Effect of Diet-induced Obesity on Glucose and Insulin Tolerance of a Rodent with a Low Insulin Response (*Acomys cahirinus*)

ARNDT GUTZEIT, ALBERT E. RENOLD, EROL CERASI, AND ELEAZAR SHAFRIR

SUMMARY

Spiny mice (*Acomys cahirinus*) from the Geneva colony tend to develop diabetes, whereas those maintained in Jerusalem do not. The role of environmental factors in the development of glucose intolerance was investigated by diet exchanges in specimens from the two colonies. Spiny mice on the Geneva diet (laboratory chow supplemented by a seed mixture containing 15% fat by weight) developed massive obesity over 8–10 months; body lipid content increased threefold compared with albino mice and was twofold higher than in spiny mice maintained on the laboratory chow in Jerusalem or in spiny mice living in their natural habitat near the Dead Sea. Spiny mice from the Geneva colony, kept on the laboratory chow alone, were as lean as animals from the Jerusalem colony. Similarly, Jerusalem *Acomys* given pellets supplemented by seeds developed marked obesity. Liver and adipose tissue enzymes in spiny mice transferred to the seed-supplemented diet showed adaptation typical for fat feeding: decrease in the capacity of glycolysis, NADPH generation, and fatty acid synthesis.

The obesity was associated with insulin resistance, evident from a negative correlation between the extent of hypoglycemia after i.v. insulin administration and body lipid content. The glucose disappearance rate (K value) was significantly reduced by obesity, but the insulin response to i.v. glucose increased only moderately. In all the *Acomys* groups studied, insulin response to i.v. glucose was markedly lower in comparison with the response in albino mice.

The following conclusions are drawn: (1) Low insulin response to glucose is a species-characteristic of spiny mice whether the animals are bred in laboratories or live in freedom. (2) Given an appropriate diet, spiny mice develop obesity, accompanied by pronounced insulin resistance. (3) Obesity may be one of the causes of the marked islet hyperplasia in laboratory-kept spiny mice, but this does not result in increased insulin output. (4) The inability of spiny mice to respond with augmented insulin secretion when insulin efficiency is reduced may be responsible for the accelerated development of glucose intolerance in this species. Thus, the liability of Geneva spiny mice to develop diabetes may be caused by the obesity-inducing diet used in this colony rather than to a specific genetic characteristic. (5) The fact that insulin resistance in spiny mice occurs without the development of hyperinsulinemia suggests that similar mechanisms may operate in the development of glucose intolerance in human, low, insulin responders. DIABETES *28*:777–784, August 1979.

The spiny mouse (*Acomys cahirinus*) is a semi-desert rodent that has been studied extensively during recent years as a model for human maturity-onset diabetes[1–3] and for carbohydrate-induced hyperlipidemia.[4,5] When bred in a laboratory environment, this species exhibits various degrees of glucose intolerance sometimes associated with spontaneous glucosuria and ketonuria.[1,2] Recently it was shown that the K value of i.v. glucose tolerance and the concomitant insulin response are decreased in normoglycemic *Acomys* as compared with albino mice or rats.[6,7] However, interspecies comparisons suffer from the limitation that the range of responses that is physiologic for one species might be pathologic for another. We compared specimens of spiny mice maintained in Geneva and Jerusalem colonies, therefore, to find out whether nutritional-environmental factors

From the Institute of Clinical Biochemistry, University of Geneva, Switzerland, and the Department of Clinical Biochemistry, Hadassah University Hospital and Hebrew University–Hadassah Medical School, Jerusalem, Israel.

Dr. Gutzeit's present address is University Eye Hospital, D-2300 Kiel, Germany.

E.C. was a Visiting Professor at the University of Geneva, on leave from the Department of Endocrinology and Metabolism, Karolinska Hospital, Stockholm, Sweden. Present address: Department of Endocrinology and Metabolism, Hadassah University Hospital, Jerusalem, Israel.

Address reprint requests to Dr. E. Shafrir, Department of Clinical Biochemistry, Hadassah University Hospital, Jerusalem, Israel.

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TABLE 1
Composition of the Geneva and Jerusalem diets

Diet		H_2O	Fat	Protein	Carbohydrate			Ash	Total calories per 100 g
					Total	Fiber	Net		
Geneva pellets	Diet 1	8.9	4.1 (10.8)	21.5 (25.1)	59.8	5.0	54.8 (64.1)	6.0	342.1
Jerusalem pellets	Diet 1	10.8	3.8 (10.2)	20.3 (24.1)	61.4	6.2	55.2 (65.7)	5.3	336.2
Seed mixture (decorticated)		6.8	15.0 (32.3)	16.2 (15.5)	58.6	3.8	54.8 (52.3)	3.4	419.0
Geneva pellets + seeds	Diet 2	7.2	13.0 (28.9)	17.2 (17.0)	58.7	4.0	54.7 (54.1)	3.9	404.6

