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Interrelationships between obesity and diabetes

BY LIESELOTTE HERBERG
Diabetes Research Institute at the Heinrich-Heine-University of Düsseldorf, Auf'm Hennekamp 65, 4000 Düsseldorf, Germany

In 1936 it was demonstrated that more than 50% of diabetic patients of both sexes and 15–25% of female diabetics were overweight by about 20 and 40% respectively (Joslin *et al.* 1936). Later studies revealed interrelationships between obesity and diabetes which can be studied best in small laboratory rodents exhibiting obesity–diabetes syndromes. In these animals obesity usually precedes diabetes. Hyperinsulinaemia, insulin resistance, increased adipose tissue mass and a diminished glucose tolerance are common in both the obese and the diabetic state. If, however, increased gluconeogenesis interferes with blood glucose regulation, inappropriate hyperglycaemia develops. This is characteristic of animal diabetes. However, not all types of adiposity show obesity–diabetes interrelationships.

Cyclic obesity is part of an adaptation syndrome. Depending on the intensity of light, hibernators or migrating animals such as various birds or reindeer increase their energy intake and multiply their adipose tissue mass. At the beginning of arousal of the subsequent hibernation period or during the following migration, the adipose depots will be mobilized and body-weight drops. Thus, periods of over-, normal- or even under-weight succeed one another. A similar type of obesity is seen in animals living in desert or semi-desert areas. In times when plenty of food is available the animals become hyperphagic and store the surplus energy as adipose tissue. During dry spells when food becomes sparse the animals live on their fat depots. If, however, these animals are maintained under laboratory conditions with abundant food, the advantage becomes a disadvantage: the animals exhibit permanent obesity with hyperinsulinaemia and inappropriate hyperglycaemia.

This type of obesity is present in sand rats, Spiny mice, and Djungarian hamsters and is suggested to be dependent on one or more traits called 'Thrifty gene' (Neel, 1962). The other type of permanent obesity which frequently precedes diabetes is also genetically determined and known to occur in small laboratory rodents. Mice and rats developing the obesity–diabetes syndrome are either monogenic or polygenic mutants (Table 1). Although these mutants have various metabolic phenomena in common, their phenotypes are more or less affected by factors such as strain, age, sex, the localization

Table 1. *Rodents with obesity–diabetes syndromes*

Common name	Gene symbol
Single gene mutations	
Yellow obese mouse	A^y A^{vy} A^{iy}
Adipose mouse	*Ad*
Obese mouse	*ob*
Diabetes mouse	*db*
Fat mouse	*fat*
Tubby mouse	*tub*
Zucker fatty rat	*fa*
Polygenic mutations	
NZO mouse (New Zealand obese)	
PBB/Ld mouse	
M16 mouse	
KK mouse	
Sand rat	
Spiny mouse	
Djungarian hamster	

type of obesity, and environmental influences such as nutrition and exercise. In experimental diabetes research the most frequently used rodents are the obese mouse, the diabetes mouse, the NZO mouse, and the Zucker fatty (*fa/fa*) rat. In the following discussion these animals will be described with respect to hyperinsulinaemia, insulin resistance, increased adipose tissue mass, diminished glucose tolerance, increased gluconeogenesis, and inappropriate hyperglycaemia.

HYPERINSULINAEMIA

The age-related pattern of plasma insulin in BL/6J-*ob/ob* and BL/KsJ-*db/db* mice as well as in the respective controls is depicted in Table 2. As can be seen from the analysis of variance, plasma insulin levels are significantly affected by strain, age, and the interaction strain × age. Hyperinsulinaemia can be detected first when the mice are about 6 weeks of age. In this age-group plasma insulin is about twice as high in BL/KsJ-*db/db* when compared with BL/6J-*ob/ob*. In old mice, however, the highest plasma insulin levels occur in BL/6J-*ob/ob*. On comparing the mutants with their controls it is obvious that in BL/6J-*ob/ob* an increased insulin secretion is already present in 6–16-d-old pups. In BL/KsJ-*db/db*, however, plasma insulin levels do not exceed the controls before the animals have reached an age of about 30 d.

