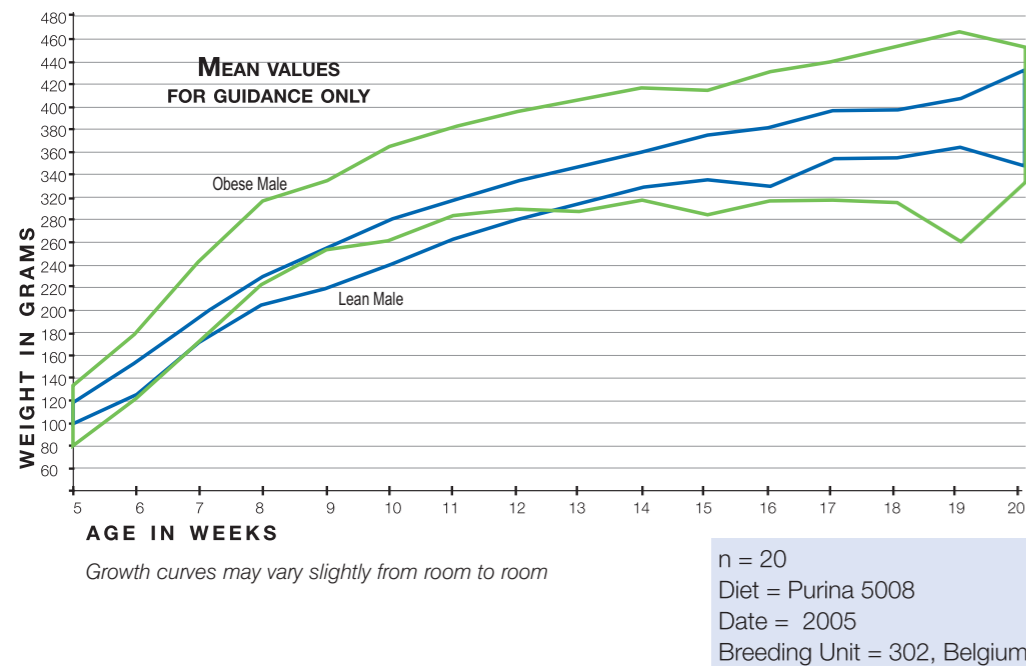


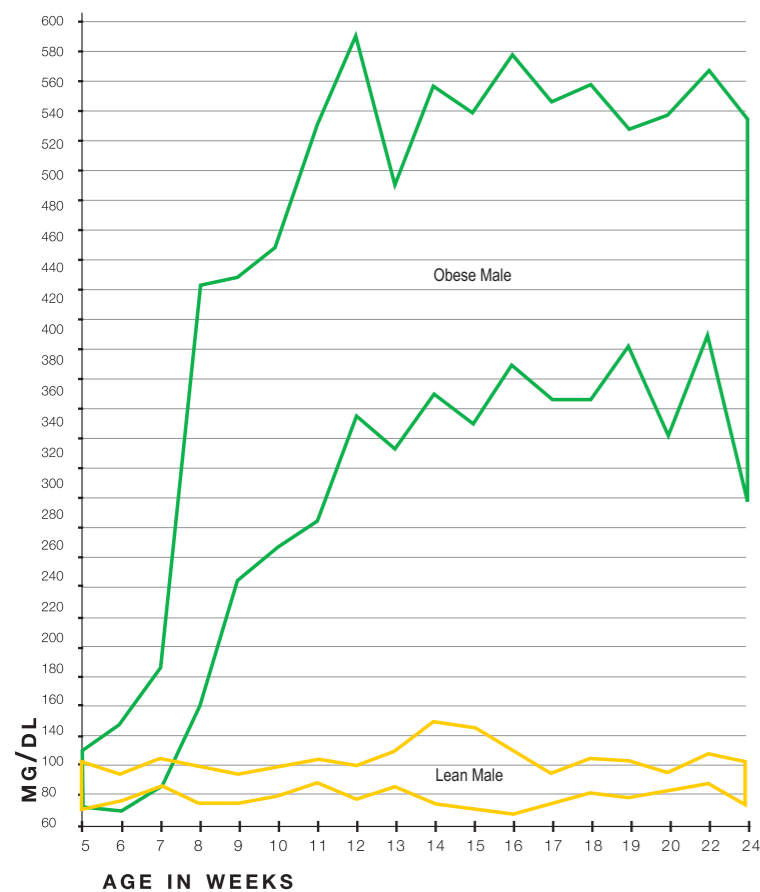
ZDF Rats

Growth Curve



Glucose level (mg/dl)

(divide by 18 to get mmol/l)



ZDF Rats

Nomenclature

ZDF/Crl-*Lep^{fa}*

Strain origin

The diabetic trait in this model originates from a colony of outbred Zucker rats kept by Dr Walter Shaw at Eli Lilly Research Laboratories in Indianapolis, IN, during 1974 – 1975. A part of this colony containing the diabetic characteristic was moved to Indiana University Medical School (IUMS) to the laboratory of Dr Julia Clark in 1977. In 1981 selected groups of diabetic individuals were rederived.