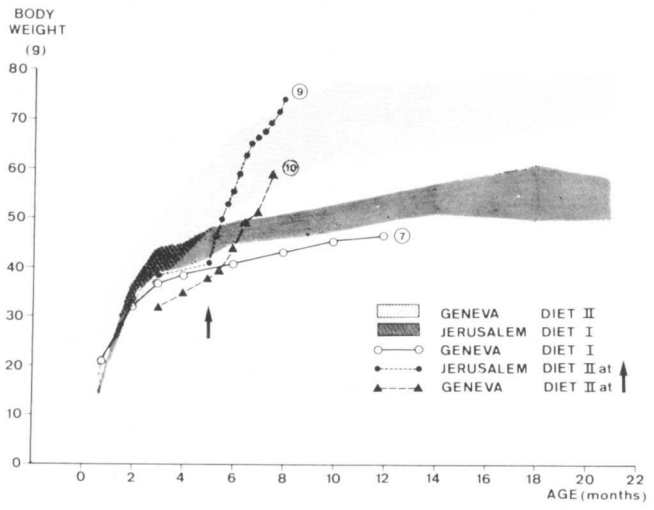
Values in the table are g/100 g wet wt; values in parentheses are percent of total calories. The seed mixture comprised about 27% sunflower, 18% wheat, 13% dari, 10% corn, and smaller quantities of hemp, pumpkin,oats, millet, and grass seeds.[1] Proportion of the decorticated seeds in diet 2 was 81.4%, disregarding the weight of the peels (12.8 g), since the animals discard them during consumption. Results in the table are means of analyses, performed on three different occasions in Jerusalem in 1975, 1976, and 1977. Vitamin supplement, added by the manufacturers per kilogram of pellets, contained at least: 12,000 U of A, 2500 U of D_3, 25 U of E, 4 mg of K, 12 μg of B_{12}, 2 mg of B_6, 6 mg of riboflavin, 50 mg of niacin, 600 mg of choline chloride, 15 mg of pantothenic acid, and 1 mg of folic acid.

are responsible for the inappropriate hyperglycemia observed only in Geneva colony. The second objective of our studies was to assess the effect of obesity on glucose tolerance in this low insulin-responding rodent species and to explore whether this model is suitable for the study of the development of glucose intolerance in human subjects.[8] Although the animals bred in Geneva were already characterized as obese,[1] this has not hitherto been quantified.

MATERIALS AND METHODS

Animals. Spiny mice (*Acomys cahirinus*) of both sexes, derived from the Geneva and the Jerusalem colonies, were studied at the age-groups of 3, 8, and 24–36 months. Groups of Jerusalem spiny mice were transferred to Geneva by plane at the age of 8 to 10 wk. In addition, animals freshly trapped near the Dead Sea were investigated on the day of capture. In some experiments, Swiss albino mice were used as a control species. They were age- and weight-matched to 3-mo-old Geneva *Acomys* fed diet 2 (see below). Both the Geneva and Jerusalem animal rooms were kept at 24 to 26 °C, on a 12/12-h light and darkness schedule. The Dead Sea animals and the Jerusalem animals kept on diet 1 (see below) were studied in Jerusalem, the other animals in Geneva, with the exception of a group of Geneva animals on diet 2 despatched to Jerusalem for enzyme activity studies. The tolerance tests were performed by the same person (A.G.). No animal studied was glucosuric.

FIGURE 1. Growth curves of Geneva- and Jerusalem-bred spiny mice. The shaded areas denote the mean ± SE body weight in the Geneva colony on diet 2 (pellets and seeds) and Jerusalem colony on diet 1 (pellets only). The individual curves represent mean values for animals that have been transferred from one diet to another. Number of animals is indicated in circles.



Diets. Spiny mice of the Jerusalem colony were fed on a pelleted laboratory chow (Amrod 931, Anbar Granot, Hadera, Israel). Albino and spiny mice of the Geneva colony received a pelleted chow from another manufacturer (U.A.R. Company, Villemoisson, Epinay/Orge, France). Since both kinds of pellets had a similar composition (Table 1), they were coded as diet 1. Spiny mice of the Geneva colony received a mixture of seeds (diet 2, Table 1) in addition to pellets ad libitum, since their reproductive capacity was more normal on this diet in earlier studies. The composition of the diets and of the seed mixture is given in Table 1.

Glucose tolerance test. Glucose was administered i.v. to animals fed ad libitum that were anesthetized with pentobarbital (Nembutal, Abbott Laboratories, Chicago, Ill.), 50 mg/kg i.p. and 25 mg/kg s.c., and the test was performed as described previously.[6] In brief, the femoral vein was exposed under a dissection microscope, and 1.5 g/kg glucose was injected within 2 min. At the indicated time intervals, blood samples were collected from the retroorbital venous plexus into heparinized hematocrit tubes.

Insulin tolerance test. The animals were prepared as above, and 0.2 U/kg of glucagon-free insulin (Actrapid, Novo Laboratories, Copenhagen) was injected rapidly. Blood was collected before and 15 min after the insulin injection, since the nadir in blood glucose occurred at this time in pilot experiments.

