Effects of adrenalectomy before weaning in the genetically obese Zucker rat (fa/fa)

BY J. M. FLETCHER
Rowett Research Institute, Bucksburn, Aberdeen AB2 9SB
(Received 5 August 1985 – Accepted 15 January 1986)

1. Lean (Fa/?) and obese (fa/fa) Zucker rats were adrenalectomized or sham-operated at 19 d of age (3 d before weaning). Injection of corticosterone for 3 d after weaning (1.0 mg/d) was necessary to ensure survival of adrenalectomized fa/fa but not Fa/? rats. Intact and adrenalectomized fa/fa rats had a lower rectal temperature than Fa/? animals before and 3 d after adrenalectomy. The post-weaning survival of adrenalectomized fa/fa rats was enhanced by maintenance at an ambient temperature of 30°C rather than 22°C.

2. Adrenalectomized and sham-operated rats were therefore kept at 30°C, fed ad-lib. and killed at 34 d. Adrenalectomy had only small effects on the growth, body composition and appetite of Fa/? animals. The hyperphagia, greater lipid content, reduced protein content and hyperinsulinaemia of fa/fa rats were completely abolished by adrenalectomy.

3. Intact fa/fa rats had higher liver glycogen contents and higher activities of the hepatic enzymes tyrosine aminotransferase (EC 2.6.1.5) and acetyl CoA carboxylase (EC 6.4.1.2) than intact Fa/? animals. Adrenalectomy abolished these phenotypic differences.

4. Injection of adrenalectomized rats with 1.0 mg corticosterone-21-acetate daily from weaning to 34 d restored the abnormal body composition, hyperphagia, hyperinsulinaemia, higher hepatic glycogen and enzyme activities of fa/fa rats.

5. In a second experiment adrenalectomized rats were injected with 1.0 mg corticosterone-21-acetate daily from weaning to 34 d and kept at 22°C. fa/fa rats adrenalectomized and injected with corticosterone had a reduced body lipid content compared with intact fa/fa rats but still contained more lipid than intact or similarly treated Fa/? animals.

6. In both experiments adrenalectomized Fa/? and fa/fa rats injected daily with corticosterone had the same plasma concentrations of this hormone when killed 3 h after the last injection at 34 d. It is concluded that corticosterone is required for expression of the abnormal appetite, hyperinsulinaemia and body composition of the fa/fa rat.

The mature genetically obese Zucker rat (fa/fa) has an abnormal body composition characterized by excessive adiposity and a reduced protein mass (Pullar & Webster, 1974). In addition several endocrine abnormalities have been noted in fa/fa animals and they have an enhanced energetic efficiency and hyperphagia (for review, see Bray & York, 1979). The primary lesion responsible for these diverse manifestations of the fa/fa phenotype has not been elucidated.

Recent reports have shown that adrenalectomy reduces in severity many features of the obese phenotype. Adrenalectomy performed at 5 weeks of age reduced the rate of weight gain, the degree of hyperinsulinaemia and the rate of fatty acid synthesis of fa/fa rats compared with intact fa/fa animals (Yukimura & Bray, 1970; Yukimura et al. 1978; York & Godbole, 1979). It should be noted, however, that plasma insulin levels remained approximately twofold greater and fatty acid synthesis rates approximately three- to fourfold higher in adrenalectomized fa/fa rats than in adrenalectomized Fa/? or intact Fa/? animals (York & Godbole, 1979). Similarly, although adrenalectomy reduced the amount of excess weight gain and food intake of fa/fa rats these remained elevated compared with adrenalectomized Fa/? animals (Yukimura & Bray, 1970; Yukimura et al. 1977). Interpretation of these findings is therefore difficult because adrenalectomized fa/fa rats were still grossly different in body composition and metabolism from Fa/? animals.

Developmental studies indicate that before weaning fa/fa rats are not hyperphagic (Bell & Stern, 1977) or hyperinsulinaemic (York et al. 1981; Turkenkopf et al. 1982) compared

Downloaded from https://www.cambridge.org/core. IP address: 54.191.40.80, on 08 Apr 2017 at 02:48:21, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1079/BJN19860094
with Fa/± animals. The bodies of fa/fa rats contain more lipid from the 12th day of age (Bell & Stern, 1977) but this difference is slight until after weaning (Bell & Stern, 1977) and there is no phenotypic difference in body protein content until 23 d of age (Reeds et al. 1982). In order to study the effects of glucocorticoids on expression of the fa/fa phenotype the present paper reports the effects of adrenalectomy performed at 18 d of age (3 d before weaning) and the effects of glucocorticoid replacement from 21 to 34 d of age.