The differences in plasma insulin in old obese and diabetes mice with the BL/6J and BL/KsJ background respectively can be understood in the light of pancreas histology. Islets from both obese and diabetes mice are both more numerous and larger than those from the respective controls. However, whereas islets from *ob/ob* mice irrespective of age, and islets from young *db/db* mice are well stained by aldehyde-fuchsin (Halmi, 1952; Plate 1), which reflects a high insulin content, islets from old *db/db* mice exhibit a weak staining (Herberg, 1982). Accordingly, in 7-month-old obese mice pancreatic insulin content was observed to be ten times higher than in 5–6-week-old mutants (Malaisse *et al.* 1968). Since pancreatic insulin content is high in young *db/db* mice and clearly
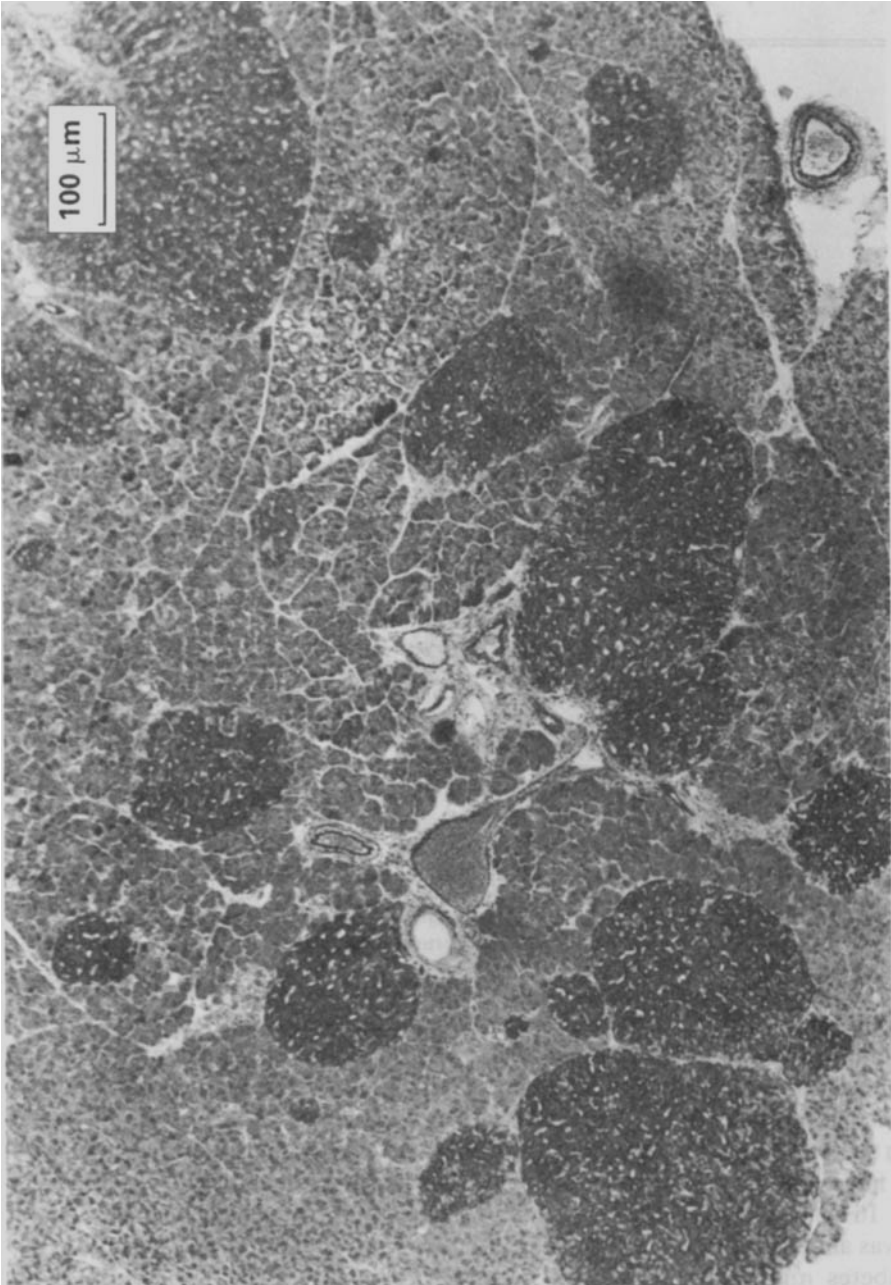
Plate 1. Pancreatic islets of a 5-month-old BL/6J-*ob/ob* mouse. Aldehyde–fuchsin staining according to Halmi (1952).

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Table 2. *Pattern of plasma insulin (IRI) in BL/6J-+/+, BL/6J-ob/ob, BL/KsJ-+/+ and BL/KsJ-db/db mice*

| Strain/line | Age (d) | Plasma insulin (µU/ml) | | | No. of mice |
		Mean	Geometric mean	1 SD	
6J-+/+	6–16	6·45	10·50	3·96	32
	18–22	7·08	18·02	2·78	31
	28–32	8·00	13·92	4·59	26
	45–55	7·59	13·83	4·17	21
	>1 year	21·60	41·69	11·19	6
6J-*ob/ob*	6–16	13·54	24·85	7·38	29
	18–22	8·52	29·58	2·45	35
	28–32	9·08	22·66	3·64	19
	45–55	93·09	202·85	42·72	29
	>1 year	606·58	1 140·75	322·54	5
KsJ-+/+	6–16	6·00	15·81	2·28	33
	18–22	7·63	16·53	3·52	32
	28–32	6·10	11·70	3·18	30
	45–55	11·61	22·81	5·91	21
	>1 year	10·21	21·05	4·96	5
KsJ-*db/db*	6–16	7·50	19·02	2·96	24
	18–22	5·32	16·58	1·71	44
	28–32	12·39	22·72	6·75	21
	45–55	165·95	250·77	109·82	22
	>1 year	224·15	501·96	100·10	5
	Source of variance	SS	df	MS	F value
	Strain/line	1·679	3	0·559	63·423*
	Age	3·373	4	0·843	95·550*
	Strain/line × age	1·868	12	0·155	17·643*
	Residual		450	0·008	