Enzyme activities were determined in liver and epididymal adipose tissue of spiny mice that were decapitated. The tissues were homogenized (1:3, w/v) in 0.20 M sucrose solution containing 20 mM triethanolamine, pH 7.4, 1 mM Na_2 EDTA, and 1 mM dithioerythreitol. Liver homogenates were centrifuged for 30 min at 100,000 *g* and 4 °C. Adipose tissue homogenates were centrifuged at 4 °C at 6000 *g* for 10 min, the fat layer was discarded, and the homogenate was respun at 100,000 *g* for 30 min. The supernatant fluids were used for the assay of pyruvate kinase, NADP-malate de-

TABLE 2
Body lipids, plasma glucose and insulin, and pancreatic insulin concentration in the animal groups

Animal groups	*n*	Age (months)	Body weight (g)	Total body lipids (% of body wt)	Plasma glucose (mg/dl)	Plasma insulin (ng/ml)	Pancreatic insulin (ng/mg)
			Diet 1				
Albino mice	6	3	37.9 ± 0.9	10.9 ± 1.2	164 ± 7	1.7 ± 0.3	34 ± 8**
Geneva *Acomys*	11	3	30.2 ± 0.9	17.5 ± 0.6*	122 ± 5	1.7 ± 0.2	281 ± 38
Jerusalem *Acomys*	11	3	32.4 ± 1.1	14.4 ± 1.1*	110 ± 6	1.8 ± 0.1	192 ± 13
Jerusalem *Acomys*	13	24–36	49.3 ± 3.4	22.5 ± 3.5*	—	—	212 ± 18
Dead Sea *Acomys*	12	?	32.3 ± 1.2	15.1 ± 0.4*	88 ± 4	0.5 ± 0.03‖	37 ± 3**
			Diet 2				
Geneva *Acomys*	10	3	38.6 ± 1.2	29.4 ± 2.5†	106 ± 5	1.3 ± 0.1	239 ± 20
Geneva *Acomys*	15	24–36	69.5 ± 2.9	39.2 ± 1.8	95 ± 6	—	398 ± 58
Geneva *Acomys*: diet 1 until 5 mo, then diet 2 until 8 mo	10	8	59.8 ± 2.5	56.1 ± 4.2‡	113 ± 4	2.0 ± 0.3	315 ± 25
Jerusalem *Acomys*: diet 1 until 5 mo, then diet 2 until 8 mo	9	8	73.4 ± 2.9	54.0 ± 1.7‡	179 ± 4§	1.6 ± 0.2	223 ± 16

* $P < 0.01$ or less compared with albino mice.
† $P < 0.001$ compared with age-matched Geneva *Acomys* on diet 1.
‡ $P < 0.001$ compared with Jerusalem *Acomys*, age 24–36 months, on diet 1.
§ $P < 0.001$ compared with other *Acomys* groups.
‖ $P < 0.01$ or less compared with all other groups.
** $P < 0.001$ compared with all other groups.

hydrogenase (malate enzyme), ATP-citrate lyase (citrate cleavage enzyme), and acetyl-CoA carboxylase, according to methods described in a previous publication.[9]

For the determination of liver glucokinase and adipose tissue hexokinase activities according to Sharma et al.[10] the homogenates were prepared in 0.15 M KCl solution, pH 7.4, containing 5 mM $MgCl_2$, 5 mM Na_2 EDTA, and 1 mM dithioerythreitol and were centrifuged as described above.

All enzyme activities were measured at 37 °C and expressed as micromoles of substrate metabolized per minute per milligram of protein in the 100,000 *g* supernatant. Protein was determined by a modification of the method of Lowry et al.[11]

Analytic procedures. Plasma glucose was measured by the glucose oxidase technique.[12] Plasma insulin was determined by radioimmunoassay, using a micromethod.[6,13] Human insulin was used as standard for *Acomys* insulin, since dilutions of spiny mouse plasma gave curves parallel to those of standard human insulin. For albino mouse plasma assays, mouse insulin standards were used. Pancreatic insulin was determined in diluted acid-ethanol extracts of the pancreas obtained according to Scott and Fisher,[14] after sonication of the tissue.

Total body fat was measured as described by Folch et al.,[15] the whole animal being homogenized in a Sorvall mixer.

RESULTS

Animal growth on different diets. Figure 1 documents the basic observation that the Geneva *Acomys*, kept on diet 2, were heavier than *Acomys* from Jerusalem maintained on diet 1, a significant difference being observed from age 6 mo and older.

To investigate the factors responsible for the body weight difference between the two colonies, a group of spiny mice was raised in Jerusalem until the age of 2 months, was then transferred to Geneva, and was kept on diet 1 until the age of 5 months, at which time diet 2 was initiated (arrow in figure 1). The body weight, which followed closely the Jerusalem pattern until this time, increased dramatically, reaching the upper limit for the Geneva colony (on diet 2) at the age of 8 months. In a parallel experiment, spiny mice born in Geneva were kept on diet 1 from weaning until the age of 5 mo and were then transferred to diet 2. Figure 1 demonstrates that body weight in these animals increased in a similar, though somewhat more sluggish, manner. Finally, Geneva spiny mice kept on diet 1 from weaning to 12 months showed a growth curve similar to that of the Jerusalem colony on diet 1 (Figure 1).

