Calophyllolide was given to five male rabbits for a period of eight weeks. A first dose of 50 mg./kg. brought down the coagulation valency to between 18 to 22 per cent after 48 hr. The subsequent doses of 30 mg./kg. on alternate days thereafter maintained the coagulation valency between 20 and 30 per cent. These rabbits were then killed after eight weeks and on macroscopic or microscopic examination of liver, kidney, spleen, skin and mucous membrane, revealed no evidence of haemorrhage. Further studies are in progress.

No fatalities were observed in rats when calophyllolide was administered orally in doses up to 1,750 mg./kg. Its intraperitoneal LD50 in rats was found to be 560 mg./kg.

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Effect of Hydrocortisone on Capillary Permeability Changes Induced by *Echis carinatus* (Saw-scaled Viper) Venom in the Rat

SIR,—During recent years the corticosteroids have been reported to be very useful, alone and in combination with the specific antivenene, in the treatment of snake poisoning (Wig and Vaish, 1960; Gupta, Bhargava and Sharma, 1960; Benyajati, Keoplung and Sribhibhadh, 1961; Arora, Wig and Somani, 1962). Since a widespread capillary endothelial damage, with the resultant haemorrhages in various viscera, in the skin, in the mucous membranes and the accompanying shock, determine to a large extent the ultimate outcome of viperine snake poisoning in man (Ahuja and Singh, 1956), we have examined the effect of hydrocortisone on the capillary permeability changes induced by the *Echis carinatus* (the saw-scaled viper, a common poisonous snake in India) venom in an attempt to elucidate the exact mechanism of protective action.

Azovan blue dye, 20 mg./kg., was administered intravenously in male albino rats, Haffkine strain, weighing 150–200 g., and the extent and intensity of blue discoloration produced by 20 μg. each of 5-hydroxytryptamine (5-HT), histamine and the *E. carinatus* venom (freeze-dried form, dissolved fresh before use) administered in 0·1 ml. distilled water intradermally in the previously depilated abdominal skin of the rat was observed. An interval of 15 min. was allowed for the dye to accumulate at the site of the drug administration when the rats were killed and the skin removed (see Parratt and West, 1957).

The extent of capillary permeability, as indicated by the area of blue discoloration which developed due to the leakage of the vital dye-plasma protein complex (Spector, 1958) induced by 5-HT, histamine and the venom in the control and the hydrocortisone pretreated group of rats is summarised in Table I.

TABLE I

Drug (20 μg. in 0·1 ml. distilled water)	Diameter in mm. of blue discoloration 15 min. after the drug administration in groups of 10 rats	
	Control	Hydrocortisone acetate 10 mg./kg. i.p. 30 min. before the test
5-HT	20 (18–22)	14 (12–16)
Histamine	6 (5–7)	nil
E. carinatus venom	18 (16–20)	4 (3–5)

The results thus obtained show that hydrocortisone pretreatment inhibited the increased capillary permeability induced by the *E. carinatus* venom in the rat abdominal skin. From the evidence available at present, it appears that the corticosteroids protect against the viperine snake poisoning mainly by suppressing the increased capillary permeability induced by the venom, though other factors, particularly the favourable effect of corticosteroids against haemorrhages and shock, may also be contributing, because once the capillary endothelial damage has been produced by the viperine venoms, it cannot be reversed even by the administration of a large amount of the specific antivenene (Ahuja and Singh, 1956) though it is checked if the venom is neutralised early by the antivenene, suggesting that probably it is not the venom itself but some substance liberated by the venom in the body which leads to the increased capillary permeability. That the *E. carinatus* venom itself does not affect the capillary permeability has been shown by Somani and Arora (1962) in the rat skin, confirming experimentally that the increased capillary permeability induced by the venom is mediated mainly through a release of histamine and to a lesser extent through 5-HT. Our results suggest that the corticosteroids in some way inhibit the effect of the antigen-antibody complex on the capillary permeability. Nevertheless, the general response of the capillary wall also appears to be depressed, as the response to 5-HT is also decreased, both in extent and intensity of blue discoloration.

The present findings, moreover, confirm our earlier observations that the *E. carinatus* venom acts mainly through a release of histamine, since hydrocortisone almost completely blocked the response to the venom and that to histamine, though there was only a slight reduction in the response to 5-HT. If, on the other hand, the action of the venom was mediated through 5-HT release, the inhibiting effect of hydrocortisone against the venom would have been less marked.

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The Effects of Ether on Potassium Flux in Skeletal Muscle Preparations

SIR,—In anaesthetic concentrations, ether increases and in higher concentrations, decreases the response of striated muscle to potassium (Torda, 1944). Lorkovic (1959) has noted that in potassium-stimulated frog muscle, ether depresses the twitch fibres and potentiates the response of the slow fibres. Ether also alters the blood potassium levels. It decreases serum potassium in the dog (Gerschman and Marenzi, 1933), an effect preceded by an initial rise (Kiersz, 1948) and confirmed in man (Goodman and Gilman, 1955). Using cat erythrocytes, Davson and Reiner (1942) showed that ether increased the rate of efflux of potassium and decreased the inward movement of sodium. The effects of ether upon serum sodium levels are, however, irregular, and small (Kiersz, 1948; Gerschman and Marenzi, 1933). The ether-induced depolarisation of nervous elements (Lorente de Nó, 1947) and the suggestion that ether had a depolarising action at the neuromuscular synapse (Secher, 1951) led us to re-investigate the effects of ether and some volatile anaesthetics on potassium flux in skeletal muscle preparations.

Saturated solutions of the volatile liquids were freshly prepared by shaking with the appropriate saline for 15 min. at room temperature. The clear, anaesthetic-saturated layer was decanted and used.

Uptake and release of potassium-42 ($^{42}K^+$) from paired frog sartorius muscles and from rectangular strips of rat diaphragm were measured by a method similar to that of Lister and Lewis (1959) and Ahmad and Lewis (1962).

The effects of ether upon the twitch height, in response to both direct and indirect stimulation, in the isolated rat phrenic-nerve diaphragm preparation (Bülbring, 1946) and, using this preparation the actions of ether and tubocurarine (1 to 3 μg./ml.) on the $^{42}K^+$ efflux from $^{42}K^+$-loaded rats were observed.

In pentobarbitone-anaesthetised cats, the effects of adrenaline (50–100 μg./kg.), neostigmine (0·25 mg./kg.) and tubocurarine (100–200 μg./kg.) on ether-induced neuromuscular block and at the same time on blood serum levels of $^{42}K^+$ were studied.

The effects of ether, methyl n-propyl ether, chloroform and halothane upon acetylcholine-induced contractions of the isolated frog rectus abdominis muscle were also investigated.

In the isolated frog sartorius muscle and isolated strips of rat diaphragm, ether decreased the uptake ($P < 0{\cdot}001$) and increased the release of $^{42}K^+$. Qualitatively similar results were obtained using saturated solutions of chloroform, halothane and methyl n-propyl ether. Methyl n-propyl ether and ether also increased the release of $^{42}K^+$ from the frog rectus abdominis muscle. Ether