Compared with Fa/± rats the metabolism of fa/fa animals is directed toward high rates of fatty acid synthesis and accelerated amino acid catabolism. Many studies have shown that the hepatic enzymes of fa/fa rats show changes in activity consistent with this abnormal metabolism (Bray & York, 1979). To assess whether these changed enzyme activities are also dependent on the presence of glucocorticoids, the activities of acetyl CoA carboxylase (EC 6.4.1.2) and tyrosine aminotransferase (EC 2.6.1.5) have been measured in the livers of intact, adrenalectomized and adrenalectomized animals given daily injections of corticosterone.

**MATERIALS AND METHODS**

Lean (Fa/?) and obese (fa/fa) female Zucker rats were bred from heterozygote parents from the colony at the Rowett Research Institute (Pullar & Webster, 1974). They were weaned at 21 d post-partum and offered ad lib. a commercial pelleted diet (Oxoid; Herbert C. Styles Ltd, Bewdley, Worcs.). After weaning the animals were housed singly at 22° or 30° with a 12 h light–12 h dark cycle (light on at 06.00 to 18.00 hours). Cumulative food intakes minus spillages were measured from 21 to 34 d.

Phenotype identification was made at 17 d post-partum on the basis of the lower rectal temperature of fa/fa rats (Godbole et al. 1978). Rectal temperatures were measured at least three times with a thermocouple and digital thermometer (Digitron Instrumentation Ltd, Merchant Drive, Hertford) in pups removed from their dam and maintained at 22° for a minimum of 1 h. Preliminary observations in this laboratory on rats allowed to reach 34 d of age and then analysed for total carcass lipid content, have confirmed that this procedure correctly identified pre-obese 17-d-old fa/fa rats with 100% accuracy.

Bilateral adrenalectomies or sham operations were performed under diethyl ether anaesthesia using a single dorsal incision at 18 d. Litters containing adrenalectomized animals were given both water and saline (9 g sodium chloride/l) to drink. After weaning, adrenalectomized animals were given glucose (40 g/l) in saline to drink. To ensure survival of adrenalectomized fa/fa rats (see p. 143) all animals were injected subcutaneously with 1·0 mg corticosterone-21-acetate in sesame oil (10 mg/ml) for 3 d after weaning. Thereafter rats were injected daily with 1·0 mg corticosterone-21-acetate or sham injected with an equivalent volume of sesame oil until the animals were killed at 34 d. Adrenalectomized animals having plasma corticosterone levels > 20 μg/l or evidence of surviving adrenal fragments at post-mortem were excluded from these studies. Similarly, adrenalectomized rats treated with corticosterone were discarded if adrenal fragments were present at post-mortem.

Rats were killed and blood samples taken at 11.00–12.00 hours, 3 h after their last sham or corticosterone injection at 34 d of age. Stomachs were removed and the remaining carcass freeze-dried, minced and analysed for total lipid by the method of Atkinson et al. (1972), and nitrogen by the Kjeldahl method: protein was calculated as N × 6·25.

Plasma glucose was analysed by the glucose oxidase (EC 1.1.3.4) method (Huggett & Nixon, 1957). Plasma insulin was measured by radioimmunoassay. Iodinated insulin was obtained from Amersham International plc (Amersham, Bucks), insulin antiserum (batch 65-101-1) from Miles Scientific plc (Stoke Court, Stoke Poges, Slough), and rat insulin standard (lot 615-063-12-3) from Eli Lilley Ltd, Indianapolis, Indiana.
Plasma corticosterone was analysed by radioimmunoassay (Gosdow-Cohen et al. 1982), tritiated corticosterone was purchased from Amersham International, antiserum (batch no. CO2) was purchased from Miles Scientific plc.

Immediately after rats were killed a liver sample was freeze-clamped in liquid N₂ and hepatic glycogen subsequently assayed (Keppler & Decker, 1984). A second liver sample was rapidly homogenized in Tris buffer pH 7·4 (50 mM) containing EDTA (0·1 mM), pyridoxal phosphate (0·05 mM) and dithiothreitol (1·0 mM). The homogenate was centrifuged at 14000 g x 60 min and tyrosine aminotransferase activity was measured in the supernatant fraction by the method of Granner & Tomkins (1970). Following gel-filtration and activation with citrate and magnesium ions, acetyl CoA carboxylase activity was assayed in the supernatant fraction by radiobicarbonate fixation (Inoue & Lowenstein, 1975). Protein concentration was determined by a modification of the Lowry method (Hartree, 1972).