SS, sum of squares; MS, mean square.
* Statistical significance as determined by analysis of variance.

lower in old diabetes mice it can be concluded that insulin production decreases with age. As has been shown by Leiter *et al*. (1981) insulin production is greatly affected by nutrients; feeding of a 830 g casein and 0 g sucrose/kg diet results in pancreatic insulin concentrations which are about twice as high as those in high-carbohydrate-diet-fed age-matched diabetes mice. Furthermore, in 7-month-old obese mice glucose-induced insulin secretion in vitro was about twenty-three times higher than that in 5–6-week-old obese mice and fifteen times higher than that in age-matched controls (Malaisee *et al*. 1968). In contrast, in 7-month-old diabetes mice glucose-induced insulin secretion in vitro was about four times lower than that in 4-month-old mutants (Berglund *et al*. 1978). In diabetes mice not only insulin production but also insulin secretion is impaired (Berglund *et al*. 1978). The secretory defect was shown to be in the stimulus-secretion coupling of glucose-induced insulin release that is manifest as inability of glucose to raise the cytosolic Ca^{2+} concentration sufficiently (Siegel *et al*. 1980). In both adult C57BL/6J-*ob/ob* mice (Herberg *et al*. 1970) and Zucker *fa/fa* rats (L. Herberg, unpublished results) a glucose load in vivo can be followed by a drop in plasma insulin.

Catecholamines like corticosterone reflect the stressing of the animals. To clarify whether or not catecholamines are involved in this phenomenon we studied glucose-induced insulin secretion as well as that induced by arginine in vivo in Zucker *fa/fa* rats and their *Fa/Fa* controls. While in *Fa/Fa* rats a glucose load resulted in an increase in insulin from 0·98 to 1·60 ng/ml ($P<0·01$; values not shown) in *fa/fa* rats plasma insulin clearly decreased from 19·36 to 11·16 ng/ml (Table 3). Plasma catecholamine levels remained unchanged in both lines of Zucker rats. In lean *Fa/Fa* (values not shown) and obese *fa/fa* rats (Table 4) arginine-stimulated insulin secretion increased by factors of two and four respectively. Since epinephrine and norepinephrine significantly increased in both obese and lean animals a causal relationship between the drop in plasma insulin after a glucose load and plasma catecholamine levels can be excluded. The reason why these animals respond to glucose with a decrease rather than an increase to glucose challenge remains obscure.

Table 3. *Effect of glucose load (25 mg glucose/kg body-weight intraperitoneally) in 16 h fasted, conscious, male Zucker* fa/fa *rats*

(Mean values with their standard errors)

		Body-wt (g)	Blood glucose (mg/l)	Plasma IRI (ng/ml)	Epine-phrine (pg/ml)	*n*-Epine-phrine (pg/ml)	Dopamine (pg/ml)	Corti-costerone (pg/ml)
Before:	Mean	524·5	1 015	19·36	458	956	299	369 850
	SE	25·7	65	2·47	67	153	19	26 689
	n	8	8	8	8	8	8	8
Statistical significance of difference			$P<0·001$	$P<0·05$	NS	NS	NS	NS
After:	Mean		3 699	11·16	792	872	229	443 113
	SE		617	2·28	147	157	39	17 763
	n		8	8	6	6	6	6

NS, not significant; IRI, immunoreactive insulin.

Table 4. *Effect of arginine load (20 mg/kg body-weight intraperitoneally) in 16 h fasted, conscious, male Zucker* fa/fa *rats*

(Mean values with their standard errors)

		Body-wt (g)	Blood glucose (mg/l)	Plasma IRI (ng/ml)	Epine-phrine (pg/ml)	*n*-Epine-phrine (pg/ml)	Dopamine (pg/ml)	Corti-costerone (pg/ml)
Before:	Mean	547·3	864	15·78	427	1 013	310	428 775
	SE	27·7	58	2·28	61	128	22	39 239
	n	8	8	8	6	6	6	8
Statistical significance of difference			$P<0·001$	$P<0·001$	$P<0·01$	$P<0·05$	NS	NS
After:	Mean		2 095	61·31	4 334	2 098	276	497 513
	SE		157	8·01	1 013	266	52	10 707
	n		8	8	8	8	8	8

NS, not significant; IRI, immunoreactive insulin.