Body fat content. The total body lipid content of the various animal groups of this study is presented in Table 2. Compared with albino mice, matched for age and weight, the spiny mice raised on diet 2 showed a threefold increase in body fat. Spiny mice, kept on pellets alone (diet 1) until the age of 3 months in Geneva or in Jerusalem, gained much less fat, their body lipids being only 50% in excess of that of albino mice. Interestingly, the Geneva *Acomys*, kept on diet 1, were slightly more obese (17.5 ± 0.6 versus 14.4 ± 1.1% fat, $P < 0.01$) than the Jerusalem animals raised on diet 1. Animals captured in the desert and having body weights in the range of the laboratory-raised *Acomys* on diet 1 had a fat content similar to that of the Jerusalem animals. Thus, major obesity seems to be closely related to diet 2, i.e., the seed supplementation.

The obesity-inducing effect of the seed mixture is further illustrated by the whole body fat content of *Acomys* (from

TABLE 3
Activities of enzymes of glycolysis and fatty acid synthesis in the liver and adipose tissue of spiny mice maintained on different diets for 3 months

	Liver				Adipose tissue		
	Gluco-kinase	Pyruvate kinase	NADP-malate dehydrogenase	Acetyl-CoA carboxylase	Hexo-kinase	NADP-malate dehydrogenase	Acetyl-CoA carboxylase
Jerusalem *Acomys* Diet 1 (8)	3.2 ± 0.4	107 ± 9	15 ± 1	3.9 ± 0.3	35 ± 4	30 ± 4	3.2 ± 0.3
Jerusalem *Acomys* Diet 2 (6)	1.4 ± 0.2*	66 ± 5*	9 ± 1*	2.6 ± 0.3*	18 ± 3*	15 ± 3*	2.3 ± 0.2*
Geneva *Acomys* Diet 2 (6)	1.1 ± 0.2*	54 ± 6*	7 ± 1*	2.2 ± 0.2*	10 ± 2*	7 ± 2*	1.9 ± 0.2*

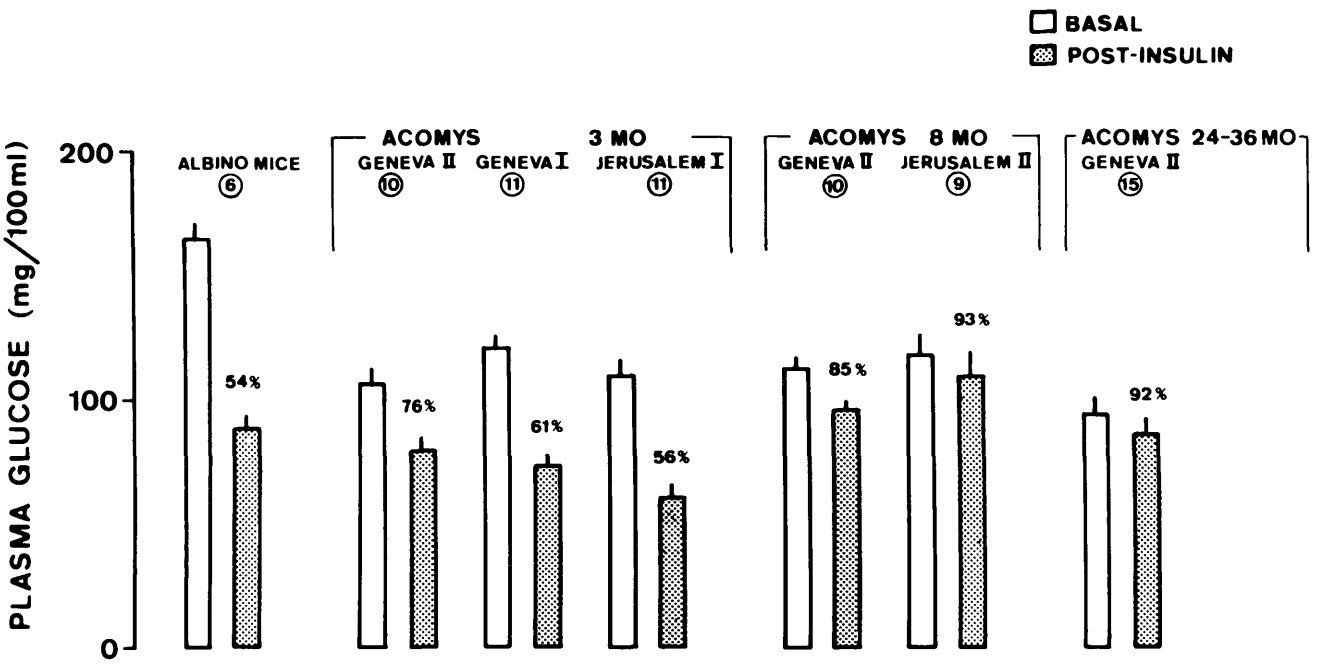
Values are means ± SE for the numbers of animals indicated in parentheses. Statistically significant differences from *Acomys* on diet 1 ($P < 0.02$ at least) are indicated by an asterisk.

both colonies) kept on diet 1 until the age of 5 months, then given diet 2 for 3 months. More than 50% of body weight in these animals consisted of lipids. That this is not due to the age of the animals is demonstrated by the values obtained in *Acomys* 24–36 months old: Jerusalem animals on diet 1 throughout life increased their body lipid mass only to 22.5% (Table 2). Geneva animals on diet 2 had 39.3% fat at this age and could be reduced to 27.9% when switched to diet 1 two months before sacrifice (data not shown).