The statistical significance of differences between means was assessed by Student’s t test and all values are expressed as means and standard deviations.

RESULTS

Preliminary observations

Groups of Fa/? and fa/fa rats, adrenalectomized or sham-operated (intact) at 18 d of age, were equally viable until weaning at 21 d. After weaning, rats were kept at an ambient temperature of 22° or 30°. At either temperature adrenalectomized fa/fa rats died within 72 h of weaning whereas adrenalectomized Fa/? rats and intact animals of both phenotypes survived indefinitely (five to six in each group). Attempts to ensure the survival of adrenalectomized fa/fa rats by (1) daily treatment with aldosterone (500 µg), (2) weaning onto a high-fat diet, (3) postponement of weaning until 25 d, were uniformly unsuccessful. Post-weaning viability of adrenalectomized fa/fa rats was, however, achieved by daily injection of corticosterone-21-acetate (1·0 mg). In order to study the effects of corticosterone deprivation, further studies revealed that indefinite survival of adrenalectomized fa/fa rats at 30° could be achieved by treatment with corticosterone (1·0 mg) on the day of weaning and for the 2 d following. This enhanced viability was attained only in rats maintained at 30°, the survival rate fell to < 50% when rats were similarly treated and maintained at 22°.

Therefore in succeeding experiments comparisons between adrenalectomized fa/fa rats and other groups were made only in animals maintained at 30°.

Effects of adrenalectomy and corticosterone injection in rats maintained from weaning at 30°

Rectal temperatures were measured before corticosterone injection in 21-d-old rats maintained at an ambient temperature of 22° and again 6 h after being moved to an ambient temperature of 30°. At 22° the rectal temperature of adrenalectomized fa/fa rats was lower (mean difference 1·8 (SD 0·4°) n 7) than that of adrenalectomized or intact Fa/? rats and did not differ significantly from that of intact fa/fa animals. Maintenance at 30° however equalized the temperature of all groups. The mean body-weights of all groups did not differ significantly at 21 d (overall mean 35 (SD 2·6) g).

At 34 d, body-weight did not differ between phenotypes (Fig. 1) but adrenalectomized rats were lighter than intact or adrenalectomized animals treated with corticosterone. Intact fa/fa rats had approximately a three times greater body lipid content than Fa/? animals and this difference was abolished by adrenalectomy (Fig. 1). Whereas the lipid content of adrenalectomized Fa/? rats was not affected by corticosterone treatment, that of adrenalectomized fa/fa rats was increased approximately twofold. Intact fa/fa rats had a lower
Fig. 1. Body-weight and composition of sham operated (Sham ADX), adrenalectomized (ADX) and adrenalectomized corticosterone-treated (ADX CST) Fa/+(□) and fa/fa (■) rats at 34 d of age. Rats were maintained at an ambient temperature of 30°C from weaning. Each value is the mean and standard deviation, represented by vertical bar. Mean values for Fa/+(□) and fa/fa (■) rats were significantly different: *P < 0.05, ***P < 0.001. NS, not significant.

Fig. 2. Cumulative food intake from weaning to 34 d of age of sham-operated (Sham ADX), adrenalectomized (ADX) and adrenalectomized corticosterone-treated (ADX CST) Fa/+(□) and fa/fa (■) rats. Rats were maintained at an ambient temperature of 30°C. Each value is the mean and standard deviation, represented by vertical bar. Mean values for Fa/+(□) and fa/fa (■) rats were significantly different: **P < 0.01, ***P < 0.001. NS, not significant.
protein content than $Fa/\?$ animals and this difference was abolished by adrenalectomy. Treatment with corticosterone restored a small but significant phenotypic difference in protein content. Intact $fa/fa$ rats ate approximately 30% more than $Fa/\?$ animals (Fig. 2). This hyperphagia was prevented by adrenalectomy and restored, albeit to a lesser degree, in corticosterone-treated animals.

Plasma concentrations of glucose were not significantly different between phenotypes and were not affected by adrenalectomy or corticosterone treatment (Table 1). Intact $fa/fa$ rats were hyperinsulinaemic compared with $Fa/\?$ animals and this phenotypic difference was abolished by adrenalectomy (Table 1) and restored by treatment with corticosterone. Plasma concentrations of corticosterone in adrenalectomized animals injected with this hormone did not differ significantly between phenotypes (mean 74 (SD 43) n 8 and 106 (SD 65) n 7 µg/l in $Fa/\?$ and $fa/fa$ rats respectively).