INSULIN RESISTANCE

Recently it was reported that transplantation of islets from coisogenic controls into hyperglycaemic *db/db* mice failed to induce a decrease in blood glucose levels (Barker *et al*. 1977). In BL/6J-*ob/ob* mice we observed an age- or weight-related pattern of insulin resistance in vivo (Table 5). In animals weighing about 40 g an insulin injection was followed by a drop in blood glucose to 55% of the pre-injection level. Obese mice weighing 53 and 71 g responded to insulin by a drop to 73 and 80% respectively. Restriction of energy intake leading to only a small reduction in body-weight failed to restore insulin sensitivity in vivo. Insulin resistance in muscle and adipose tissue of obese mice has been reported by Stauffacher *et al*. (1965) and subsequently by various other investigators.

In BL/6J-*ob/ob* mice the age- or weight-related pattern of insulin resistance in vivo was also present in adipose tissue in vitro. Glucose oxidation and glucose incorporation into adipose tissue were similar in obese mice and their lean controls until weaning (Fig. 1). With increasing age and weight of the obese animals both glucose oxidation and glucose incorporation decreased to values which were less than 50% of those seen in the controls. Adipose tissue from lean BL/6J mice responded to increasing insulin concentrations in the medium with increasing metabolic activity (values not shown). Therefore, the apparent continuous decrease in glucose oxidation and glucose incorporation into adipose tissue samples from obese mice merely reflects insulin insensitivity of the tissue which also responded similarly to increasing insulin concentrations.

BL/KsJ-*db/db* differed from BL/KsJ-+/+ mice in that the age- or weight-metabolic activity relationship was altered (Fig. 2). Adipose tissue from diabetes mice of only

Table 5. *Insulin sensitivity in C57BL/6J*-ob/ob *mice*

(Mean values with their standard errors)

| Dietary regimen | Body-wt (g) | | Blood glucose (mg/l) | | | | | |
| | | | Before insulin | | Statistical significance of difference: $P<$ | 60 min after 20 U insulin/kg body-wt ip | | Per cent of basal value |
	Mean	SE	Mean	SE		Mean	SE	
I	40·17 12	3·31	2 275·8 12	223·3	*0·001*	1 261·7 12	85·8	55·44
I	53·10 30	1·36	2 033·3 30	161·9	*0·001*	1 483·0 30	37·9	72·94
I	71·32 28	0·83	1 499·3 28	109·9	*0·001*	1 199·3 28	64·9	79·99
I	44·73 15	1·00	2 504·0 15	287·0	*0·001*	1 676·7 15	134·3	66·96
Statistical significance of difference: $P<$	*0·05*		NS			NS		
II	42·07 15	1·27	2 257·1 14	211·5	*0·001*	1 653·6 14	125·8	73·26

I, *ad lib*. feeding regimen; II, 2 g pellets/mouse × day for 6 weeks; NS, not significant; ip, intraperitoneally.
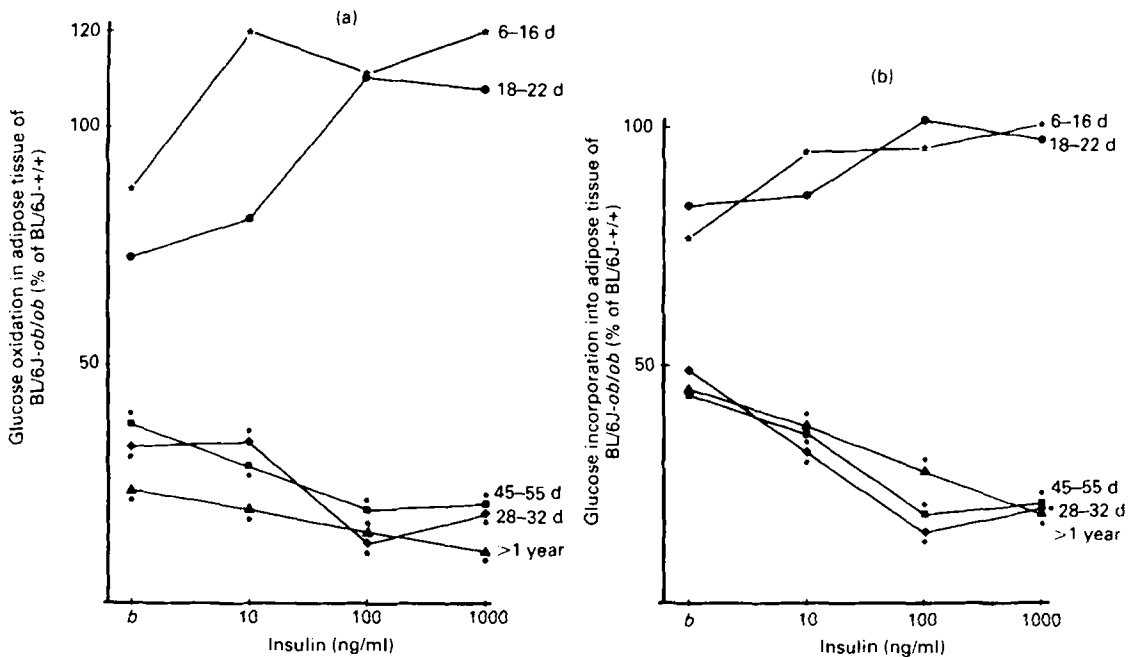* Student's *t* test.

