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33(3):861-864, 1966

24. PHARMACOLOGICAL EFFECTS OF THE VENOM OF *HAPALOCHLAENA MACULOSA*

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The octopus *Hapalochlaena maculosa*, banded octopus, was pinned out on cork and the brain pierced with a sharp instrument. The venom gland on each side was dissected. The gland was weighed and ground up with silica in Tyrode. Initial studies have been carried out with this Tyrode extract and more specialized chromatography is being done on an acid acetone extract.

Fig. 1 — Dissected venom glands removed from the Octopus.

In Australia fatal cases of poisoning from handling this octopus have occured and some near fatal cases. The beak like process allows venom injection. The most obvious physical feature is respiratory paralysis and prolonged artificial respiration can be expected to end in survival.

The venom gland is the posterior salivary gland and the banding on the octopus is not unlike that on the cone shell and the tiger snake which also produce neurotoxin.

The isolated jejunum of the guinea pig was tested for activity and the responses are similar to those produced by snake venom. They differ in that this venom greatly reduces the sensivity of the gut to histamine and contraction to the venom is immediate. Following the immediate contraction there is a typical delayed S.R.S. reaction such as we have in anaphylaxis and with snake venom. We are now engaged in purification studies to dissociate these responses.

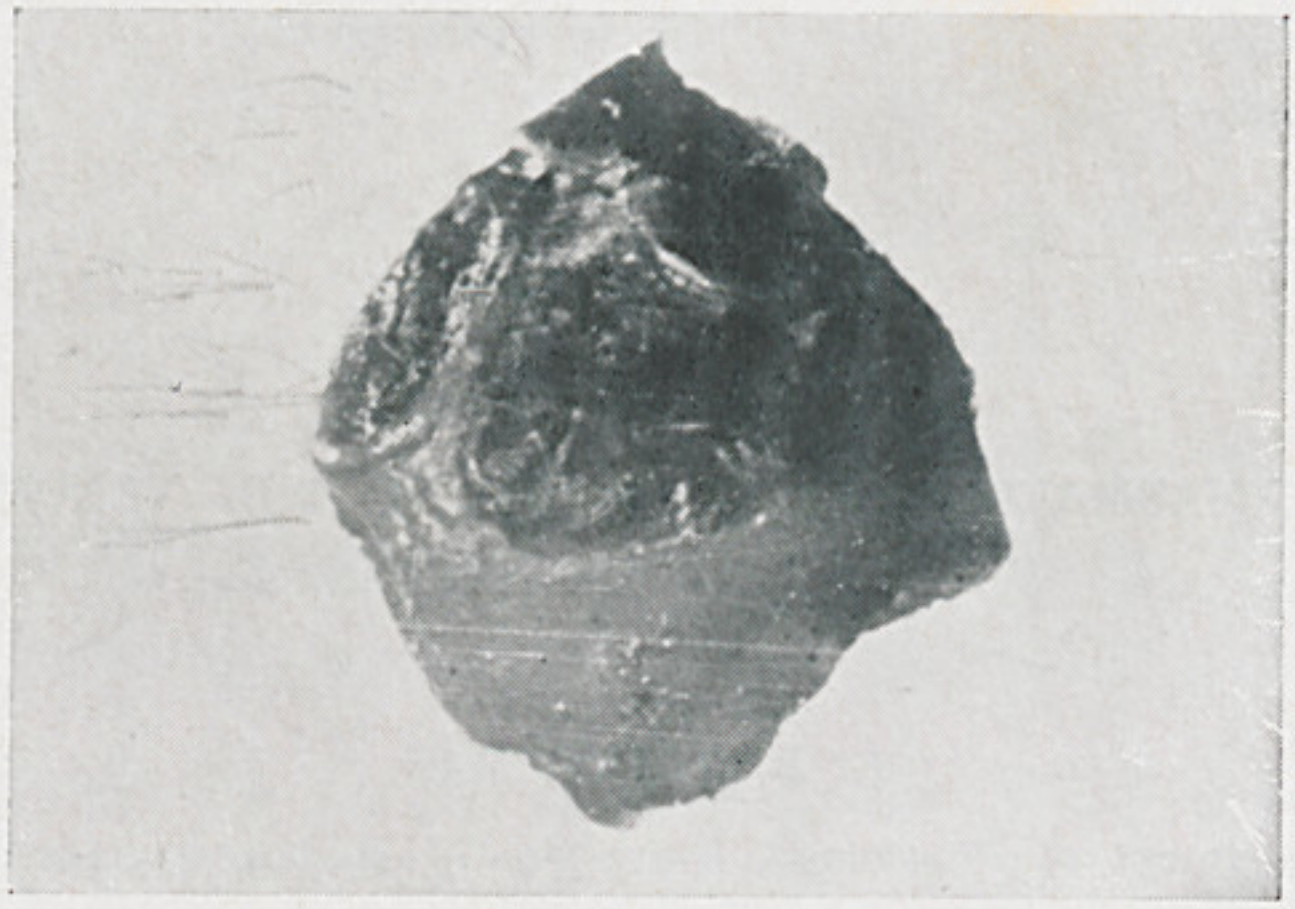

Fig. 2 — Beak like process attached to the terminal ducts of the gland.