The activities of hepatic tyrosine aminotransferase and acetyl CoA carboxylase were both higher in intact $fa/fa$ rats (Table 2). Adrenalectomy reduced the activity of tyrosine aminotransferase in both phenotypes to levels not significantly different and corticosterone treatment reversed these effects. Acetyl CoA carboxylase activity was reduced by adrenalectomy in $fa/fa$ rats to the same level as found in $Fa/\?$ animals, corticosterone treatment restored a phenotypic difference but this was partially attributable to a lowered activity in $Fa/\?$ rats. Hepatic glycogen levels were higher in intact $fa/fa$ rats (Table 2) and this phenotypic difference was abolished by adrenalectomy and restored by treatment with corticosterone.

**Effects of adrenalectomy and corticosterone injection in rats maintained at 22°C**

Intact rats showed a similar phenotypic difference in body protein and lipid content as rats maintained at 30°C (see p. 143 and Fig. 3). This phenotypic difference in body lipid content was smaller in adrenalectomized rats treated with corticosterone (Fig. 3). Plasma glucose concentrations did not differ between phenotypes but $fa/fa$ animals were hyperinsulinaemic compared with $Fa/\?$ animals (Table 1). Plasma corticosterone levels in adrenalectomized $fa/fa$ and $Fa/\?$ rats receiving exogenous corticosterone did not differ significantly, mean values in $fa/fa$ and $Fa/\?$ rats were 63 (SD 31) n 7 and 59 (SD 61) n 8 µg/l respectively.

**DISCUSSION**

The present study demonstrates that if performed early enough adrenalectomy completely normalizes the body composition, appetite and insulinaemia of $fa/fa$ rats maintained at 30°C. Replacement with corticosterone was sufficient to allow development of the obese phenotype, implying that lack of glucocorticoids was responsible for the effects of adrenalectomy.

The failure of adrenalectomized $fa/fa$ but not $Fa/\?$ rats to survive weaning without exogenous corticosterone demonstrates an important phenotypic difference that may indicate the nature of the defect responsible for genetic obesity. Food intake during the weaning period declines and animals utilize their body lipid reserves. In accord with the autonomic theory proposed by Bray & York (1979) an explanation for the greater mortality of weaned adrenalectomized $fa/fa$ rats may lie in an impaired mobilization of their adipose tissue triglyceride because of reduced sympathetic nervous system activity. Intact or corticosterone-treated adrenalectomized $fa/fa$ rats may be enabled to survive weaning by glucocorticoid-mediated gluconeogenesis using skeletal muscle protein as a source of glucogenic precursors. Furthermore this hypothesis would explain the reduced rates of protein deposition and synthesis found in $fa/fa$ rats during the weaning period (Reeds et al. 1982).
Table 1. Plasma insulin and glucose concentrations of adrenalectomized (ADX) or sham-operated (Sham ADX) rats maintained at an ambient temperature of 22 °C or 30 °C

(Operations were performed at 17–18 d post-partum and rats were injected daily with 1-0 mg corticosterone-21-acetate (CST) or sham-injected from 21 to 34 d. Blood samples were taken at 34 d. Values are means and standard deviations for seven to eight rats/group)

<table>
<thead>
<tr>
<th></th>
<th>Sham ADX</th>
<th>ADX</th>
<th>ADX CST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fa/?</td>
<td>fa/fa</td>
<td>Fa/?</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>30 °C:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mm)</td>
<td>7.12 0.26</td>
<td>6.89 0.74</td>
<td>7.38 0.50</td>
</tr>
<tr>
<td>Plasma insulin (ng/ml)</td>
<td>1.37 0.49</td>
<td>8.95*** 4.01</td>
<td>1.39 0.24</td>
</tr>
<tr>
<td>22 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mm)</td>
<td>7.24 2.31</td>
<td>6.99 0.49</td>
<td>—   —   —   —</td>
</tr>
<tr>
<td>Plasma insulin (ng/ml)</td>
<td>2.63 1.57</td>
<td>5.46*** 2.59</td>
<td>—   —   —   —</td>
</tr>
</tbody>
</table>

* Mean values were significantly different from that for Fa/? phenotype: *** P < 0.001.
Table 2. Activity of hepatic enzymes and hepatic glycogen concentration of sham-operated (Sham ADX), adrenalectomized (ADX) and adrenalectomized corticosterone-treated (ADX CST) rats maintained at 30°C

