>( ) Number of animals.
<sup>c</sup>Significantly different from genotypic diabetic, P<0.05.
<sup>d</sup>Significantly different from control, P<0.05.
<sup>e</sup>Significantly different from control, P<0.01.
### TABLE VI

Blood Sugar Levels of Two Month Old Chinese Hamsters\(^a\)

<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting</th>
<th>30 minutes post-glucose administration</th>
<th>Change from fasting to 30 minute level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (20)(^b)</td>
<td>86 ± 2</td>
<td>336 ± 18</td>
<td>250 ± 19</td>
</tr>
<tr>
<td>Genotypic Diabetic (12)</td>
<td>82 ± 9</td>
<td>409 ± 34(^d)</td>
<td>327 ± 28(^d)</td>
</tr>
<tr>
<td>Phenotypic Diabetic (14)</td>
<td>122 ± 5(^c,e)</td>
<td>470 ± 16(^e)</td>
<td>348 ± 15(^e)</td>
</tr>
</tbody>
</table>

\(^a\) All blood sugar values expressed in mg/dl. ± standard error of the mean.

\(^b\) ( ) Number of animals.

\(^c\) Significantly different from genotypic diabetic, \(P<0.01\).

\(^d\) Significantly different from control, \(P<0.05\).

\(^e\) Significantly different from control, \(P<0.01\).
### TABLE VII

**Plasma Insulin Levels of Three Month Old Chinese Hamsters**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting</th>
<th>30 minutes post-glucose administration</th>
<th>Change from fasting to 30 minute level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (19) b</td>
<td>53 ± 9</td>
<td>438 ± 32</td>
<td>385 ± 31</td>
</tr>
<tr>
<td>Genotypic Diabetic (12)</td>
<td>47 ± 24</td>
<td>207 ± 46c</td>
<td>160 ± 50c</td>
</tr>
<tr>
<td>Phenotypic Diabetic (14)</td>
<td>64 ± 13</td>
<td>213 ± 37c</td>
<td>149 ± 33c</td>
</tr>
</tbody>
</table>

*All plasma insulin values expressed as uU/ml ± standard error of the mean.*

b( ) Number of animals.

cSignificantly different from control, P<0.01.
TABLE VIII
Blood Sugar Levels of Three Month Old Chinese Hamsters\textsuperscript{a}

<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting</th>
<th>30 minute post-glucose administration</th>
<th>Change from fasting to 30 minute level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (19)\textsuperscript{b}</td>
<td>86 ± 3</td>
<td>304 ± 12</td>
<td>218 ± 16</td>
</tr>
<tr>
<td>Genotypic Diabetic (12)</td>
<td>98 ± 5</td>
<td>447 ± 27\textsuperscript{d}</td>
<td>349 ± 24\textsuperscript{d}</td>
</tr>
<tr>
<td>Phenotypic Diabetic (14)</td>
<td>139 ± 6\textsuperscript{c,d}</td>
<td>476 ± 15\textsuperscript{d}</td>
<td>337 ± 13\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All blood sugar values expressed in mg/dl. ± standard error of the mean.
\textsuperscript{b}( ) Number of animals.
\textsuperscript{c}Significantly different from genotypic diabetic, P<0.01.
\textsuperscript{d}Significantly different from control, P<0.01.
from fasting to the 30 minute level in both genotypic and phenotypic diabetics were significantly less than in nondiabetic controls. Genotypic and phenotypic diabetics were indistinguishable with regard to these parameters.

Table VIII shows blood sugar responses to oral glucose administration in three month old Chinese hamsters. Fasting blood sugar levels of phenotypic diabetics were significantly greater than those of both genotypic diabetics and nondiabetic controls. Blood sugar 30 minutes after oral glucose administration and the change from fasting to the 30 minute level in genotypic and phenotypic diabetics were significantly greater than those of nondiabetic controls. Genotypic diabetics and phenotypic diabetics were not different from each other with regard to these parameters.

Table IX shows plasma insulin responses to oral glucose administration in four month old Chinese hamsters. Fasting plasma insulin levels of phenotypic diabetics were significantly greater than those of both genotypic diabetics and nondiabetic controls. Genotypic diabetics and nondiabetic controls did not differ with regard to this parameter. Plasma insulin 30 minutes after oral glucose administration in phenotypic diabetics was significantly less than that of both genotypic diabetics and nondiabetic controls. Genotypic diabetics were not different from nondiabetic controls however. Plasma insulin changes from fasting to the 30 minute levels in phenotypic diabetics were significantly less than those of both genotypic diabetics and nondiabetic controls, the later two groups being indistinguishable once again.


