Spontaneous Diabetes Mellitus in Mystromys Albicaudatus

Repeated Glucose Values from 620 Animals

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SUMMARY

The serum glucose values of 1,423 blood samples from 620 *Mystromys albicaudatus* have been determined and defined as orthoglycemic or hyperglycemic. Analyses of variance tests and regression analyses of the data revealed a significant difference between orthoglycemic and hyperglycemic serum glucose means and indicated that serum glucose is not affected by sex, inbreeding, or age in these animals. However, within classifications of orthoglycemic and hyperglycemic, weight did affect serum glucose. Therefore, while obesity did not occur during this study, obese-hyperglycemia syndromes might be expected should the animals become overweight.

The data and their analyses are strongly indicative that spontaneous diabetes mellitus in *M. albicaudatus*, as related to hyperglycemia, is very similar to the disease in man. DIABETES *21*:715-21, June, 1972.

Diabetes mellitus has been described as the most important metabolic disease in man, affecting biochemical processes which go on in all body cells.[1] Over the centuries, study of the disease in man and animal models has resulted in the accumulation of a vast fund of knowledge. However, because of the diverse nature and complexity of diabetes mellitus, many aspects of this disease syndrome remain obscure. One task of each investigator of diabetes is to define the disease in his subjects because no clear, concise definition exists at present.[2] While animal models have been discovered to develop spontaneous diabetes mellitus,[3] some with degrees of variation in their syndromes, studies have revealed that none shows as wide and varied a range of signs nor the diverse nature of the disease that is described in man.

The latest animal known to develop spontaneous diabetes mellitus is the white-tailed rat or South African hamster, *Mystromys albicaudatus.* The disease was first discovered in our colony of *Mystromys* in 1969.[4] Since that time, the animals have been studied to determine their suitability as a model for the disease. The purpose of this paper is to present the results of repeated serum glucose determinations on 620 animals from this colony.

MATERIALS AND METHODS

1. *Animals.* The anatomy, appearance, behavior, care, handling, and physiology of *Mystromys* have been reported.[5] The history of the University of Missouri-Columbia Medical Center breeding colony used in this study has been documented[6] also. Six hundred and twenty animals were tested.

The animals received Purina Laboratory Chow* and tap water ad libitum and were housed and cared for as suggested in the "Guide for Laboratory Animal Facilities and Care."[7] The complete details of feeding, housing, breeding, and record keeping have been documented[6] elsewhere. The inbreeding method followed was that of mating full brothers and sisters, with littermates given first consideration. In addition, the animals were maintained on a cycle of nine hours light, fifteen hours dark.

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2. *Blood collection.* Each of 620 members of the colony was bled periodically to determine his serum glucose value. The schedule was to bleed each animal when it reached 4, 6, 9, 12, 18, 24, 36, and 48 mo. of age. The animals already in the colony when the study began were bled and then subsequently rebled as they reached the various scheduled ages. Breeding females were bled as close to the scheduled ages as possible but not while nursing. Blood samples were obtained from the tail. The technic used has been described elsewhere.[8]

Random samples were collected in the mornings between 9 and 11:30 a.m. Immediately after the blood was collected, sodium fluoride was added to, and gently mixed with, the blood to halt glycolysis. Animals selected for bleeding on any given day were weighed after the sample was collected. After the last sample was collected, all samples were centrifuged for twenty minutes between 1,200 and 2,000 R.C.F. and each serum sample harvested and frozen at —10 ± 4° C. Serum glucose values were determined by standard AutoAnalyzer microtechnic.

Fasting blood samples were collected in the afternoons. The animals to be bled were selected between 3:30 and 4:30 p.m. of the preceding day and placed in individual metabolism cages to collect urine for simultaneously ongoing studies. At 8 a.m., all food was removed from the metabolism cages. Starting at 12 p.m., the bleeding procedure[8] was followed and each animal weighed. Immediately following each collection, the tube was placed in crushed ice instead of adding sodium fluoride. All samples, usually twelve per day, were collected within a two-hour period between 1 and 3:30 p.m. Twenty to thirty minutes after collecting the last sample, each clot was ringed, followed by centrifugation and serum harvest as previously described.

3. *Definitions.* In man and all other animals known to develop spontaneous diabetes mellitus, no single criterion uniformly identifies all diabetics. Therefore, various criteria have been used by investigators and terms must be defined to prevent confusion.

