References

Moussatché, H. & Prouvost-Danon, A. (1958). *Experientia*, **14**, 414.
Rocha e Silva, M. & Schild, H. O. (1949). *J. Physiol., Lond.*, **109**, 448–458.
Rothschild, A. M., Vugman, I. & Rocha e Silva, M. (1961). *Biochem. Pharmac.*, **7**, 248–255.
Rothschild, A. M. (1962). *Ibid.*, **11**, 979–980.
Rothschild, A. M. & Corrado, A. P. (1963). *Acta physiol. latinoam.*, **13**, 388.
Rothschild, A. M. (1966). *Handb. exp. Pharmakologie* (Histamine and Anti-Histaminics), editor Rocha e Silva, M., p. 143, Berlin: Springer.
Uvnäs, B. & Diamant, B. (1961). *Acta physiol. scand.*, **53**, 315–329.
Yamasaki, H., Muraoka, S. & Endo, K. (1960). *Jap. J. Pharmac.*, **10**, 21–28.
Yamasaki, H. & Saeki, K. (1965). *Proc. Japan Acad.*, **41**, 958–961.

Enlargement of liver in rats after chronic administration of flumedroxone acetate

SIR,—The synthetic steroid flumedroxone acetate (17-acetoxy-6α-trifluoromethylpregn-4-ene-3,20-dione; WG537; Demigran) has been used as a prophylactic treatment for migraine (summarized in Lundberg, 1966). The experiments reported here followed the observation that 100 mg/kg of flumedroxone acetate produced in the laboratory rat, after chronic intraperitoneal treatment, a liver weight increase. This steroid drug, together with 17-acetoxy-3β(β-carboxypropionyloxy)-6-trifluoromethylpregn-5-ene-20-one (VD682) was synthesized and provided by Leo Pharmaceutical Products Ltd., Ballerup, Denmark.

Female albino Porton rats weighing between 100–200 g, maintained on standard laboratory chow with water *ad libitum*, were used. Each steroid was suspended in water (1 ml) using compound tragacanth powder and introduced by gastric intubation. Control and treated animals were killed 24 hr after the last treatment and body and liver weights determined.

Table 1 shows that rats treated with flumedroxone acetate and VD682 have an increased liver weight when compared to control animals, or animals treated

TABLE 1. LIVER WEIGHT OF RATS AFTER TREATMENT WITH FLUMEDROXONE AND VD682

Drug	Dose mg/kg (No. days)	Animal weight range g	Mean body weight g (No. animals)	Liver weight g/100 body weight (range, g)
Flumedroxone acetate	10 (7)	100–149	130·4 (3)	5·7 (6·9–8·3)
	20 (7)		145·2 (2)	6·3 (7·6–8·9)
	50 (7)		141·5 (4)	6·3 (7·9–9·6)
	100 (7)		145·2 (4)	7·3 (9·4–11·8)
Flumedroxone acetate	100 (3)	100–200	152·5 (3)	5·7 (8·2–9·2)
	100 (5)		150·4 (2)	6·0 (8·8–10·6)
	100 (7)		145·2 (4)	7·3 (9·4–11·8)
	100 (14)		195·0 (2)	8·2 (15·0–16·7)
VD682	50 (7)	100–149	137·2 (3)	7·1 (8·4–10·8)
	100 (14)	150–200	185·4 (4)	10·5 (18·6–20·1)
Compound tragacanth powder	700 (14)	100–149	137·2 (6)	3·9 (4·3–6·0)
	700 (14)	150–200	161·4 (5)	4·1 (4·9–7·9)
None	—	100–149	138·1 (8)	3·8 (4·4–7·5)
	—	150–200	176·2 (9)	3·9 (5·3–8·2)

TABLE 2. LIVER WEIGHT OF RATS AFTER TREATMENT WITH STEROID COMPOUNDS FOR 9 DAYS

Drug	Dose mg/kg	Mean body weight g (No. of rats)	Liver weight g/100g body weight (range, g)
Progesterone	25	160·2 (5)	3·8 (5·4–6·8)
	50	152·5 (6)	5·0 (7·2–7·9)
	100	163·3 (4)	5·2 (7·2–8·1)
Flumedroxone acetate	50	138·2 (4)	7·2 (8·7–10·6)
VD682	50	136·7 (4)	7·8 (9·4–12·1)
None	—	164·1 (10)	3·8 (4·2–7·1)

with compound tragacanth powder. The relationship between dose level and duration of treatment was not completely elucidated by these experiments, although 50 mg/kg for a period of 7 days always gave an appreciable liver weight increase. Progesterone at 50 or 100 mg/kg gave a much smaller increase in liver weight than either of the synthetic steroids, Table 2. Other experiments have shown that the intraperitoneal route can reduce the treatment time or the dose level needed to achieve a liver weight increase comparable to that obtained when using the oral route. This held true for all drugs tested. An isolated experiment involved a pregnant rat on progesterone treatment in which the liver grew at striking rate: the rat had a final weight of 150 g; after progesterone 20 mg/kg for 6 days, the animal had a liver weight of 10·65 g or 7·1 g/100 g body weight: this increase is comparable to the liver weight reached after treatment with 50–100 mg/kg of flumedroxone acetate for 7–9 days.

These increases in liver weight have been shown to be accompanied by a change in the esterase electropherogram of serum and of liver tissue (Pantelouris & Hines, 1966). Chlorpromazine, phenylbutazone, SKF525-A and benzydamine can each produce in mice, after weekly treatment, a liver weight increase, a reduction in hexobarbitone sleeping time and a decrease in the retention of blood serum phosphatase (Silvestrini, Catanese & Del Basso, 1966). These drugs have also been implicated in the induction of microsomal enzymes, which in turn activates the breakdown of the inducer, or of quite different compounds (Conney & Burns, 1962; Remmer, 1964).

Phenobarbitone sodium can produce in mice an increased liver weight and a proliferation of the endoplasmic reticulum (Hart & Fouts, 1965). Probably of more significance to the present study is the report of enhanced development of pituitary tumours and the occurrence of some hepatomas in virgin female mice following repeated oral administration of synthetic progestins, including mestranol (Poel, 1966).

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References

Conney, A. H. & Burns, J. J. (1962). *Advances in Pharmacology*, **1**, 31–58, New York: Academic Press.
Hart, L. G. & Fouts, J. R. (1965). *Biochem. Pharmac.*, **14**, 263–272.
Lundberg, P. O. (1966). *Lancet*, **1**, 495.
Pantelouris, E. M. & Hines, W. J. W. (1967). *J. Endocr.*, in the press.
Poel, W. E. (1966). *Science, N.Y.*, **154**, 402–403.
Remmer, H. (1964). *Some Factors Affecting Drug Toxicity*, International Congress Series, Excerpta Medica Foundation, Amsterdam. n. 81. **4**, 57–77.
Silvestrini, B., Catanese, B. & Del Basso, P. (1966). *Biochem. Pharmac.*, **15**, 249–254.