(Mean values and standard deviations for seven to eight rats/group)

<table>
<thead>
<tr>
<th></th>
<th>Sham ADX</th>
<th>ADX</th>
<th>ADX CST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fa/?</td>
<td>fa/fa</td>
<td>Fa/?</td>
</tr>
<tr>
<td>Tyrosine aminotransferase (EC 2.6.1.5) (nmol/min per mg protein)</td>
<td>46.7</td>
<td>14.3</td>
<td>78.7**</td>
</tr>
<tr>
<td>Acetyl CoA carboxylase (EC 6.4.1.2) (nmol/min per mg protein)</td>
<td>2.64</td>
<td>1.29</td>
<td>8.69**</td>
</tr>
<tr>
<td>Glycogen (μmol glucose/g liver)</td>
<td>244</td>
<td>86</td>
<td>458**</td>
</tr>
</tbody>
</table>

* Mean values were significantly different from that for Fa/? phenotype (calculated using a pooled estimate of variance (ANOVA)); *P < 0.05, **P < 0.01.
Fig. 3. Body-weight and composition of sham operated (Sham ADX), and adrenalectomized corticosterone-treated (ADX CST) $Fa/?$ (□) and $fa/fa$ (■) rats at 34 d of age. Rats were maintained at an ambient temperature of 22° from weaning. Each value is the mean and standard deviation, represented by vertical bar. Mean values for $Fa/?$ and $fa/fa$ rats were significantly different: * $P < 0.05$, *** $P < 0.001$. NS, not significant.

That all the abnormalities displayed by the $fa/fa$ rat were not rectified by adrenalectomy is indicated by the observations that these animals remained hypothermic 3 d after surgery and they had a greater mortality when maintained at an ambient temperature of 22° rather than 30°. Saito & Bray (1984) have similarly shown that $ob/ob$ mice also continue to manifest a lower body temperature after adrenalectomy. These observations suggest that adrenalectomy does not remedy the thermogenic defect of obese mutants. Others have, however, reported that adrenalectomy of $fa/fa$ rats at 5 weeks of age eliminated their hypothermia (Holt et al. 1983) as well as their greater energetic efficiency (Marchington et al. 1983) and restored the function of their brown adipose tissue to that found in $Fa/?$ rats (Holt & York, 1982). In this latter study, however, brown adipose tissue thermogenic function was only assessed indirectly by measurement of mitochondrial purine-nucleotide-binding capacity. Further studies are clearly necessary to define fully the effects of adrenalectomy and glucocorticoids on heat production and thermoregulation in genetically-obese rodents.
Adrenalectomy in the genetically obese Zucker rat

In agreement with previous studies (Fletcher et al. 1983) intact fa/fa rats kept at 22° or 30° consumed approximately 30% more food than intact Fa/– animals (Fig. 2). Adrenalectomy abolished this hyperphagia and prevented the deposition of excess body lipid (Fig. 1). It is a striking finding, however, that fa/fa rats pair-fed to the intake of Fa/– animals accumulate nearly as much lipid as ad lib-fed fa/fa rats (Bray et al. 1973; Cleary et al. 1980). The effect of adrenalectomy on body lipid content of fa/fa rats is therefore not simply a consequence of reduced food intake. Insulin is a potent stimulator of lipogenesis and the elimination of hyperinsulinaemia in adrenalectomized fa/fa rats (Table 1) may contribute to their reduced lipid content. The mechanism by which adrenalectomy lowered the plasma insulin levels and treatment with corticosterone restored the hyperinsulinaemia of fa/fa rats (Table 1) is not clear. As with lipid deposition, changed food intake is not an adequate explanation as pair-fed fa/fa rats remain hyperinsulinaemic compared with Fa/– animals (Bray et al. 1973; Cleary et al. 1980).

In contrast with intact fa/fa rats, adrenalectomized fa/fa animals had the same amount of body protein as adrenalectomized and intact Fa/– rats (Fig. 1). Intact ob/ob mice also manifest a reduced lean body mass and Saito & Bray (1984) have shown that adrenalectomy normalizes the growth of their skeletal muscle and tail length. Administration of glucocorticoids to young animals may result in stunted growth and reduced rates of muscle-protein synthesis (Loeb, 1976). It is possible therefore that differences in growth of lean tissues between fa/fa and Fa/– rats (or ob/ob and Ob/– mice) may be caused by direct actions of endogenous glucocorticoids.