As may be seen from Table 2, no animal group demonstrated clear hyperglycemia in the fed state. As a matter of fact, albino mice had higher plasma glucose concentrations than most spiny mice, with the exception of the Jerusalem spiny mice rendered obese between ages 5 and 8 months. No significant differences were found in plasma insulin concentration between the different groups, the only exception being the recently captured Dead Sea spiny mice, in whom significantly lower plasma insulin values were found. In contrast to the circulating insulin levels, pancreatic insulin content was six- to twelvefold higher in spiny mice than in albino mice, confirming previous data.[1–3] Again, Dead Sea animals were the exception, pancreatic insulin content in these being similar to that of Swiss mice. In general, the Geneva *Acomys* seemed to have higher pancreatic insulin values, especially in the obese, older age groups.

Enzyme activity changes. The effect of the diets on the glycolytic and lipogenic capacities in the liver and adipose tissue is seen in Table 3. Transfer of the Jerusalem-bred spiny mice, kept on diet 1, to the seed-supplemented diet 2 induced a marked fall in liver glucokinase and pyruvate kinase and in adipose tissue hexokinase activities, the rate-limiting enzymes of glycolysis. Likewise the activity of NADP-malate dehydrogenase, concerned with NADPH generation, and acetyl-CoA carboxylase, which directly controls fatty acid synthesis, fell both in the liver and adipose tissue. The low activities of these enzymes, caused by substituting diet 2 for diet 1 in the Jerusalem-bred spiny

FIGURE 2. Insulin tolerance test in spiny and albino mice. Plasma glucose was measured before and 15 min after i.v. injection of 0.2 U/kg of insulin to animals fed ad libitum. The bars represent mean ± SE for the number of animals given in circles. The numbers above the hatched columns indicate the postinsulin plasma glucose as percentage of the basal values. Animal groups and diets are as those described in Table 2.



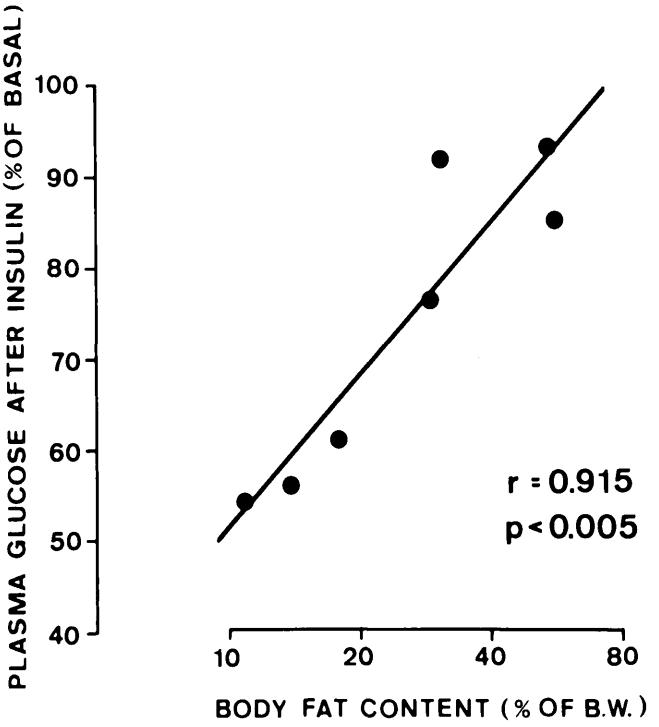


FIGURE 3. Correlation between plasma glucose concentration after i.v. insulin and body lipid content. The original data are presented in Figure 2 and Table 2.

mice, were similar to those found in the Geneva-bred animals maintained on diet 2 from weaning.

Insulin tolerance tests. The effect of obesity on the sensitivity to insulin in vivo was investigated by measuring plasma glucose after i.v. injection of exogenous insulin. Figure 2 demonstrates clearly that the largest fall in plasma glucose was observed in albino mice. This animal group, however, showed significantly higher plasma glucose values than any other of the animal groups tested (164 ± 7 versus 124 ± 5 mg/dl or less, $P < 0.001$). On a percentage basis, lean *Acomys* from Geneva or Jerusalem (both on diet 1) exhibited a similar sensitivity to insulin as albino mice (plasma glucose fell 39% in Geneva, 44% in Jerusalem spiny mice, and 46% in albino mice, all differences being significant at $P < 0.001$). The 3-month-old Geneva spiny mice on diet 1 were markedly more sensitive to insulin than a similar age-matched group on diet 2, their plasma glucose dropping by 39% and 24%, respectively, in the latter ($P < 0.05$).