<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting</th>
<th>30 minutes post-glucose administration</th>
<th>Change from fasting to 30 minute level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (19)</td>
<td>36 ± 4</td>
<td>242 ± 27</td>
<td>206 ± 26</td>
</tr>
<tr>
<td>Genotypic Diabetic</td>
<td>43 ± 8</td>
<td>234 ± 30</td>
<td>191 ± 28</td>
</tr>
<tr>
<td>Phenotypic Diabetic</td>
<td>67 ± 8c,f</td>
<td>141 ± 20c,e</td>
<td>74 ± 16d,f</td>
</tr>
</tbody>
</table>

**a** All plasma insulin values expressed in uU/ml. ± standard error of the mean.

**b** ( ) Number of animals.

**c** Significantly different from genotypic diabetic, P<0.05.

**d** Significantly different from genotypic diabetic, P<0.01.

**e** Significantly different from control, P<0.05.

**f** Significantly different from control, P<0.01.
<table>
<thead>
<tr>
<th>Animal</th>
<th>Fasting</th>
<th>30 minutes post-glucose administration</th>
<th>Change from fasting to 30 minute level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>87 ± 4</td>
<td>302 ± 14</td>
<td>215 ± 15</td>
</tr>
<tr>
<td>Genotypic Diabetic</td>
<td>90 ± 3</td>
<td>443 ± 22d</td>
<td>353 ± 22d</td>
</tr>
<tr>
<td>Phenotypic Diabetic</td>
<td>146 ± 11c,d</td>
<td>488 ± 25d</td>
<td>342 ± 25d</td>
</tr>
</tbody>
</table>

a All blood sugar values expressed in mg/dl. ± standard error of the mean.
b ( ) Number of animals.
c Significantly different from genotypic diabetic, P<0.01.
d Significantly different from control, P<0.01.
Table X shows blood sugar responses to oral glucose administration in four month old Chinese hamsters. Fasting blood sugar levels of phenotypic diabetics were significantly greater than those of both genotypic diabetics and nondiabetic controls. Fasting blood sugar levels of genotypic diabetics and nondiabetic controls were indistinguishable. Blood sugar 30 minutes after oral glucose administration and the change from fasting to the 30 minute level of both genotypic and phenotypic diabetics were significantly greater than those of nondiabetic controls.
DISCUSSION

The data suggests blood sugar levels alone could be used to separate genotypic, phenotypic, and prediabetic Chinese hamsters from nondiabetic controls. Fasting blood sugar levels of phenotypic diabetics and thirty minute postglucose blood sugar levels of genotypic, phenotypic, and prediabetics were significantly greater than nondiabetic controls. However, postglucose blood sugar levels of genotypic, phenotypic, and prediabetics could not be distinguished from each other. As I mentioned previously, blood sugar levels are quite variable even within normal ranges. Blood sugar levels can be affected by many endocrine and environmental factors. In addition, blood sugar is a highly remote phenotypic character. Therefore, studying such a parameter has little relevance for understanding the etiology of the disease. A diagnostic procedure for prediabetics or even diabetes employing some metabolic parameter other than blood sugar would be more beneficial.

The observation that blood sugar levels of genotypic, phenotypic, and prediabetic Chinese hamsters were significantly elevated over nondiabetic controls may have several explanations. The most likely explanation is a lack of insulin in the blood. Vallance-Owen, (1964) described a synalbumin insulin antagonist in man which may interfere with the effective concentration of plasma insulin. This theory has met considerable criticism however. Gerritsen and Dulin, (1967) observed that plasma insulin levels in mild diabetic Chinese hamsters were normal even though glucosuria, hyperglycemia, and ab-
normal glucose tolerance persisted. They suggested that mild diabetes in the Chinese hamster may involve interference with insulin action or increased gluconeogenesis.

