Characterization of Diabetes Mellitus in South African Hamsters (*Mystromys albicaudatus**)

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Summary. Spontaneous diabetes mellitus has been studied in *Mystromys albicaudatus* (South African hamster) at the University of Missouri, Columbia Medical Center since its original discovery here in 1969. Thus far, characteristics established as part of the diabetic syndrome in this species included hyperglycemia, glucosuria, ketonuria, polyuria, polyphagia and polydipsia with variations in age of onset, degree of severity, and rate of progression. In addition, decreased glucose tolerance has been demonstrated and statistical analyses of data collected indicated that diabetes mellitus in *M. albi-*

caudatus has a polygenic, nonsex-linked mode of inheritance. — Histologic findings involving the pancreas, kidneys, and liver were found to be positively correlated to diagnostic parameters as well as to their degree of severity and duration. Pancreatic lesions included β -cell vacuolization, glycogen infiltration, nuclear pyknosis, margination of organelles, and β -cell death.

Key words: Diabetes mellitus, characterization, *Mystromys*, South African hamster.

The South African hamster or white-tailed rat, *Mystromys albicaudatus*, is a member of the order *Rodentia*, family *Cricetidae* and is the only recognized member of the subfamily *Cricetinae* in Africa [1]. Although *Mystromys* were first introduced into the laboratory in 1941 in Africa, it was not until 1962 that the first colony was established in the United States at the Armed Forces Institute of Pathology (A.F.I.P.) [2].

The University of Missouri Columbia Medical Center (U.M.C.M.C.) colony of *Mystromys albicaudatus* was started in April 1968 with six adult animals, plus six of their unweaned offspring, provided by the A.F.I.P. In February 1969, the colony contained 88 animals, and it was at this time that some animals were noted repeatedly to have excessively wet cages, which lead to a diagnosis of spontaneous diabetes mellitus [3]. After the original survey of the colony, involving 118 animals [3], systematical studies were undertaken to define and characterize the syndrome of spontaneous diabetes mellitus in the colony [4–9].

Since 1968, over 850 progeny have been weaned in the U.M.C.M.C. colony. Nearly 400 of these are still living, of which 140 are over 40 months of age. The biology and husbandry of *Mystromys* have been documented in detail [2, 5, 10].

Metabolic Studies

Blood samples were collected from the tails of animals that were either non-fasted or fasted 5–7 h [5], using a specifically designed vacuum-tube apparatus [11]. Serum glucose values were initially determined

by the total reduction ferric cyanide autoanalyzer technique¹. However, since May 1972, the hexokinase microtechnique for D-glucose² has been employed. Values obtained with the autoanalyzer technique ranged from 60 to 2300 mg/100 ml and those obtained with the hexokinase technique have ranged from 40 to 1000 mg/100 ml. Using data from our studies [4, 5] as well as data from other rodent models of diabetes [12–15], hyperglycemia in *Mystromys* was established as:

- a) a nonfasted serum glucose value greater than 169 mg/100 ml by autoanalyzer or 152 mg/100 ml by hexokinase, or
- b) a 5 to 7 h fasted value greater than 150 mg/100 ml by autoanalyzer or 135 mg/100 ml by hexokinase.

Hyperglycemia has been the most consistent characteristic of diabetes mellitus in our animals and is not affected by age, sex, or inbreeding [5] nor is it related to obesity [3, 5, 7]. However, it has varied in incidence, age of onset, degree of severity, and rate of progression as well as repeatability within individual animals. Table 1 depicts the variations in incidence of hyperglycemia with time and lists the April 1974 data in greater detail, illustrating that some variation in incidence may be the result of differences in exactly what is being reported as well as in what frame of reference. However, variations in incidence will occur, and are to be expected, when the number of reproducing diabetic and nondiabetic adults continually varies because of the need to determine whether or not the disease could be reproduced. Also, variation in age of onset will tend to increase the incidence of

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¹ Modified Method of W.S. Hoffman, J. biol. Chem. **120** (1937) as published by Technicon (1965).

² Eskalab Instruction Manual, Smith Kline and French: Palo Alto, California. 1962.

hyperglycemia as the number of older animals increases.

In some *Mystromys*, hyperglycemia is well established by four months of age [3, 5], while others have been various ages up to 40 months old before hyperglycemia was detected with the animals being normoglycemic on as many as 7 previous occasions. The majority of hyperglycemic values have been below 300 mg/100 ml. However, 67 higher values have been recorded with 2300 mg/100 ml being the highest serum glucose value thus far determined. These high values have been consistently indicative of severe, rapidly progressing diabetes mellitus whereas the less extreme hyperglycemic values have not been as predictable

weight; and 6. depression, debilitation, lethargy, ketoacidosis, coma and death usually within two months after the onset of signs if not treated. This form of the disease has been seen in less than 10% of the diabetic *Mystromys*.