Fig. 1. (a) Glucose oxidation in and (b) glucose incorporation into epididymal adipose tissue of BL/6J-*ob/ob* mice (% of controls (BL/6J-+/+)). * Mean values for BL/6J-*ob/ob* mice were significantly different from those for BL/6J-+/+ mice. *b*. Before insulin administration.

6–16 d of age showed a rate of glucose oxidation which was similar to that in the controls. In mice of 18–22 d of age glucose oxidation had already started to drop to about 50% of that seen in the controls. Glucose incorporation into adipose tissue from diabetes mice did not exceed 70% of that observed in the controls and dropped to less than 30% in older mice. However, when the animals had reached an age of about 1 year or more glucose incorporation had clearly increased to about 50% of that in the controls.

Insulin receptor defects are known to contribute to both adipose tissue and muscle unresponsiveness to insulin. In cardiocytes from Zucker *fa/fa* rats two different types of post-insulin receptor defects seem to be involved in the development of insulin resistance: on the one hand a lipid-metabolism-dependent defect and on the other hand a lipid-metabolism-independent defect (Eckel *et al.* 1985; Rösen *et al.* 1986).

INCREASED ADIPOSE TISSUE MASS

Table 6 shows that the pattern of body fat content in obese and diabetes mice is affected by strain, age, and the interaction strain × age. In preweaning pups of either mutant, body fat content was found to be slightly higher than that in the controls. At the time when the pups were weaned body fat content was clearly higher in *ob/ob* and *db/db* mice than in the controls. In both mutants older than 1 year of age body fat content was found to account for more than 50% of total body-weight.
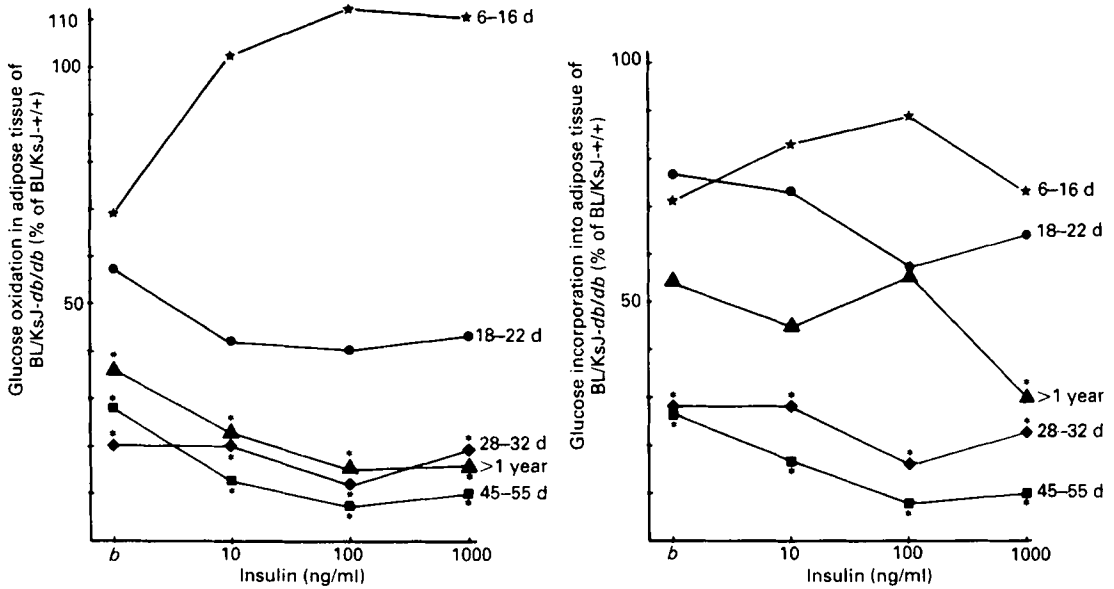
Fig. 2. (a) Glucose oxidation in and (b) glucose incorporation into epididymal adipose tissue of BL/6J-*ob/ob* mice (% of controls (BL/6J-+/+)). * Mean values for BL/6J-*ob/ob* mice were significantly different from those for BL/6J-+/+ mice. *b*, Before insulin administration.