Hyperglycemia in this study refers to (a) a random serum glucose value of 170 mg./100 ml. or greater, or (b) a fasting serum glucose value greater than 150 mg./100 ml. It is realized that these values may be conservative and that eventually, when diabetes in *M. albicaudatus* is more fully defined, hyperglycemia may be truly indicated by lower values.

Intermittent hyperglycemia in this study signifies: (a) hyperglycemia followed by orthoglycemia followed by hyperglycemia, or (b) repeated hyperglycemia followed by orthoglycemia, but does not include animals demonstrating repeated hyperglycemia preceded by orthoglycemia.

RESULTS

Serum glucose values. An analysis of variance test of the grand means of orthoglycemic and hyperglycemic values, regardless of sex (table 1) disclosed that they are significantly different ($P < .05$) from each other. An analysis of comparable random and fasting values (referred to in *Methods—Blood collection*) revealed no significant difference ($P > .05$) between them. A regression analysis of the effect of age upon serum glucose mean values, within orthoglycemic and hyperglycemic classifications, is presented in figure 1. The lack of an effect of sex upon serum glucose values is indicated also, in that there is no significant difference ($P > .05$) between sexes, within classifications, at any age. An analysis of the effect of inbreeding upon the serum glucose values listed in table 1 also resulted in a regression line of zero slope for each one. The regression lines (figure 1) represent 1,423 serum samples. Each sample was classified as orthoglycemic or hyperglycemic, whether from a male or female, by the age of the animal when the sample was collected, and by the generation of inbreeding to which the animal belonged. In addition to the regression analyses after classifying all values, serum glucose means and corresponding numbers of samples (N) were determined and are listed by classification in table 1. The regression analyses (figure 1) and an analysis of variance test of these serum glucose values (table 1) disclosed that age, sex, and inbreeding have no effect on the values within classifications.

The regression analysis of the effect of weight on serum glucose values is presented in figure 2. The mean weights analyzed are listed in table 2 and the corresponding serum glucose values in table 1. The weights were classified and listed exactly as the serum glucose values were in table 1 (described under *Results-Serum glucose values*). Analyses disclosed that average weights decrease with inbreeding, increase with age, are affected by sex, but have no effect on the overall serum glucose values. However, within classifications (figure 2 and tables 1 and 2), serum glucose and weight have a positive correlation. Orthoglycemic males and females both have a significant increase ($P < .05$) in serum glucose means with increased weight, while hyperglycemic males and females both have a significant decrease ($P < .05$) in serum glucose means with increased weight.