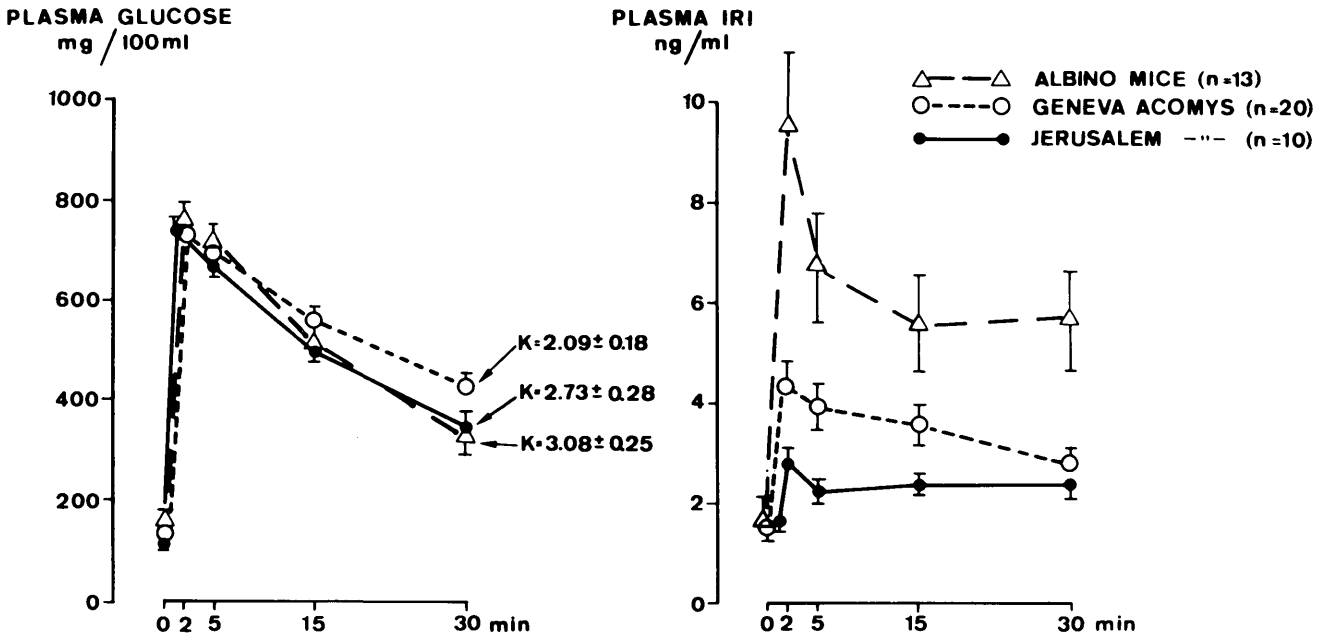
Finally, the older and more obese animals (8 months or 24–36 months old) on diet 2 showed markedly reduced insulin sensitivity, the glucose fall being statistically insignificant in all three groups. The insensitivity was not due to the age of the animals, since a group of 12-mo-old Geneva *Acomys* (not shown in Figure 2) on diet 1 showed a drop in plasma glucose after insulin injection from 122 ± 12 to 85 ± 11 mg/dl, i.e., 30.3% ($n = 6$, $P < 0.02$).

As shown in Figure 3, a highly significant correlation was obtained between the postinsulin blood glucose (in percent of basal) and the body fat content of the animal groups studied.

Glucose tolerance tests. The glucose disappearance and insulin release pattern after glucose was injected i.v. in *Acomys* from Geneva and from Jerusalem, given diets 2 and 1, respectively, is shown in Figure 4. Swiss albino mice, weight- and age-matched to the Geneva *Acomys*, were used as controls. It is clearly seen that all *Acomys* had a much lower insulin response than the albino mice; the kinetics of the response were not modified, however. The less obese Jerusalem *Acomys* displayed a lower response than the animals from Geneva. The glucose disappearance constant K was highest in albino mice and lowest in the Geneva *Acomys* ($P < 0.01$).

The effect of the diet was further investigated in *Acomys* from Geneva (Figure 5). Animals kept on diet 1 since wean-

FIGURE 4. Plasma glucose disappearance and insulin response after i.v. glucose injection to animals fed ad libitum. Glucose, 1.5 g/kg, was given at 0 min. The albino mice and Jerusalem *Acomys* were on diet 1, while Geneva *Acomys* were on diet 2. All animals were 3 months old.