Activity of the enzyme acetyl CoA carboxylase is an important regulator of the rate of fatty acid synthesis (Volpe & Vagelos, 1976) and, as expected, hepatic levels of this enzyme were higher in intact fa/fa rats than in intact Fa/– animals (Table 2). Adrenalectomy abolished and corticosterone treatment restored this phenotypic difference. Insulin or glucocorticoids administered to other strains of rats in vivo increases the activity of this enzyme (Diamont & Shafrir, 1975) but induction by glucocorticoids was found to be secondary to glucocorticoid-induced hyperinsulinaemia (Diamont & Shafrir, 1975). It is possible therefore that the increased activity of acetyl CoA carboxylase found in intact and corticosterone-treated fa/fa rats is due to their hyperinsulinaemia.

Tyrosine aminotransferase catalyses the first step in tyrosine breakdown and from studies in isolated rat liver cells it has been proposed that this enzyme may be rate-limiting for tyrosine catabolism (Dickson et al. 1981). Increased food intake and administration of insulin, glucagon or glucocorticoids increase the hepatic activity of this enzyme (Lin & Knox, 1957; Kenney, 1970) and, consistent with their hyperphagia and hyperinsulinaemia, higher tyrosine aminotransferase activities were found in the livers of intact fa/fa rats (Table 2). Adrenalectomy abolished and treatment with corticosterone restored this phenotypic difference. Because of the multi-factorial control of tyrosine aminotransferase activity the direct cause of these changes cannot be established. In a previous study (Shargill et al. 1983) adrenalectomy only reduced the magnitude of the difference in hepatic tyrosine aminotransferase between fa/fa and Fa/– rats and short-term corticosterone treatment was more effective in stimulating enzyme activity in Fa/– animals. In that study, however, adrenalectomy was performed at 5 weeks of age and adrenalectomized fa/fa animals remained hyperinsulinaemic and although body lipid contents were not reported, adrenalectomized fa/fa rats probably remained obese (Shargill et al. 1983).

Hepatic glycogen levels are very sensitive to changes in plasma glucocorticoid concentrations. This sensitivity formed the basis of a bioassay for corticosterone before the advent of competitive binding and fluorimetric assays (Reineke & Kendall, 1942). Corticosterone treatment restored the higher hepatic glycogen levels in adrenalectomized fa/fa rats (Table 2), although plasma corticosterone concentrations did not significantly differ between
phenotypes. Because hyperphagia and hyperinsulinaemia were also induced by this treatment the response in glycogen levels cannot be directly attributed to the actions of corticosterone alone.

The mechanism(s) by which adrenalectomy and treatment with corticosterone influence the development of the obese phenotype is not clear. Several characteristics of the intact fa/fa rat and the effects of exogenous corticosterone in adrenalectomized fa/fa animals are reminiscent of those found in lean strains of rat and other species treated with glucocorticoids. Hyperphagia (Galpin et al. 1983), increased lipid and decreased protein deposition (Hausberger & Hausberger, 1960), hyperinsulinaemia (Diamont & Shafrir, 1975), elevated hepatic tyrosine aminotransferase and acetyl CoA carboxylase (Kenney, 1970; Diamont & Shafrir, 1975), and increased hepatic glycogen concentrations (Reineke & Kendall, 1942) have all been reported as consequences of high-dose glucocorticoid administration. There is uncertainty regarding the plasma corticosterone levels in intact fa/fa rats with some reports suggesting no phenotypic difference (Bray et al. 1973; Shargill et al. 1983) and others higher levels in fa/fa animals (Martin & Gahagan, 1977). In the present study the profoundly different effects of exogenous corticosterone in adrenalectomized fa/fa and Fa/? rats were obtained at the same administered dose and corticosterone levels in plasma did not differ between phenotypes. It has been suggested that the tissues of the fa/fa rat may be more sensitive to the actions of glucocorticoids (Yukimura et al. 1978). Alternatively a merely 'permissive' action of glucocorticoids may be required to allow expression of the fa/fa genotype. Study of the interaction between glucocorticoids and the fa/fa genotype has been hindered by the abnormal body composition, endocrine status and metabolism which remains when adrenalectomy is performed several weeks after weaning. The ability to completely normalize the phenotype of the fa/fa rat by adrenalectomy before weaning, will facilitate investigation of the actions of glucocorticoids in expression of genetic obesity.

The expert technical assistance of Linda Robertson is gratefully acknowledged. Rat insulin standard was a generous gift from Eli Lilly Ltd.

REFERENCES
Adrenalectomy in the genetically obese Zucker rat