Letters to the Editor

Traumatic and endotoxin shock in rats

SIR,—Previous investigations have shown that an increase in the generalised capillary permeability plays an important role in the pathogenesis of traumatic shock. Histamine production may be enhanced by activating the enzyme, L-histidine decarboxylase (Karady, Gecse & Horpacsy, 1962) and a fibrin film may develop on the interior surface of some of the capillaries (Jancsó, 1961), with the accompanying loss of fibrinogen. The administration of a substance Phlogodym, which decreases both fibrinogenesis and capillary permeability, was therefore tested in traumatic shock in rats. As endotoxins are considered to play an important role in the pathogenesis of traumatic shock (Fine, Frank, Schweinburg, Jacob & Gordon, 1952), a study has also been made of the effect of Phlogodym on endotoxin shock induced in rats. Phlogodym is a complex of pyrocatechin disulphonic acid and neodymium (Jancsó, 1961).

Traumatic shock. Rats weighing 180–250 g and of both sexes were used. Traumatic shock was elicited using the Noble-Collip technique (rotating drum method, 15 min at 40 rotations/min). Blood from the tail vein was collected and its fibrinogen concentration was determined using Schneider's method (1952). The extent of fibrinolysis in the blood was measured using the method of Burdon, McGovern, Barkin & Meyers (1961) and fibrinogen B was estimated by Cummine & Lyons' method (1948). Phlogodym (50 mg/kg) was injected 30 min before the traumatic shock, whereas heparin (200 units/kg) was given 15 min before and 15 min after the shock. ϵ-Aminocaproic acid was used in an intravenous dose of 1,000 mg/kg. The activity of endothelial system was reduced for 12 hr in a few experiments using saccharated iron oxide (2 g/kg intravenously).

There was a moderate decrease (50%) in the fibrinogen levels after traumatic shock. When Phlogodym was used before the shock, the fibrinogen level decreased almost to zero and the mortality rate increased sharply. The disappearance of the fibrinogen from the blood was confirmed by electrophoretic and immunological studies. The administration of ϵ-aminocaproic acid (which inhibits fibrinolysis) did not prevent the disappearance of the fibrinogen, but heparin (which enhances fibrinolysis) inhibited the reaction. This antagonism of Phlogodym by heparin was the result of the heparin removing fibrinogen B formed by Phlogodym, thereby inhibiting intravascular fibrin formation. When the endothelial system was blocked, Phlogodym was much more effective in potentiating the mortality rate after trauma.

Endotoxin shock. Groups of 10 albino rats (body weight about 200 g) were injected intravenously with 200 μg typhoid endotoxin after the animals had received either Phlogodym (50 mg/kg) or neodymium nitrate (100 mg/kg) intravenously 30 min previously. The results showed that both substances aggravated the endotoxin shock. For example, the mortality rate recorded over 24 hr rose from 20 to 80% with Phlogodym and to 90% with neodymium. On the other hand, in rats receiving the intravenous dose of endotoxin every second day in increasing amounts from 50 to 200 μg so as to achieve endotoxin resistance, the mortality rate only increased from 0% to 11% with Phlogodym.

The fibrinogen levels measured by Schneider's method (1952) were significantly decreased with Phlogodym and with neodymium but only about 4 hr after

the endotoxin. For example, the decrease with endotoxin alone was 50% but with endotoxin and each of the two agents the values were reduced almost to zero (minimum reduction was 90%). In rats made resistant to endotoxin, there was only a 50% decrease in the fibrinogen level using Phlogodym.

Thus, Phlogodym renders rats more sensitive to traumatic shock. The blood fibrinogen level falls dramatically, probably due to the promotion of intracapillary thrombi formation. As Phlogodym is an anticoagulant and an agent decreasing capillary permeability other factors are also involved.

As endotoxin enhances coagulation and reduces the fibrinogen (McKay, Shapiro & Shanberge, 1958), Phlogodym may exert a similar effect in both traumatic and endotoxin shock, thereby aggravating both the reactions.

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Some effects of propranolol on the central nervous system

SIR,—Propranolol, 1-isopropylamino-3-(1-naphthyloxy)-2-propanol, has been described by Black, Crowther, Shanks, Smith & Dornhurst (1964) as a potent β-adrenergic blocking agent. We wish to report the results of some experiments which show that propranolol has sedative and anti-convulsant properties (Table 1).

TABLE 1. DOSES AND ROUTES OF ADMINISTRATION FOR EACH OF THE EFFECTS MEASURED. THE VALUES QUOTED ARE THE MEANS AND 95% CONFIDENCE LIMITS FROM GROUPS OF 10 ANIMALS

Test	Species	Route	Dose mg/kg
Toxicity	mouse	i.v.	LD50 = 38·0 (26·0–55·5)*
	,,	s.c.	LD50 = 244 (224–289)*
Potentiation of narcosis	,,	,,	ED_{min} = 10**
,, ,,	rat	,,	ED_{min} = 25†
Ataxia	mouse	,,	ED50 = 17·4 (12·9–23·3)*
Muscular hypotonus	,,	,,	ED_{min} = 20‡
Partial blocking of electroshock	,,	,,	ED50 = 6·0 (4·55–7·93)*
,, ,, ,,	rat	,,	ED50 = 4·9 (3·20–8·96)*
Complete inhibition of electroshock	mouse	,,	ED50 = 14·4 (11·8–17·6)*
Antagonism of nicotine toxicity	,,	,,	ED50 = 10·0 (6·72–15·1)*
Antagonism of strychnine toxicity	,,	,,	ED50 = 38·5 (22·8–65·0)*
Antagonism of amphetamine grouped toxicity	,,	,,	ED_{min} = 5

*Results calculated from experimental data by the method of Litchfield & Wilcoxon (1949); **$P < 0.02$; †$P < 0.001$; ‡$P < 0.05$.

Narcosis was induced in mice by propranolol in a dose of 100 mg/kg, or more, administered subcutaneously. The duration of sleeping time in rats or