Table 2 presents data on glycosuria and ketonuria in chronically diabetic animals as of April, 1974. In 251 males with chronic diabetes, 72% have been glucosuric (80% of these intermittently) and 96% ketonuric (39% of these intermittently). In 277 females with chronic diabetes, 29% have been glucosuric (87% of these intermittently) and 29% ketonuric (94% of these intermittently). However, hyperglycemia, glycosuria, and ketonuria have not always

Table 1. Variations in incidence of hyperglycemia in *Mystromys*

	Jul. '69 ^a	Nov. '69 ^b	Mar. '70 ^b	Mar. '73 ^b	Apr. '74 ^a
Hyper F	12% (5 of 47)	31% (29 of 93)	48% (59 of 123)	50% (182 of 364)	74% (288 of 389)
Hyper M	30% (21 of 71)	33% (39 of 118)	54% (85 of 158)	49% (205 of 418)	69% (297 of 430)
Total Hyper	22% (26 of 118)	32% (68 of 211)	51% (144 of 281)	49% (387 of 782)	71% (585 of 819)
April 1974: Details of hyperglycemia					
	288 of 389 females (74%)		297 of 430 males (69%)		
Repeated ^c	195 of 389 (50%)		194 of 430 (45%)		
	195 of 288 (68%)		194 of 297 (65%)		
	195 of 585 (33%)		194 of 585 (33%)		
Always ^d	100 of 288 (35%)		83 of 297 (28%)		
Classic ^e	11 of 288 (4%)		46 of 297 (15%)		

^a At least one hyperglycemic value

^b Repeated hyperglycemic values

^c Two or more hyperglycemic values

^d All glucose determinations hyperglycemic (includes classic)

^e Same as ^d but also all urinalyses detect glycosuria and ketonuria

Table 2. Glycosuria and ketonuria in *Mystromys* with chronic diabetes

Number	Glycosuric	Intermittent	Ketonuric	Intermittent
251 males	181	144	242	94
277 females	79	69	81	76

as indicators of degree of severity or rate of progression of the disease. In addition, nearly 56% of the males and 45% of the females have demonstrated intermittent hyperglycemia as defined by one or more normoglycemic determination following recorded hyperglycemia.

Urinalyses consisted of measuring the volume of 16 to 20 h samples collected overnight and detecting the presence of glucose and/or ketones by the Lab-Stix® method. The classic, severe, rapidly progressing, acute form of diabetes in *Mystromys* was characterized by: 1. polyuria and polydipsia — a 400% to 2000% increase; 2. glycosuria — 0.4 g/100 ml or more consistently; 3. ketonuria — consistent moderate to large reading on the Lab-Stix; 4. extreme hyperglycemia — values continuously above 400 mg/100 ml; 5. polyphagia with severe weight loss — up to several times normal food intake while losing 50% of body

occurred together, nor have the degrees of severity of each always reflected the others.

Therefore, while polyuria, polydipsia, glycosuria and ketonuria were the first observed characteristics of diabetes in *Mystromys* [3], the consistency and degree of severity with which they have occurred in the presence of other, more definitive characteristics of the disease have varied greatly. Similar variations have been reported in humans [16–20].

Decreased glucose tolerance has been demonstrated in diabetic *Mystromys* and the details reported elsewhere [9].

Morphologic Studies

Pancreatic islet cells from normoglycemic *Mystromys* showed distinct cell outlines and contained no

cytoplasmic vacuoles or PAS positive materials (Fig. 1). The morphologic alterations described in the β -cells of a few selected, hyperglycemic *Mystromys* consisted of progressive vacuolization, glycogen infiltration demonstrated by PAS-hemotoxylin stained sections before and after diastase digestion, and nuclear pyknosis (Fig. 2) [3, 4]. A comparison of the degree of severity of pancreatic islet lesions at the light microscopy level to the serum glucose means in 127 animals gave statistical validity to the decision to use nonfasted serum glucose values greater than 169 mg/100 ml as denoting hyperglycemia [7].

tromys and to study the somatic chromosomes. Based on data accumulated in our studies [3–5, 7, 9], animals were categorized as:

1. diabetic — repeated hyperglycemia and/or decreased glucose tolerance and/or characteristic pancreatic lesions;
2. suspect — multiple serum glucose determinations but only one instance of hyperglycemia with all other criteria normal; or
3. normal — for all criteria.