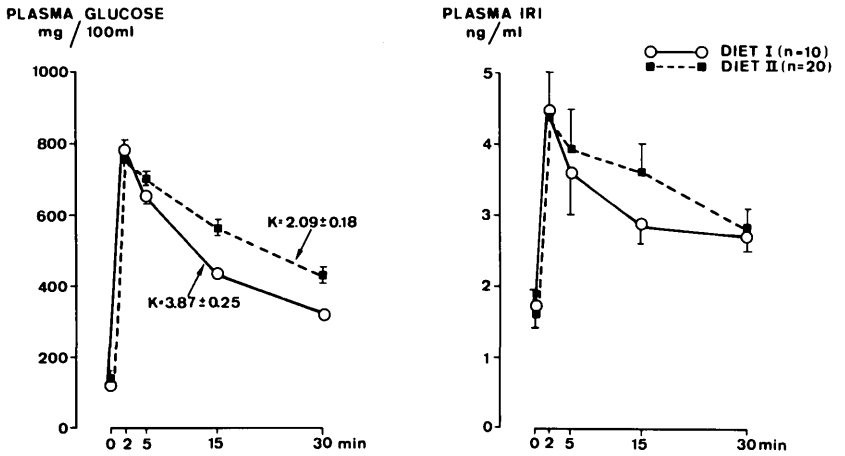


FIGURE 5. Plasma glucose disappearance rate and insulin response after i.v. glucose (1.5 g/kg) in 3-month-old, ad libitum–fed *Acomys* from the Geneva colony maintained on pellets only (diet 1) or on pellets plus seeds (diet 2) since weaning. Body lipid content was 17.5 ± 0.6% of total body weight when animals were on diet 1 and 29.4 ± 2.5% when on diet 2.

ing had a better glucose disappearance than those on diet 2 ($P < 0.001$). In contrast, the plasma insulin values were not significantly different in these two groups of *Acomys*.

A group of seven Jerusalem *Acomys* was also studied on two occasions—at the age of 3 months while on diet 1 and at 8 months after 3 months of diet 2 (Figure 6). Basal plasma glucose was higher in the obese state (179 ± 4 versus 132 ± 10 mg/dl, $P < 0.001$) and showed higher levels throughout the glucose tolerance test. The K value was significantly lower on diet 2 ($P < 0.02$). The plasma insulin concentrations after the glucose injection were higher in the obese animals. However, the insulinogenic index of the response (insulin area divided by glucose area) was unchanged (0.23 ± 0.07 versus 0.15 ± 0.03).

DISCUSSION

The data presented here indicate that, in many respects, the spiny mice are analogous to human subjects with chemical or latent diabetes (decreased K value, decreased insulin output, obesity, liability to develop a mild form of diabetes), and they are a good laboratory model for this condition.

The appearance of spontaneous diabetes was originally described in the Geneva colony of *Acomys*,[1,2] which stems from animals captured in the surroundings of Jerusalem in the late 1950s.[1] The Jerusalem spiny mice were caught in the same region in 1967 but no spontaneous hyperglycemia or glucosuria has ever been discovered in this colony.[17] This discrepancy suggested that laboratory-environmental factors may be important to develop the syndrome.

One important difference between the two colonies regards body weight, which is higher in the Geneva *Acomys* for the major part of their life span (Figure 1). Our studies show that the weight gain is not due to genetic differences, since animals in both colonies could be kept lean or rendered obese by appropriate diet. Interestingly, spiny mice that had never before been offered seeds, once given this diet increased promptly and considerably in body weight, the increase being almost exclusively due to gain in body lipids (Table 2). It is highly probable, therefore, that the obesity-inducing effect of the seeds is due to their high fat content relative to the regular laboratory chow and the fact that the spiny mice consumed large amounts of seeds in addition to the pellets. This behavior seems to be specific for spiny mice, since a group of albino mice, given diet 2 from 2 to 6 months of age, did not gain more weight than mice kept on diet 1 (A. Gutzeit, unpublished observations). This also indicates that food intake in *Acomys* is regulated in a large measure by taste rather than by caloric needs.

Enzyme responses in the liver and adipose tissue of animals maintained on the seed-supplemented diet were typical of a high fat ration, featuring the suppression of the pathways of glycolysis and lipogenesis. The weight gain was mainly confined to adipose tissue and was not accompanied by hyperlipidemia or liver fat accumulation (E.