As mentioned earlier, diabetes in man and the Chinese hamster is accompanied by decreased islet volume, β-cell number, and β-cell degranulation. All of these suggest a physical lack of insulin which may explain the elevation in blood sugar in diabetic Chinese hamsters seen in this investigation. Carpenter et al., (1970) suggested that defective insulin biosynthesis was a major factor contributing to hyperglycemia and glucosuria in the Chinese hamster.

Cerasi and Luft, (1972 and 1975), showed evidence in man which suggests abnormal insulin secretion in response to glycemic stimuli. They proposed that blunted and delayed insulin release may have resulted from defective glucose receptor sites on the β-cell. Grodsky et al., (1974), reported evidence suggesting abnormal insulin release in diabetic Chinese hamsters.

Seltzer et al., (1967), reported a decreased insulin response to a glycemic stimulus in patients having mild or moderate diabetes mellitus. Serrano-Rios et al., (1969); Pyke et al., (1970); Cerasi and Luft, (1972); and Tattersall and Pyke, (1972), have all observed a similar depressed insulin response upon glycemic stimulation in prediabetics. All of the investigators mentioned above have, at one time or another, postulated that insulin release mechanisms may be genetically controlled; thus, suggesting the etiology of diabetes in man may result in part from a defective genetic component.

As mentioned previously, the symptoms and morphologic characteristics of diabetes mellitus in the Chinese hamster closely resemble
those of diabetes in man. The results obtained in this investigation (represented graphically in Figure IV) clearly indicate that insulin secretion following a glycemic stimulus is significantly decreased in prediabetic Chinese hamsters. It is also of interest that the insulin responses observed during the time prior to the onset of symptomatic diabetes (during prediabetes) were not different from those observed after positive diagnoses were made. At their young age, prediabetic Chinese hamsters may have normal blood sugar levels but abnormal insulin secretion. Prediabetic hamsters may be able to maintain normal fasting blood sugar levels, but cannot control their blood sugar under the severe stimulus given. This implies the existence of defective insulinogenic and/or secretion mechanisms in pre-diabetic Chinese hamsters as well as in Chinese hamsters having the symptoms of diabetes mellitus. Because of the high degree of selective inbreeding associated with the Chinese hamster colony and the observations made in this investigation, it seems reasonable to suggest that insulin secretion may be determined genetically, as postulated by various authors mentioned above. In addition, decreased insulin availability may be a factor contributing to the onset of glycosuria in the Chinese hamster.

Results of this investigation suggest that glucose stimulated insulin secretion may be useful in separating Chinese hamsters having a diabetic genotype from those lacking the trait. Although insulin secretion seems to be inadequate in both prediabetic and diabetic Chinese hamsters, it is unlikely that depressed, glucose-stimulated insulin secretion can be used as a predictive index for future dia-
betes. Plasma insulin levels following glycemic stimulation in genotypic diabetic Chinese hamsters could not be distinguished from those of prediabetics. This strongly suggests that there may be other factors which either singularly or in combination with depressed insulin secretion act to precipitate glucosuria. Some environmental factors which may increase the likelihood of diabetes appearing in man have been discussed. Possible explanations for this observation in the Chinese hamster will now be discussed.

Gerritsen et al., (1974), have shown that appetite control mechanisms are abnormal in prediabetic Chinese hamsters. These abnormalities lead to hyperphagia, which may act as a precipitating agent for diabetes in Chinese hamsters possessing the proper genotype. This is supported by studies showing that diet limitation retards, and in some cases ameliorates, the course of diabetes in the Chinese hamster. This could be a possible explanation for the onset of diabetes in some of the hamsters used in this investigation while others having similar genotypic characteristics were asymptomatic. Unfortunately, food consumption was not monitored in this investigation.