TABLE 1

Two populations of mean serum glucose values by age and sex over six generations

Generation	Age (mo.)	Orthoglycemic N*	Orthoglycemic Males†	Orthoglycemic N*	Orthoglycemic Females†	Hyperglycemic N*	Hyperglycemic Males†	Hyperglycemic N*	Hyperglycemic Females†
1	4	17	113 ± 5.7	10	119 ± 8.7	43	242 ± 18.7	23	204 ± 8.0
	6	24	119 ± 5.8	7	114 ± 10.3	23	223 ± 22.2	11	193 ± 9.3
	9	9	113 ± 8.5	4	113 ± 45.0	7	187 ± 17.0	8	233 ± 53.3
	12	11	107 ± 8.8	6	101 ± 6.8	0	—	1	170
	15	6	113 ± 4.6	5	123 ± 12.0	4	186 ± 11.6	3	325 ± 25.0
	18	3	123 ± 12.5	1	141	3	231 ± 34.7	2	200 ± 36.5
	> 18	5	134 ± 10.3	4	119 ± 10.0	5	223 ± 27.6	5	209 ± 23.6
Generation	Means	75	116 ± 7.0	37	116 ± 17.7	85	228 ± 20.2	53	213 ± 18.5
2	4	21	118 ± 7.7	25	121 ± 7.0	14	258 ± 28.1	6	265 ± 31.5
	6	20	113 ± 7.4	21	100 ± 8.3	13	211 ± 18.5	5	219 ± 21.7
	9	47	109 ± 5.8	21	119 ± 9.0	21	202 ± 13.9	21	219 ± 20.9
	12	27	123 ± 7.9	13	117 ± 12.9	22	217 ± 17.6	17	217 ± 12.4
	15	22	121 ± 6.8	9	111 ± 11.4	8	220 ± 24.1	6	216 ± 35.3
	18	21	130 ± 4.5	13	124 ± 6.7	16	215 ± 26.7	15	216 ± 25.6
	> 18	10	110 ± 7.6	6	123 ± 4.8	6	197 ± 17.5	6	187 ± 20.1
Generation	Means	168	124 ± 6.6	108	115 ± 8.6	100	218 ± 20.4	76	219 ± 21.9
3	4	26	118 ± 6.6	21	111 ± 8.7	14	198 ± 18.1	14	265 ± 53.3
	6	15	117 ± 8.8	12	114 ± 11.2	20	216 ± 11.1	12	210 ± 14.7
	9	54	113 ± 4.6	26	114 ± 5.3	37	190 ± 6.4	58	196 ± 4.0
	12	27	110 ± 5.9	21	121 ± 7.8	16	169 ± 3.3	30	211 ± 19.7
	15	5	98 ± 21.5	4	120 ± 10.6	4	170 ± 9.7	4	254 ± 50.3
	18	10	118 ± 6.9	8	132 ± 9.3	10	191 ± 11.3	5	175 ± 3.5
	> 18	2	94 ± 3.5	1	130	2	171 ± 13.5	2	155 ± 0.0
Generation	Means	139	113 ± 6.4	93	117 ± 7.9	103	192 ± 9.2	125	209 ± 15.7
4	4	5	129 ± 7.7	5	126 ± 10.9	4	191 ± 20.4	5	190 ± 11.5
	6	16	126 ± 3.2	5	123 ± 13.7	21	202 ± 8.9	14	187 ± 9.1
	9	23	125 ± 4.2	12	131 ± 4.8	18	174 ± 4.5	21	193 ± 6.8
	12	12	127 ± 4.4	4	140 ± 3.6	11	174 ± 6.4	12	192 ± 11.3
	15	1	94	0	—	2	600 ± 48.0	3	185 ± 20.9
	18	0	—	1	120	3	191 ± 20.0	1	174
Generation	Means	57	126 ± 4.2	27	130 ± 7.5	59	200 ± 9.8	56	190 ± 9.6
5	4	0	—	4	117 ± 9.6	6	229 ± 25.0	8	189 ± 9.1
	6	5	137 ± 3.4	5	135 ± 7.4	4	200 ± 16.6	5	218 ± 20.0
	9	3	96 ± 15.3	7	122 ± 8.8	1	152	3	175 ± 5.7
	12	0	—	1	117	0	—	0	—
Generation	Means	8	122 ± 7.9	17	124 ± 8.6	11	211 ± 19.7	16	195 ± 11.9
6	4	1	120	3	134 ± 6.4	1	158	1	155
	6	2	136 ± 2.5	1	141	0	—	1	158
Generation	Means	3	130 ± 1.7	4	136 ± 4.8	1	158	2	157
Grand	Means	450	117 ± 1.2	286	118 ± 1.6	359	209 ± 4.1	328	208 ± 4.3

* Number of individual animals (one sample/animal) analyzed at the age indicated.

† Mean serum glucose values in mg./100 ml. ± S.E.M.

Intermittent hyperglycemia was also a finding of this study. Each of the 620 animals in the study had two or more serum glucose values determined, depending upon age, spontaneous deaths, and the protocols of simultaneously ongoing studies. Of sixty-seven males and forty-six females with repeated hyperglycemia based on three or more determinations, 37 per cent and 33 per cent respectively demonstrated intermittent hyperglycemia. In addition, thirty-seven males and nineteen females were hyperglycemic on their first test, but not subsequently; sixteen males and seventeen females had one hyperglycemic value preceded and followed by one or more orthoglycemic values; and thirty-three males and thirty-nine females were hyperglycemic on their last test, but not previously.

DISCUSSION

Defining spontaneous diabetes mellitus is difficult because of variations in blood glucose, urine glucose, and glucose tolerance found in normal and diabetic individuals. No one test or combination of tests is known which detects diabetes with 100 per cent accuracy.[9-14] Therefore, it is imperative when working with diabetes that definitions be set forth, and explained in de-