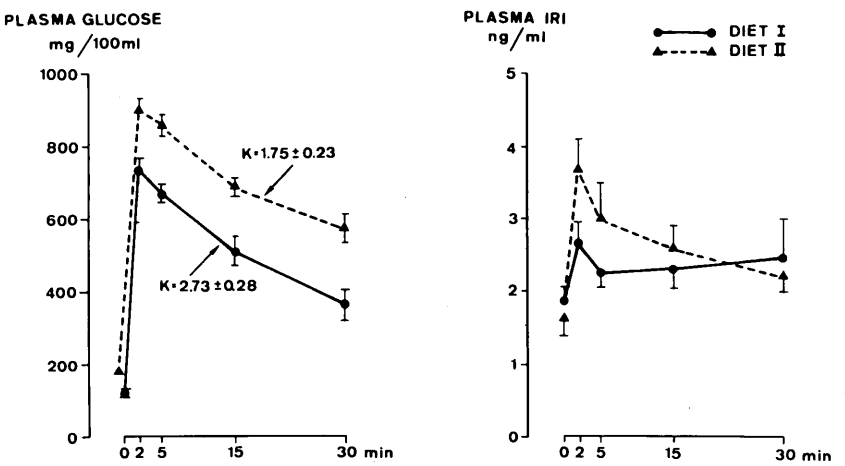


FIGURE 6. Effect of diet on glucose disappearance and insulin response after i.v. glucose (1.5 g/kg) in *Acomys* from the Jerusalem colony. A group of seven animals was given diet 1 from weaning until the age of 5 mo and was then changed to diet 2. An i.v. glucose tolerance test was performed in the same animals at the age of 3 months (diet 1) and at the age of 8 months, after a 3-month period of diet 2. The body lipid content in similarly treated animals was 14.4 ± 1.1% of total body weight at the age of 3 months and 56.1 ± 4.2% at 8 months.

Shafrir, unpublished observations). On the other hand, spiny mice challenged with synthetic carbohydrate diets for a few months did not respond with excessive weight gain or hyperinsulinemia, although the pancreatic insulin content did increase.[5] Furthermore, there was a marked hyperlipidemia associated with liver hypertrophy and a pronounced adaptive induction of enzymes of glycolysis and lipogenesis in the liver but not in adipose tissue.[5] The liver increased its share in carbohydrate intake and conversion to lipids, which were in part retained in situ or in the circulation. Thus, the peripheral weight gain on fat-rich diet as opposed to hepatomegaly with hyperlipidemia on carbohydrate diets seem to characterize the responses of a rodent with limited insulin secretion capacity: insulin requirement appears to be less critical for the deposition of preformed fat than for the disposal of carbohydrate-derived fat.

Several studies in man and in laboratory animals showed that obesity decreases the sensitivity of the tissues to insulin.[18–23] In our present study, the effect of obesity on insulin-induced hypoglycemia is evident: the insulin tolerance decreased with increasing body weight. Since the heaviest animals were also the oldest ones, one may argue that the reduced effectiveness of insulin might be related to age. However, the significant negative correlation between insulin effectiveness and body lipid content (Figure 3) suggests that insulin resistance in these animals is indeed closely related to obesity.

It is generally accepted that insulin resistance in obesity is due to downregulation of receptors, induced by the hyperinsulinism that prevails in obesity (for a review, see ref. 24). In spiny mice, however, obesity was induced without major enhancement of insulin secretion. Our data clearly show that plasma insulin responses during the i.v. glucose load were not appreciably higher in obese spiny mice than in leaner ones, the basal plasma insulin concentrations were not different, and, certainly, in no group was gross hyperinsulinism present similar to that found in obese man[25,26] or in mice with the *ob/ob* syndrome.[20] We assume, therefore, that in low insulin-responding *Acomys*, major hyperinsulinemia is not essential for developing hormone resistance. Obesity apparently induces other changes, leading to gross resistance to the blood glucose–lowering effect of the hormone. Evidently, this hypothesis needs further experimental exploration.

Our findings further emphasize the basic characteristic of *Acomys cahirinus*, namely its low insulin-secretory capacity.[5–7,27,29] This species, even when raised under different laboratory conditions or investigated in its natural surroundings, repeatedly presents low insulin response to glucose or to other secretagogues in comparison with albino mice or rats.[5,27,29] The data presented here have a greater pathophysiologic bearing: the ability of the islets to be modulated by chronic stimulators like obesity is also low. Obviously, the constellation of hypoinsulinism together with profound insensitivity to insulin in obesity cannot be but deleterious for the control of glucose homeostasis in these animals. This is reflected in the lower K values seen in obese animals compared with lean *Acomys* and in the higher plasma glucose concentrations observed in the obese Jerusalem animals (Figure 6).

It may be suggested that one of the reasons for the occurrence of overt diabetes in the Geneva but not the Jerusalem *Acomys* colony is the obesity that developed in Geneva as a consequence of the diet selected. Ketonuria with glucosuria was induced in chemically diabetic hamsters when placed on a high fat diet,[30] and the evolution of overt diabetes with ketoacidosis in long-standing, gross human obesity is reported.[31] Obesity would probably have a more marked effect on blood glucose control in spiny mice if some, albeit limited, adaptation of the islet function had not occurred. This is reflected by the higher pancreatic insulin content and the previous observations that islet hyperplasia is more pronounced in Geneva than in Jerusalem *Acomys*.[1,17] The reason for the lack of islet hyperplasia (F. Malaisse-Lagae and E. Shafrir, unpublished data) and presence of normal pancreatic insulin concentrations in desert *Acomys* is not known but may be related to their low caloric intake.

To conclude, we suggest that, in *Acomys* as in low insulin-responding man,[8,32,33] low insulin-secretory capacity is a major factor predisposing to glucose intolerance or to diabetes. When the insulin requirement is increased as a result of reduction of sensitivity to the hormone, like in obesity, the islets may not be able to adapt by a major increase in hormone secretion, and glucose intolerance may result. In this sense, obesity may be regarded as an additive factor in the development of diabetes in *Acomys*, as in low insulin–responding man.[34]

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