In young diabetes mice the enlargement of adipose tissue mass is mainly due to hyperplasia. In young obese mice fat cell hypertrophy mainly contributes to the developing obesity (Table 7). In older mutant mice of both strains mean fat cell volume is about ten times larger than that in age-matched controls.

In contrast to obese and diabetes mice, the highest carcass fat contents in NZO mice were about 300 g/kg. NZO mice carry the majority of their adipose tissue within the peritoneal cavity; the total:intraperitoneal adipose tissue ratio is 3·4 and 2·7 in 4-week-old and 9-month-old NZO mice respectively. In contrast, in obese mice the ratio was found to be 7·1 and 4·4 in young and old mice respectively.

If the localization type of adipose tissue is related to the pattern of glucose tolerance it becomes obvious that in the subcutaneous or extraperitoneal type of obesity, which is represented by obese mice, glucose tolerance spontaneously improves. In the abdominal or intraperitoneal type of obesity as characterized by NZO mice, glucose tolerance progessively deteriorates (Herberg, 1988).

In all rodents with obesity or obesity–diabetes syndromes, or both, lipogenesis is increased even under energy intake restriction. Persistent lipogenesis is due to a highly efficient fuel utilization which already begins in suckling pups (Romsos *et al.* 1979). Accordingly, in Zucker *fa/fa* rats fed *ad lib.* a standard rat chow, body fat accounted for about 440 g/kg total body-weight (Table 8). Restriction of body-weight to less than 50% of that of the *ad lib.*-fed *fa/fa* rats resulted in a body fat content which was significantly lower than that observed in the *ad lib.*-fed obese rats and at the same time significantly higher than that seen in the *ad lib.*-fed lean controls.

Table 6. *Pattern of body fat content in BL/6J-+/+, BL/6J-ob/ob, BL/KsJ-+/+ and BL/KsJ-db/db mice*

| Strain/line | Age (d) | Body fat content (% of total body mass) | | | No. of mice |
		Mean	Geometric mean	1 SD	
6J-+/+	6–16	12·26	17·21	8·73	12
	18–22	9·03	12·16	6·71	13
	28–32	7·72	10·39	5·73	10
	45–55	7·15	8·40	6·09	14
	>1 year	13·01	18·72	9·04	14
6J-*ob/ob*	6–16	15·23	18·47	12·56	9
	18–22	16·46	22·00	12·32	8
	28–32	18·92	19·17	18·68	2
	45–55	29·27	34·19	25·05	13
	>1 year	59·05	63·27	55·12	19
KsJ-+/+	6–16	10·80	11·53	10·11	8
	18–22	9·94	12·60	7·85	11
	28–32	5·31	6·20	4·55	11
	45–55	6·58	8·50	5·10	15
	>1 year	9·76	10·13	9·40	4
KsJ-*db/db*	6–16	16·22	17·89	14·71	8
	18–22	17·93	20·99	15·32	7
	28–32	16·71	20·42	13·68	4
	45–55	32·66	38·44	27·75	14
	>1 year	52·83	57·42	48·61	20

Source of variance	SS	df	MS	F value
Strain/line	0·967	3	0·322	294·129*
Age	0·314	4	0·078	71·583*
Strain/line × age	0·253	12	0·021	19·294*
Residual		196	0·001	

SS, sum of squares; MS, mean square.
* Statistical significance as determined by analysis of variance.

DIMINISHED GLUCOSE TOLERANCE

All rodents exhibiting obesity or obesity–diabetes syndromes are characterized by diminished glucose tolerance. Severeness of glucose intolerance is closely related to the age or the adipose tissue mass of the animals, or both. In older obese mice glucose tolerance spontaneously increases. Therefore, we found glucose tolerance of obese mice weighing 60–70 g to approach the pattern of glucose tolerance observed in the controls. In NZO mice glucose tolerance continuously decreased with age. The basal pre-challenged blood glucose levels, however, were close to normal, regardless of the age of the mice (Herberg *et al.* 1970).

Normal basal blood glucose concentrations are also characteristic of Zucker *fa/fa* rats. In this rat, which is a model of morbid obesity rather than of diabetes, we (Berger *et al.* 1982) as well as other authors have shown that glucose intolerance can be improved by exercise. Whereas the rats responded to a mild treadmill programme with only a slight improvement, a more intensified programme prevented the deterioration of glucose

