(AA) concentrations and survive longer than males (Odumosu & Wilson, 1971). AA plays an important role in the anti-obesity action of fenfluramine (Wilson and Odumosu, 1972), and so its effect has been investigated on changes in fat metabolism. Four groups of male and female guinea-pigs received scorbutic diets for 24 days after an initial maintenance period (Odumosu & Wilson, 1970). Individual groups received 30 (mg/kg)/day supplementary ascorbic acid subcutaneously (S), supplementary ascorbic acid and fenfluramine 15 (mg/kg)/day (SF), fenfluramine alone (F), or no treatment (Sc), The effect of fenfluramine was compared on change in weight, plasma and tissue AA, cholesterol and triglyceride concentrations (Table 1).

Both sexes gained weight significantly on the supplemented diet. Administration of fenfluramine caused loss of weight in the males. Weight gain was significantly reduced among the treated, in comparison with the untreated, supplemented, females. Fenfluramine caused similar changes in the scorbutic animals, in whom overall weight loss occurred.

In both sexes, supplemented and scorbutic, fenfluramine administration was associated with significantly lower liver AA concentrations, the effect being more evident in the males. In the supplemented animals, hepatic cholesterol was significantly higher in the male fenfluramine treated group. In the scorbutic groups, plasma and hepatic cholesterol values were significantly lower when fenfluramine was administered. Fenfluramine reduced triglyceride values in scorbutic, but had little effect in supplemented animals. During fenfluramine administration, male weight gain is more retarded, but AA catabolism is enhanced in both sexes. When AA is available, fenfluramine administration is associated with raised cholesterol, when AA is deficient, hepatic cholesterol is reduced.

TABLE 1 *The effect of fenfluramine (F) on guinea-pig tissues (mean and standard deviations) after 24 days on a scorbutic diet (Sc) on a normal ascorbic acid intake (S). Significance of difference between normal and fenfluramine treated animals at $p < 0.05$ indicated*

	Normal intake					
Tissue values	Males			Females		
	S	FS	Sig	S	FS	Sig
Body wt. (g)	564±19	470±42	S	524±46	469±35	S
Plasma AA (mg/100 ml.)	1·40±0·09	1·05±0·15	S	1·89±0·13	1·05±0·15	S
Liver AA (mg/100 g)	31·2±2·1	9·6±1·4	S	34·7±4·4	18·2±2·0	S
Plasma chol. (mg/100 ml.)	150±15	115±30	S	124±15	150±14	S
Liver chol. (mg/100 g)	522±51	802±54	S	375±39	553±83	S
Plasma triglyc. (mg/100 ml.)	102±19	103±13	NS	125±18	122±18	NS
Liver triglyc. (mg/100 g)	1,859±104	1,626±173	S	1,969±137	1,954±167	NS
	Scorbutic					
Tissue values	Males			Females		
	Sc	FSc	Sig	Sc	FSc	Sig
Body wt. (g)	406±32	343±35	S	463±33	382±47	S
Plasma AA (mg/100 ml.)	0·22±0·07	0·30±0·11	S	0·58±0·11	0·39±0·12	S
Liver AA (mg/100 g)	6·0±1·1	3·2±0·9	S	12·2±2·2	9·3±2·4	S
Plasma chol. (mg/100 ml.)	240±28	73±15	S	179±19	108±23	S
Liver chol. (mg/100 g)	1,089±118	387±69	S	744±102	393±79	S
Plasma triglyc. (mg/100 ml.)	144±5	86±5	S	172±15	104±9	S
Liver triglyc. (mg/100 g)	1,304±288	1,312±80	NS	1,386±135	1,250±124	S

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The effect of glibenclamide on two enzymes important in gluconeogenesis

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Glibenclamide is a new and very potent hypoglycaemic sulphonylurea. The main mode of action of this latter group of drugs is now commonly accepted as being to

stimulate insulin release from the β cells of the Islets of Langerhans. However, many findings have come to light which cannot be explained by a pancreatic locus of action (Madsen, 1967 and Feldman *et al.*, 1969). In the case of glibenclamide, skeletal muscle and liver have already been proposed as potential extrapancreatic sites and indeed the present authors have shown that glibenclamide will enhance glucose uptake into the rat hemidiaphragm preparation in the absence of insulin (Foy & Standing, 1970).

The current investigation explored the possibility that the sulphonylureas may, in some way, reduce glucose release from the liver. Decreased liberation of glucose from the liver may be attributed to the blocking of key enzymes concerned either in the glycogen-glucose conversion, or in the conversion of non-carbohydrate precursors to glucose (gluconeogenesis). The effect of glibenclamide on two such enzymes, glucose-6-phosphatase (G-6-P) and phospho(enol)pyruvate carboxykinase (PEPCK, responsible for oxaloacetate→PEP), was investigated in rats both *in vivo* and *in vitro*.

In vitro, using the enzyme assay procedures of Wimhurst & Manchester (1970) statistically significant inhibitions were only shown at 0·39 mM for G-6-P and at 0·39 and 0·97 mM in the case of PEPCK.

In vivo alloxan diabetic animals were selected for the experimental group on the basis of a high blood sugar, care being taken to ensure that the hypoglycaemic phase was well past. No inhibition of enzyme activities was observed in animals which showed no evidence of functional pancreatic tissue.

If, as has been proposed, glibenclamide does in fact inhibit hepatic glucose output, it is unlikely that inhibition of these two enzymes plays a significant role.

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The effect of cyproheptadine on water and food intake and on body weight in the fasted adult and weanling rats

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Appetite stimulation and body weight increases following the use of cyproheptadine have been reported in man (Lavenstein, Dacaney, Lasagna & Van Mere, 1962; Bergen, 1964; Shah, 1968; Noble, 1969; Sanzgiri, Mohamad & Raja, 1970) and in cats (Chakrabarty, Pillai, Anand & Singh, 1967), and an increased food consumption in fasted rats (Baxter, Miller & Soroko, 1970) while no effect was observed in mature dogs or in mature or weanling rats or guinea-pigs (Lavanstein *et al.*, 1962; Bergen, 1964). However, we have observed some increase in body weight and in the water intake in fasted adult, but not in weanling rats.

Male adult rats (mean body weight range 133–176 g) and weanling rats (mean body weight range 33–37 g) were individually caged and fasted overnight but water allowed *ad libitum*. Body weight and 4 h water and food intake were recorded daily throughout the experimental period. After 1 week of control observation, 5 rats were given saline and 5 rats were given cyproheptadine 30 min before receiving food and water daily during the subsequent week.