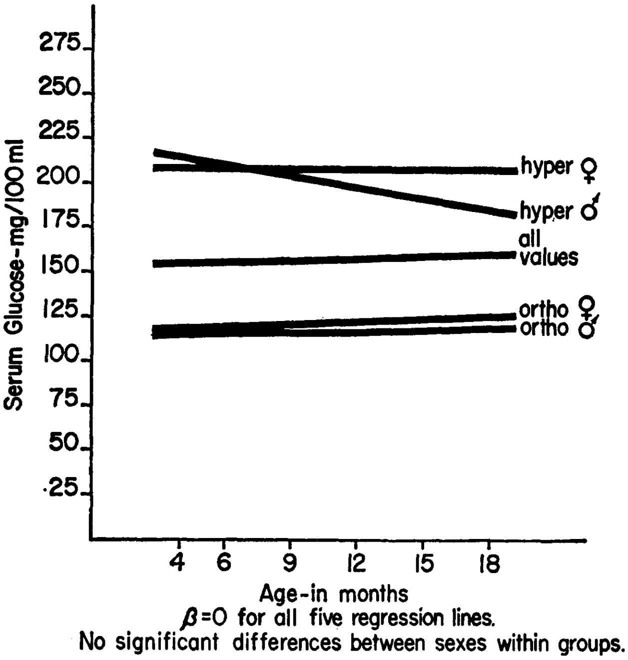

FIG. 1. Glucose vs. age: regression of ortho- and hyperglycemic values by sex and overall values.

tail, especially if the animal under investigation is a new model for the disease.

Basing a diagnosis of diabetes on one hyperglycemic serum glucose value alone is probably the second least accurate method commonly used, with glycosuria being the least.[9,10,12,14,15] Although 140 mg./100 ml. was originally chosen as the maximum normal serum glucose value,[4] our continuing studies, as well as data from other rodent models,[16-19] indicated that random samples with values up to 169 mg./100 ml. and fasting samples of up to 150 mg./100 ml. might be more realistic in *M. albicaudatus*. Therefore, for this study, the latter values were chosen, and anything above them was judged hyperglycemic. Use of these higher values, it was felt, would decrease the number of false positive diagnoses without significantly increasing false normal ones. Following decision of the criteria and methods to follow, it becomes necessary to apply them to the data.

Serum glucose values. Because of technical problems, not all of the 620 animals have a serum glucose value for each scheduled bleeding age that they reached (table 1). Animals not represented in figure 1 and tables 1 and 2 are those which were too young to have been bled at least twice at the conclusion of this study, those which died prior to sampling, and the two original nonrelated adults[6] (both were orthoglycemic for three bleedings starting at twenty-four months of age).

One school of thought concerning hyperglycemia associated with diabetes is that orthoglycemics and hyperglycemics constitute one population and that hyperglycemia falls within the upper tail of the normal curve of serum glucose values.[20] If this were true in *M. albicaudatus,* significantly fewer hyperglycemic values would be expected than were observed (table 1). The significant difference between orthoglycemic and hyperglycemic values found in our animals, as well as the large number of hyperglycemic values, indicates that there are two separate populations (based on serum glucose) within the colony rather than one and the data has been interpreted based on this assumption.

The fact that comparable random and fasted values are not significantly different may be explained by several alternatives. For one, the emptying time of the stomach and small intestine of *M. albicaudatus* is unknown. Convenience dictated either an eighteen-hour fast or a five- to seven-hour fast. Attempts at collecting blood samples following an eighteen-hour fast resulted in the death of several animals. Therefore, a five- to seven-hour fast was adopted even though it

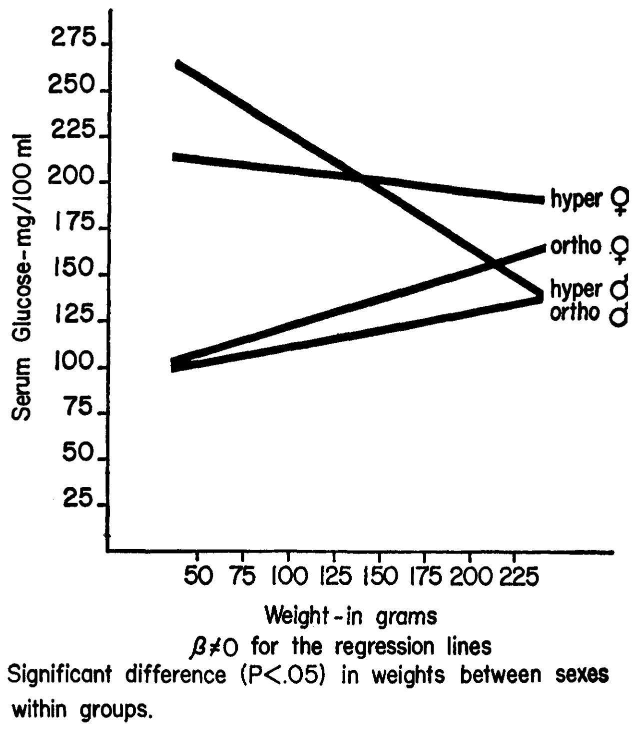

FIG. 2. Glucose vs. weight: regression lines of ortho- and hyper glycemic values by sex.