Table 7. *Pattern of fat cell volume in BL/6J-+/+, BL/6J-ob/ob, BL/KsJ-+/+ and BL/KsJ-db/db mice*

| | | Fat cell volume (($\times 10^3$) μm^3) | | | |
| | | | Geometric | | |
Strain/line	Age (d)	Mean	mean	1 SD	No. of mice
6J-+/+	6–16	33·73	39·04	29·14	9
	18–22	25·05	32·24	19·46	6
	28–32	30·61	34·86	26·88	6
	45–55	48·33	68·54	34·08	6
	>1 year	111·49	173·07	71·82	14
6J-*ob/ob*	6–16	198·70	240·13	164·41	8
	18–22	207·98	289·87	149·22	6
	28–32	165·36	223·56	122·32	6
	45–55	668·53	779·57	573·31	6
	>1 year	1 106·32	1 247·68	980·97	21
KsJ-+/+	6–16	33·43	37·06	30·15	6
	18–22	24·56	27·38	22·03	5
	28–32	23·54	34·95	15·86	6
	45–55	49·76	63·59	38·94	6
	>1 year	91·40	115·82	72·13	5
KsJ-*db/db*	6–16	44·00	52·48	36·88	6
	18–22	163·47	199·41	134·01	6
	28–32	175·16	290·71	105·54	6
	45–55	599·33	750·12	478·85	6
	>1 year	1 092·69	1 397·42	854·42	26
Source of variance	SS	df	MS	F value	
Strain/line	3·705	3	1·235	635·237*	
Age	1·793	4	0·448	230·633*	
Strain/line × age	0·435	12	0·036	18·669*	
Residual		146	0·001		

SS, sum of squares; MS, mean square.
* Statistical significance as determined by analysis of variance.

tolerance which usually develops in untrained *fa/fa* rats. In addition to this favourable effect on glucose tolerance, skeletal muscle uptake of glucose in vitro was significantly more insulin sensitive in trained than in untrained *fa/fa* rats (Becker-Zimmermann *et al.* 1982).

INCREASED GLUCONEOGENESIS

Hepatic gluconeogenic enzyme activity was reported to be twice as high in obese mice when compared with controls (Seidman *et al.* 1967). We studied gluconeogenic capacity of liver slices by means of $^{14}CO_2$ fixation. We observed that in 12-week-old and 48-week-old obese mice gluconeogenic capacity was clearly lower than that in 28-week-old mutants (Herberg *et al.* 1970). The age-related pattern of hepatic gluconeogenic capacity clearly runs parallel to the age-related pattern of blood glucose levels. From the enlargement of the cortical part of the adrenals and the increase in the in vitro

Table 8. *Effect of food restriction in obese Zucker rats**

(Mean values and standard deviations for five rats/group except obese restricted rats where values are for four rats/group)

Treatment group . . .	Lean *ad lib.*		Statistical significance of difference†:	Obese *ad lib.*		Statistical significance of difference†:	Obese restricted		Statistical significance of difference†:
	Mean	SD	P<	Mean	SD	P<	Mean	SD	P<
Body-wt (g)	440·80 5	64·39	0·001	622·0 5	57·44	0·001	274·25 4	12·31	0·001
Blood glucose (mg/l)	974·0 5	57·3	NS	1 114·0 5	128·2	NS	990·0 4	101·7	NS
Plasma insulin (ng/ml)	6·80 5	2·71	0·01	57·44 5	33·30	0·02	6·85 4	0·68	NS
Plasma triacylglycerols (mM)	1·95 5	0·93	0·001	5·59 5	1·01	0·001	1·60 4	0·55	NS
Body fat content (g/kg)	94·1 5	33·2	0·001	440·1 5	52·9	0·001	234·3 4	34·8	0·001

* Animals received standard lab chow.
† Student's *t* test.

biosynthesis of corticosterone which is the main corticosteroid in mice, it was suggested that adrenal hyperactivity might contribute to increased gluconeogenesis characteristic of obese mice (Hellerström *et al.* 1962).

In mice with the BL/6J background we found that the plasma corticosterone levels were 19 μg/l in homozygous lean (+/+), 86 μg/l in heterozygous (*ob*/+), and 137 μg/l in homozygous obese (*ob/ob*) mice (Herberg & Kley, 1975). The differences in corticosterone levels were statistically significant. Accordingly, Yen *et al.* (1968) observed that the glucose oxidation rate in epididymal adipose tissue was highest in *ob/ob*, lowest in +/+, and intermediate in *ob*/+ mice. The authors explained this observation as a 'gene dosage effect'. So far, the only known phenotypic symptoms which differ in BL/6J-+/+ and BL/6J-*ob*/+ mice are the rate of glucose oxidation in adipose tissue and the levels of plasma corticosterone.

INAPPROPRIATE HYPERGLYCAEMIA

In contrast to Zucker *fa/fa* rats, mice exhibiting the obesity syndrome develop inappropriate hyperglycaemia. The degree of inappropriate hyperglycaemia is lowest in NZO mice, intermediate in KK mice, and highest in *db/db* and *ob/ob* mice. The severity depends greatly on the interaction of the mutant gene with the genetic background; both *db/db* and *ob/ob* mice maintained on the BL/6J genome exhibit a less severe syndrome than either gene on the BL-KsJ background (Coleman & Hummel, 1975).