Cerasi and Luft, (1972), have shown that the liver plays a central role in the etiology of diabetes in man. Small increases in arterial glucose concentration virtually shut off gluconeogenesis by the liver in normal subjects (Wahren et al., 1972). However, even large blood glucose levels fail to shut off liver gluconeogenesis in diabetics. Cerasi and Luft, (1972), showed preliminary evidence suggesting that uncontrolled, liver gluconeogenesis may be present in subjects having a strong inclination of developing diabetes. Chang, (1970), showed that phosphoenol-pyruvate carboxykinase and
glucose-6-phosphatase, two liver gluconeogenic enzymes, were elevated in diabetic Chinese hamsters compared to nondiabetic controls. Chang was also able to show that pyruvate incorporation into blood glucose, an accepted method for measuring gluconeogenesis, was much faster in diabetic than in nondiabetic Chinese hamsters. It was tempting to speculate that these liver enzyme abnormalities may be present in prediabetic Chinese hamsters. However, Chang's experiments were inconclusive. Increased gluconeogenesis may have resulted from increased peripheral tissue metabolism. Nevertheless, liver abnormalities may play a key position in the etiology of diabetes in the Chinese hamster as well as in man. Noble, (1974), observed that the activity of several of the gluconeogenic enzymes was significantly greater in diabetic Chinese hamsters than in their presently aglucosuric siblings; those of the latter being like control. This decrease or lack of increase in gluconeogenic enzyme activity in genotypic diabetic hamsters may influence the onset of diabetes thus explaining the observation made in this investigation that some genotypically diabetic hamsters remained phenotypically normal.

Adams and Kupieciki, (1974), studied insulin secretion by isolated islets of Langerhans of normal Chinese hamsters and compared them to insulin responses of islets from phenotypic and genotypic diabetic hamsters. They observed that, although less than in normal hamsters, insulin secretion from islets of genotypic diabetic hamsters was significantly greater than in those from phenotypic diabetics. Depressed insulin secretion in phenotypic diabetics may have been a factor contributing to the onset of diabetes in these hamsters. It must be noted that this observation did not entirely
agree with data obtained in this investigation. This anomaly may have resulted from stress imposed on the Chinese hamsters during experimental procedures; i.e. handling, orbital sinus bleeding, etc. Blanks and Gerritsen, (1974), reported that stress inhibits glucose-stimulated insulin release and elevates blood sugar in the Chinese hamster. It is also difficult to extrapolate between in vitro and in vivo studies.

Grodsky et al., (1974), using an in vitro pancreas perfusion technique, were able to show an excessive glucagon and impaired insulin response to glucose in diabetic Chinese hamsters. It may be that impaired alpha cell sensitivity to glucose, coupled with impaired insulin secretion could be a factor contributing to the onset of diabetes. Grodsky's studies were also of interest in that eight diabetic sublines were compared with regard to insulin secretion following a glucose stimulus. It was noted that certain diabetic sublines exhibited significantly less insulin release than others even though the severity of glucosuria was similar among all sublines. Grodsky found the glucose stimulated insulin release in hamsters that I chose to define as genotypic diabetics to be like that of phenotypic diabetics. This suggests the existence of genetic heterogeneity and points out that environmental factors could play a deciding role in the onset of diabetes in the Chinese hamster. Specific gene loci may be different in Chinese hamsters from different sublines. Gene variations between sublines may influence the onset and severity of diabetes. For example, environmental factors may react differently with one genome than another thereby affecting diabetes in different ways.
Gerritsen et al., (1974), reported evidence which supports the hypothesis that genetic heterogeneity, which could explain the absence of glucosuria in genotypically diabetic hamsters used in this study, exists in the Chinese hamster population. When two individual sublines were selectively inbred (brother to sister mating) the incidence of diabetes was 65% and 78% respectively. However, when these same two sublines were cross bred, the resulting hybrid yielded essentially no diabetics. Since these individual sublines were inbred for 9 and 10 generations, they are theoretically at least 90% genetically homozygous (Falconer, 1966). Assuming this to be true, the genes contributing to diabetes in hamsters from these two sublines must be at different loci. Thus, diabetes in these two sublines may very probably be genetically heterogeneous. This could explain the lack of continuity among hamsters having a diabetic genotype as observed in this investigation.

Colman and Hummel, (1974), have shown that the genetic background plays an important role in the expression of the disease syndrome in family inbred obese and diabetic mice. Although merely speculation, it could be that the genetic background influences the phenotypic expression of diabetes in the Chinese hamster. The genome may affect metabolism of diabetics by modifying the expression of the diabetic genes. For example, genes determining insulin secretion may be affected differently by different genomes. Insulin release may be less when influenced by a specific genome than another. Another possibility may be that glucose metabolism is affected differently by different genomes. Maybe glucose release into the blood from peripheral tissues varies with different genomes. Still another
speculation may be that environmental factors are interpreted differently by different genomes. Therefore, the genetic background may be a factor influencing the type of diabetes expressed. This might explain why some hamsters showed glucosuria while others remained aglucosuric.
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