TABLE 2

Two populations of mean weights by age and sex over six generations

Generation	Age (mo.)	Orthoglycemic				Hyperglycemic			
		N*	Males†	N*	Females†	N*	Males†	N*	Females†
1	4	17	117.8	10	82.5	43	126.2	23	96.6
	6	24	129.0	7	96.9	23	132.9	11	107.5
	9	9	131.1	4	95.7	7	126.9	8	98.9
	12	11	136.9	6	100.8	0	—	1	93.0
	15	6	140.5	5	101.9	4	151.0	3	101.5
	18	3	139.5	1	132.0	3	153.7	2	114.0
	> 18	5	135.4	4	99.0	5	144.2	5	107.0
Generation	Means	75	133.5	37	94.8	85	131.3	53	101.0
2	4	21	118.5	25	95.2	14	129.9	6	94.7
	6	20	132.8	21	103.8	13	126.3	5	90.4
	9	47	129.5	21	99.4	21	133.0	21	105.2
	12	27	133.4	13	107.1	22	139.0	17	104.6
	15	22	136.9	9	102.1	8	134.1	6	110.5
	18	21	142.4	13	110.3	16	140.4	15	118.6
	> 18	10	132.7	6	110.3	6	155.5	6	93.8
Generation	Means	168	132.1	108	102.7	100	135.7	76	105.3
3	4	36	109.0	21	79.6	14	108.1	14	92.1
	6	15	114.6	12	85.9	20	126.0	12	101.8
	9	54	123.9	26	88.7	37	127.2	58	99.7
	12	27	127.0	21	88.0	16	129.6	30	194.9
	15	5	125.1	4	98.0	4	135.0	4	101.3
	18	10	132.7	8	104.0	10	140.4	5	92.4
	> 18	2	94.0	1	121.0	2	117.0	2	111.0
Generation	Means	139	121.3	93	88.9	103	125.6	125	97.7
4	4	5	113.0	5	80.9	4	118.2	5	89.5
	6	16	120.3	5	93.4	21	123.5	14	96.5
	9	23	125.1	12	89.5	18	129.9	21	98.2
	12	12	136.1	4	97.2	11	136.1	12	99.9
	15	1	136.0	0	—	2	sick	3	94.3
	18	0	—	1	97.0	3	149.0	1	97.0
Generation	Means	57	125.3	27	90.0	59	127.8	56	97.2
5	4	0	—	4	73.3	6	117.5	8	85.5
	6	5	111.5	5	70.1	4	116.5	5	89.2
	9	3	112.4	7	86.7	1	131.0	3	109.3
	12	0	—	1	72.0	0	—	0	—
Generation	Means	8	111.9	17	77.2	11	118.4	16	91.1
6	4	1	122.0	3	78.7	1	111.0	1	64.0
	6	2	123.0	1	71.0	0	—	1	75.0
Generation	Means	3	122.7	4	76.8	1	111.0	2	69.5
Grand	Means	450	122.4	286	86.6	359	127.5	328	95.7

* Number of individual animals (mean weight/animal) analyzed at the age indicated.
† Mean weight in grams.

was suspected that this was insufficient to empty the stomach. Subsequent necropsies revealed that the stomach still contained a substantial amount of ingesta following this short fast. Consequently, the term "fasted" sample as described under *Methods-Definitions* might be better termed "modified-random" sample. Because there is no difference between the random and fasted samples, they are combined throughout this paper and considered only as orthoglycemic or hyperglycemic.

The regression analyses disclosing no significant effect of sex, inbreeding or age on serum glucose values are of interest. No sex effect indicates no sex-linkage in the transmission of the disease, as it relates to hyperglycemia, in this species as was suggested originally.[4] Sex-linkage in human spontaneous diabetes mellitus has been suggested but is not generally accepted.[21-23] That inbreeding has no effect suggests a polygenic mode of inheritance of spontaneous diabetes, based on hyperglycemia, in *M. albicaudatus* because a monogenic trait, with inbreeding, would increase the numbers of animals expressing the phenotype which in turn would increase serum glucose averages.