On compiling blood glucose and plasma insulin levels in diabetes mice on the BL/KsJ background we found that the degree of inappropriate hyperglycaemia depended on both the weight and the age of the animals and was most pronounced in mice exhibiting an accelerated weight gain (Fig. 3). Thus, in *db/db* with a mean body-weight of 55 g

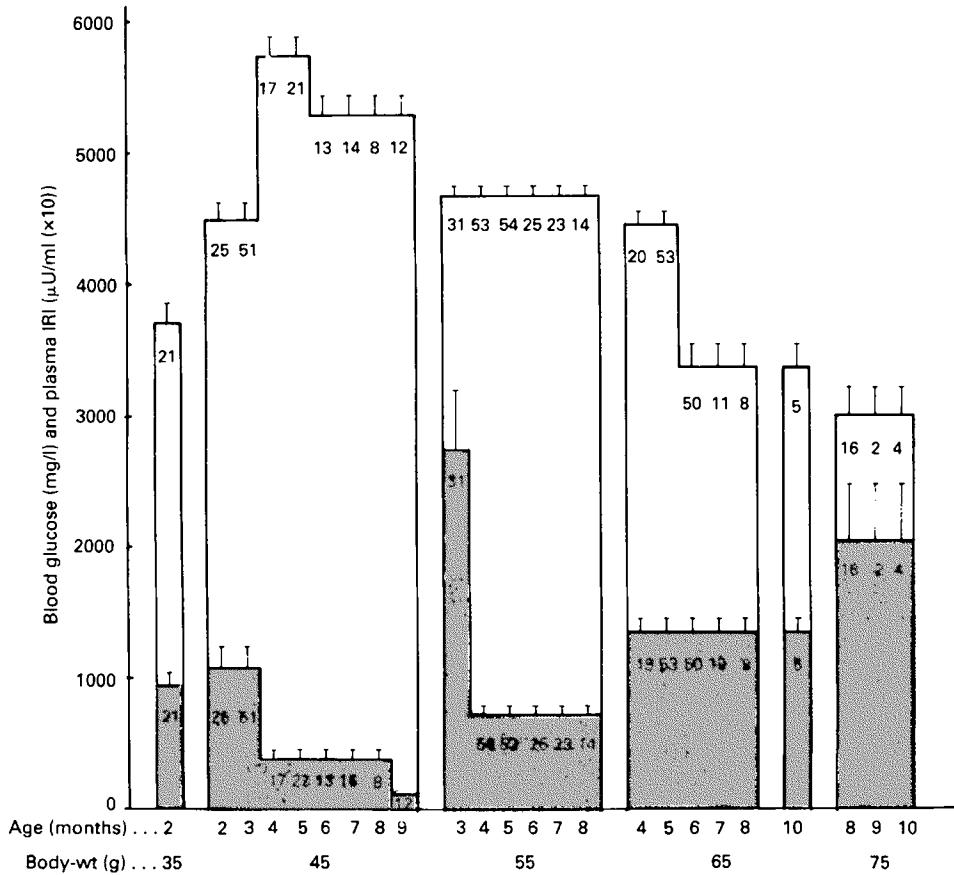Fig. 3. Blood glucose (□) and plasma insulin (▨; IRI) in non-fasted C57BL/KsJ-*db/db* mice relative to age and body weight. Values are means with their standard errors represented by vertical bars for no. of mice shown.

plasma insulin was highest in 3-month-old mice and significantly lower in 4–8-month-old mice. The drop in plasma insulin was reflected by a degranulation of pancreatic β cells (Herberg, 1982). This is suggested to be due to an exhaustion of the cells. Blood glucose levels were nearly identical regardless of the age of the mice. In diabetes mice with a mean body-weight of 65 g plasma insulin increased even more while blood glucose levels decreased. The spontaneous improvement in both pancreatic β cell function and insulin sensitivity was most pronounced in mice weighing about 75 g. This pattern of blood glucose and plasma insulin is characteristic of BL/KsJ-*db/db* and BL/6J-*ob/ob* mice and does not occur in NZO mice.

The findings on obese–hyperglycaemic small laboratory rodents reveal that the obesity–diabetes syndromes differ with respect to both genotype and phenotype. The

metabolic peculiarities which are characteristic of the strains clearly indicate that the interrelationships between obesity and diabetes are many-fold. The metabolic derangements present in both the obese and the diabetic state include hyperinsulinaemia, insulin resistance, increased adipose tissue mass, and a diminished glucose tolerance. If the animals are capable of adjusting pancreatic β cell function to its demand they represent the type of morbid obesity. If, however, pancreatic β cell function is insufficient to cope with the high blood glucose concentration the animals develop diabetes-like syndromes.

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