Selection and inbreeding was performed by Dr Richard Peterson at IUMS and the ZDF (Zucker Diabetic Fatty) strain was established in 1985, then transferred to Genetic Models Inc. (GMI), then to Charles River Laboratories in 2001 after the acquisition of GMI. The foundation colony is based at CRL Wilmington. Production colonies were started in Charles River Laboratories US in 2001 and in Europe in 2002.

Control

The ZDF lean is strongly recommended as the control. For a control that will not become diabetic it is possible to use the Zucker outbred rat.

Appearance

Black hooded with a black stripe down the length of the neck

Research applications

Model for general use including

- **Diabetes and obesity research**

- Type 2 Diabetes (NIDDM)
- Hyperglycemia
- Impaired wound healing
- Neuropathy
- Nephropathy
- Insulin resistance
- Hyperinsulinemia
- Mild hypertension
- Hypertriglyceridemia
- Hypercholesterolemia



Strain characteristics

The ZDF rat is an inbred rat model that through genetic mutation and a managed diet of Purina 5008 will closely mimic human adult onset diabetes (Type 2) and related complications. When fed with a diet of Purina 5008, homozygote recessive males (*fa/fa*) develop obesity, hyperlipidemia, fasting hyperglycemia, and Type 2 diabetes. Wildtype (+/+) and heterozygous (*fa/+*) lean genotypes remain normoglycemic. The obese female ZDF rat requires a special diet to induce Type 2 diabetes.

The ZDF rat is an accurate model for Type 2 diabetes based on impaired glucose tolerance caused by the inherited obesity gene mutation which leads to insulin resistance. The *fa* mutation which occurs in both the ZDF and Zucker rat results in shortened leptin receptor which does not effectively interact with leptin. This mutation is phenotypically expressed as obesity with high levels of leptin in the blood. Islets from ZDF rats are resistant to the lipopenic action of leptin.

Hyperinsulinemia, the loss of glucose-stimulated insulin secretion, and peripheral insulin resistance coexist in non-insulin dependent diabetes mellitus (NIDDM). In the ZDF, hyperglycemia is initially manifested at about 7 weeks of age, and all obese male rats fed Purina 5008 are fully diabetic by 12 weeks. Between 7 and 10 weeks, blood insulin levels are high but this subsequently drops as the pancreatic beta cells cease to respond to the glucose stimulus.

This loss of response to glucose is associated with the disappearance of GLUT2 transporters on the beta cells in the islets. Beta-cell mass in prediabetic ZDF rats is similar to non-diabetic Zucker fatty rats and greater than that in lean control rats. However, after the onset of diabetes, the beta-cell mass in the ZDF rats is significantly lower than that of the Zucker fatty rats.

Hyperglycemia

- Hyperglycemia develops between 7 and 10 weeks of age
- Fasting hyperglycemia appears first at 10 to 12 weeks of age and progresses with aging

Hyperinsulinemia

- Early hyperinsulinemia, which rapidly falls as the beta cells fail
- Insulin resistance & abnormal glucose tolerance, which becomes progressively worse with age

Retinopathy

- The ZDF rat develops quantifiable retinal vascular changes (microvascular retinopathy)

Hypercholesterolemia

- The ZDF rats exhibits hyperlipidemia, hypertriglyceridemia and hypercholesterolemia resulting in mild hypertension

Nephropathy

- The ZDF exhibits a tendency to develop hydronephrosis

Growth curve

- Obese diabetic rats demonstrate less weight gain relative to non-diabetic obese and lean ZDF controls

Neuropathy

- Peripheral nerve changes in obese ZDF males
- Impaired wound healing

Breeding system

Mating system	Pair heterozygous male x heterozygous female
Litter size at birth	8 - 12
Gestation period	21 - 24 days
Weaning age	21 days
Watering system	Filtered water (0.1 μm), bottle system
Bedding	Litalabo – SPPS (hardwood)
Diet	Purina 5008 irradiated 25 Kgy or equivalent, <i>ad libitum</i>
Room Temperature	21 ± 1 °C
Light cycle	12 – 12 (6:00 pm – 6:00 am)

*COLONY MANAGEMENT

Progeny is 25 % *fa/fa*, 50 % *fa/+* and 25 % of +/+ (ie 75% ?/+). ZDF *fa/fa* and ?/+ are distinguished phenotypically. It is not possible to differentiate phenotypically lean ZDF (+/+) and lean ZDF (*fa/+*) but PCR testing is possible .