It has been suggested that, because diabetes mellitus has a variable age of onset, the average serum glucose value of a population containing diabetics can be expected to increase with age. Our animals have shown no such increase to date. This is explained by three sets of circumstances, either separately or in combination. *M. albicaudatus* are reported to live six or more years with an average life span of over two years.[5] Our colony contained very few animals over eighteen months of age at the conclusion of this study but very many under this age. Therefore, our population may not have aged enough at present to reflect an increase. Secondly, almost all of the animals presently over eighteen months of age were in the colony when the study began and were not bled at the early scheduled ages. Their values influence the older ages averages, but not the younger ones. The opposite is true of those animals included in the younger ages averages. This may, at least in part, explain why no age effect was observed. The final set of circumstances which offers an explanation concerns young animals with severe diabetes. These severe cases of the disease usually result in the death of the animal prior to one year of age. Their extremely high serum glucose values are included in the average values of the four, six and perhaps even nine month old groups only. The animals in the colony which have had an increase in serum glucose with age would then tend to level out the overall mean as they aged, resulting in the observed lack of age effect. More closely controlled studies as the colony continues to age should elucidate the exact reason or reasons why no effect was noted at the conclusion of this study.

The relationships between weight and sex, age, inbreeding, and serum glucose values (figure 2 and tables 1 and 2) are such that, without an explanation of each effect, they may be easily misinterpreted. The decrease in mean weights as generations increase may be the expected result of inbreeding. However, the numbers and ages of animals also decrease as generations increase. Therefore, the relationship between mean weights and inbreeding, as revealed by the analyses, is probably more the result of fewer numbers and younger animals in the fourth through sixth generations than the result of inbreeding, although both are involved. As numbers, ages, and generations increase, a decreased mean weight with increased generations may truly be the expected result of inbreeding. That weight increases with age and is affected by sex are both expected findings and require no individual explanations. On the other hand, the opposite effects of weight on the serum glucose values classified as orthoglycemic and hyperglycemic requires discussion. Two factors may influence orthoglycemic values and their increase with weight (figure 2). First, it has already been established that weigh increases with age and that age has no effect on serun glucose values in these animals, as presented in thi paper. Therefore, this increase appears to be a tru positive correlation between weight and serum glu cose. Secondly, the regression lines predict that i the weights of either orthoglycemic males or fe males continued to increase, their serum glucose value would begin to fall in the hyperglycemic range. B our standards, such animals would be obese becaus the weight ranges of these animals were 100 to 22 gm. for males and 60 to 147 gm. for females. Hyper glycemia related to obesity is not unexpected as it oc curs in both man and other animals. However, the actua weights of orthoglycemic animals in this colony hav not increased to the point where hyperglycemia as sociated with obesity would result.

The significant decrease in hyperglycemic values a weight increases (figure 2) also has two consideration First, as the disease becomes progressively severe, weigh loss and serum glucose gain are a part of the syndrom This is expected and in itself could account for the re sults. The second consideration is that severe diabetes i young animals usually resulted in their deaths prior t one year of age, either spontaneously or as selecte terminations. Of the higher hyperglycemic values de picted in figure 2, 50 per cent are from animals selecte for euthanasia before they were one year old. Thes young animals with severe diabetes contributed hig serum glucose values at low weights only, due to ag and thereby increased the negative slope of the regre sion lines. The latter consideration probably had a mor significant effect on the slope of the line than di weight. The most important information learned fro these data and their analyses is that hyperglycemia not associated with obesity in *M. albicaudatus* as it in all other animal models of spontaneous diabetes me litus, except the Chinese hamster.[3]

The intermittent nature of hyperglycemia has bee documented in man.[12,15] Therefore, its occurrence i *M. albicaudatus* is not unexpected because diabetes me litus in this species appears to be very similar, in bo complexity and diversity, to what has been described i man. Of the 161 animals which have had multiple seru glucose determinations with only one hyperglycem value, some are expected to demonstrate repeated hype glycemia, with or without intermittent hyperglycemi and to progress into overt, clinical diabetes mellitus they are repeatedly monitored. Others are not expecte to show any further indications of the disease. This also in keeping with the disease as it occurs in man.

Investigations involving the morphologic characteristics of the pancreas of normal and diabetic *Mystromys,* the genetic mode of transmission of diabetes in *Mystromys,* the plasma insulin concentrations and response to glucose loading, the effects of insulin therapy, comparison of hepatic enzymes of diabetics and nondiabetics, the development of secondary complications (such as cataracts, fatty livers, glomerulosclerosis, atherosclerosis, reduced life span), and the presence of primary manifestations of diabetes are currently underway. The results of these and other studies will be reported as they are completed. While all of the data has not been collected nor analyzed, the preliminary findings of these continuing studies seem to support our belief that spontaneous diabetes mellitus in *M. albicaudatus* has a marked similarity to the disease in man.

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