Comparison of the numbers of each phenotype

Fig. 1. Normal pancreatic islet (vascular spaces scattered throughout the islet are not degenerative changes). Hematoxylin and eosin stained ($\times 1500$)

Additional morphologic studies have included electron microscopic analysis of the pancreatic islets [4], ultrastructures of hepatic mitochondria [6] and light microscopic evaluation of renal glomeruli [8]. The morphologic changes in the hepatic mitochondria were reflected by increased respiratory control ratios and elevated activity of β -hydroxybutyrate dehydrogenase [6].

Genetic Studies

These investigations were undertaken to determine the mode of inheritance of diabetes mellitus in *Mys-*

born to the diabetic $\times$ diabetic and normal $\times$ normal matings resulted in a chi-square of 663.8, thereby providing the criterion necessary to prove that heredity plays a significant role in the causation of diabetes mellitus in *Mystromys*.

The number of offspring, by sex, from each of the nine possible mating arrangements were analysed. There were no significant differences in the numbers of offspring per phenotype from the three reciprocal crosses, hence no sex-linkage. There was no significant difference in the numbers of each sex within the mating arrangements, hence no sex-control or sex-influence.

Statistical analyses of repeated serum glucose

values from 620 *Mystromys* suggested a polygenic mode of inheritance of the disease in this species [5]. Further support was obtained when a midparent regression analysis yielded a heritability estimate of 0.391, indicating a polygenic trait composed of small additive effects.

The chromosome complement of *Mystromys* from the U.M.C.M.C. colony was studied using heart blood culture [21] and our findings differ from the only other two reports, which also differ from each other,

some was the longest submetacentric and the Y was an acrocentric, ranking seventh in the order of decreasing size. Both of the two previous reports described the Y chromosome as the smallest of the complement. When the Y chromosome is not the smallest, its identification is equivocal. By analyzing the G-banding patterns (Fig. 4), it becomes obvious that the X and Y were the only nonhomologous pairs and that their banding patterns were unique. Therefore, we were reasonably sure about our identification of the sex chromosomes.

Fig. 2. Pancreatic islet with severe lesions (mostly vacuoles, glycogen infiltrated cells and pyknotic nuclei; few, if any, normal islet cells). Hematoxylin and eosin ($\times 1500$)

on the chromosomes of this species [22, 23]. A diploid number of 32 chromosomes was reported in all three publications but the descriptions of the chromosomes varied greatly. We arranged them in the order of decreasing length on the basis of form and size (Fig. 3). The autosome pairs numbered 1, 2, and 15 were submetacentric; 3, 4, 5, 10, 11, 13, and 14 were metacentric; and 6, 7, 8, 9, and 12 were acrocentric. Taitz [22] described all chromosome pairs as submetacentric. Hsu and Benirschke [23] did not provide a precise morphological description of individual chromosome pairs.

Sex chromosomes of the males were determined in our study by the process of elimination. The X chromo-

Comments

The data presented has demonstrated that spontaneous diabetes mellitus develops in the U.M.C.M.C. colony of *Mystromys albicaudatus*. The disease has a complex, diverse nature characterized by hyper-

Fig. 3. Somatic chromosomes of *M. albicaudatus*. The autosomes are arranged in decreasing order of length (pair 1 to 15). The sex chromosomes are in the bottom line ($\times 2800$)

Fig. 4. G-banding patterns of a male *M. albicaudatus*. Chromosomes are in midprophase. Note the nonhomologous nature of the X and Y chromosomes ($\times 3000$)

Fig. 3

Fig. 4

glycemia, glucosuria, ketonuria, polyuria, polydipsia, and polyphagia which are variable in age of onset, degree of severity, and rate of progression. In addition, decreased glucose tolerance occurs as part of the syndrome [9].

Histologic characteristics of this metabolic disorder include cytoplasmic vacuolization and glycogen infiltration, margination of organelles, and nuclear pyknosis of pancreatic islet cells [3, 4]; capillary basement membrane thickening and mesangial proliferation in renal glomeruli [8]; generalized ballooning and vacuolization of hepatic nuclei and centrolobular fatty infiltration [6]; and hepatic mitochondrial enlargement with abnormal shapes [6]. The morphologic alterations of the hepatic mitochondria are reflected by increased respiratory control ratios and increased specific activity of β -hydroxybutyrate dehydrogenase [6].

Evaluation of the accumulated data indicates that spontaneous diabetes mellitus in *M. albicaudatus* is reproducible and has a polygenic, nonsex-linked mode of inheritance.

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