packed to nearly 100 per cent with fibrin (quantitative counting of involved glomeruli in per cent).

The four negative results in the group of animals killed after 48 h suggested that even the rabbit with its poor fibrinolytic system can lyse fibrin in the kidney after the infusion is ended. This suggestion was confirmed by the experiments in which one kidney was removed at the end of the endotoxin infusion, whereas the second kidney was obtained 34 h later after the animals had been killed. This agrees with a previous observation that glomerular fibrin produced by thrombin and protease inhibitors are lysed spontaneously after the inhibitor is metabolized from the tissue in the rabbit[12]. One animal which did show fibrin deposition after 14 h developed macroscopic renal cortical necrosis, but only very little fibrin was found at that time.

We suggest that this new experimental model of endotoxin infusion enables a continuous study of the biological events of endotoxaemia and the development of renal cortical necrosis as a pharmacological dose response reaction to be made.

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Toxicity and Teratogenicity of Optical Isomers of Thalidomide

THE thalidomide molecule contains an asymmetric carbon atom, but the form of the drug which has been used therapeutically and which has produced congenital malformations in man is the optically inactive form, that is (±)-thalidomide. The optical antipodes of thalidomide have been synthesized[1,2], and Dr A. M. Creighton has supplied samples of both (+)- and (−)-thalidomide. The (+)-isomer, melting point 240°–241° C, showed $[\alpha]_D^{20} + 60°$ ($c = 2$ in dimethylformamide) and the (−)-isomer, melting point 241°–242° C, showed $[\alpha]_D^{20} - 58°$ ($c = 2$ in dimethylformamide). (±)-Thalidomide has a melting point of 271° C and, of course, is optically inactive. With these samples, we have determined the acute oral toxicities of the three forms in mice, their teratogenic activity in the New Zealand white rabbit and their effect on the hypnosis induced by hexobarbitone in mice.

Acute oral toxicities were determined by administering the compounds suspended in 1 per cent (w/v) carboxymethylcellulose in water to groups of twelve male *SAS ICI* albino mice (20–26 g body weight) and counting the mortalities after 24 h. The results (Table 1) show that the optically active isomers are much more toxic than the (±)-modification. After the administration of any one of the three forms at 0·25 g/kg, the mice were sedated but were capable of being aroused. With lethal doses of the (+)- and (−)-isomers, however, depression of the central nervous system was severe and the mice died after 4–15 h.

The teratogenicity of the compounds was determined by administering them orally in a dose of 150 mg/kg daily from days 7 to 12 inclusive of pregnancy to New Zealand white rabbits. On day 28 of pregnancy the animals were killed and the resorption sites and normal and abnormal foetuses were counted. The types of malformations produced by the (+)- and (−)-isomers were similar to those found with the (±)-form[3] and, as Table 2 shows, all three modifications were teratogenic.

Table 1. ACUTE TOXICITY OF THE OPTICAL ISOMERS OF THALIDOMIDE IN MICE

Optical form	Oral LD_{50} (g/kg)
(±)	> 10·0
(+)	0·4
(−)	0·7

Table 2. TERATOGENICITY OF THE OPTICAL ISOMERS OF THALIDOMIDE IN NEW ZEALAND WHITE RABBITS

Optical form administered	No. of rabbits	Implantations	Resorptions	Normal foetuses	Malformed foetuses
None	5	42	3	39	0
(±)	6	54	19	25	10
(+)	7	67	13	46	8
(−)	8	80	15	56	9

Table 3. EFFECT OF THE OPTICAL ISOMERS OF THALIDOMIDE ON THE TIME OF SLEEP INDUCED BY HEXOBARBITONE IN MICE

Optical form administered	Mean sleeping time min ± standard deviation
None	23 ± 7
(±)	45 ± 9
(+)	43 ± 6
(−)	49 ± 8

(±)-Thalidomide extends the time of sleep induced by hexobarbitone in rats[4]. This effect was examined in male *SAS ICI* albino mice with the three forms of thalidomide. The compounds (200 mg/kg) were administered orally to at least ten mice, 30 min before an intraperitoneal injection of 100 mg/kg of hexobarbitone sodium. The sleeping time was taken as the time between the loss and recovery of the righting reflex. Table 3 shows that any one of the three forms, in the conditions of the experiment, approximately doubles the sleeping time.

Thus, the three optical forms of thalidomide are teratogenic in the New Zealand white rabbit, are central nervous system depressants in mice, and are able to extend the time of sleep induced by hexobarbitone in mice. But the (+)- and (−)-isomers of the drug are much more toxic when given orally to mice than the (±)-form. The optically inactive form is known to be less soluble than the active isomers[5] and this could result in smaller concentrations in the blood. Crystalline (±)-thalidomide is probably a racemic compound and not simply a mixture or conglomerate of the two optical isomers. The physical properties of these isomers are being investigated.

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