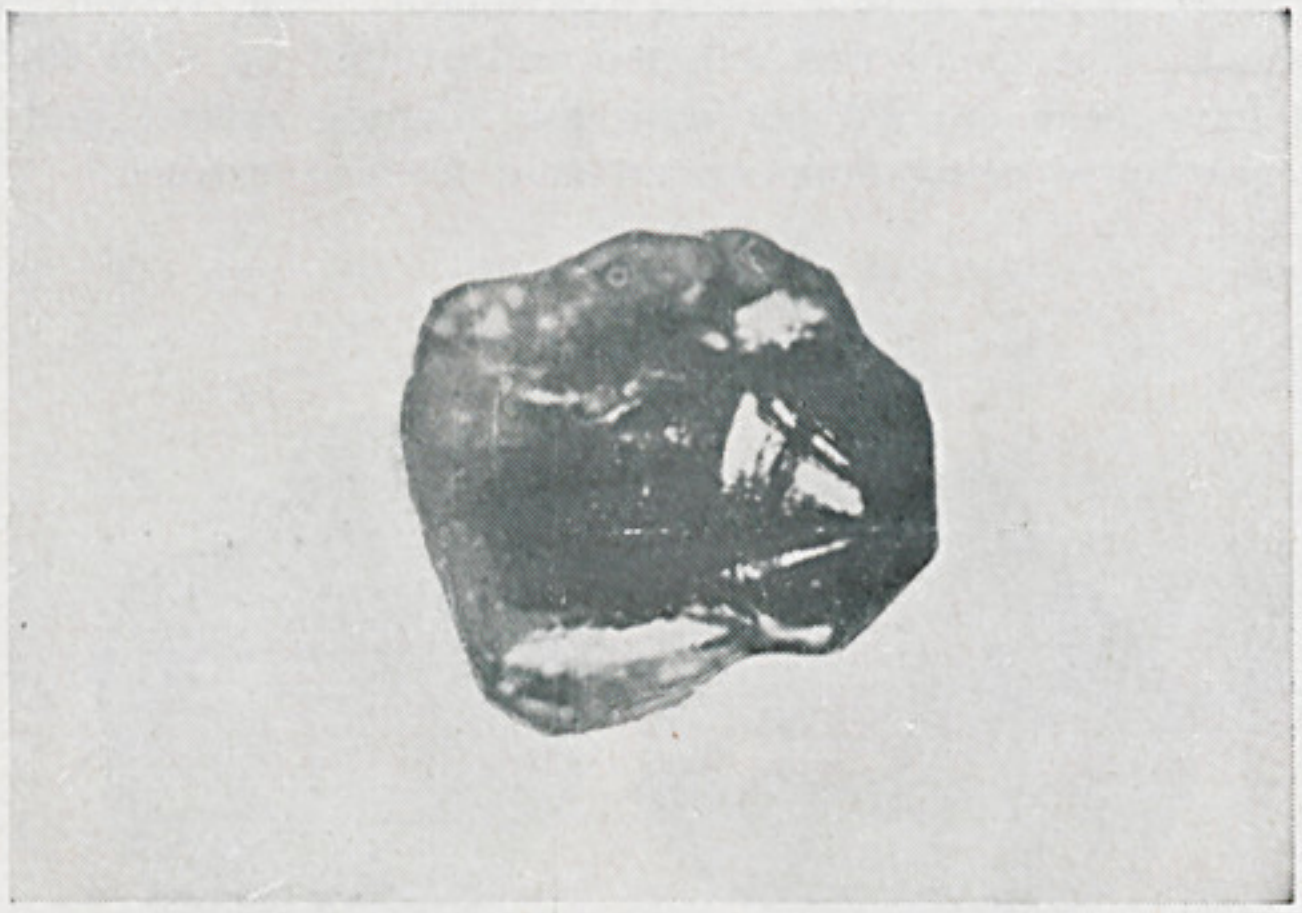

Fig. 2a — View of beak like process indicating the solidity of the beak allowing skin penetration.

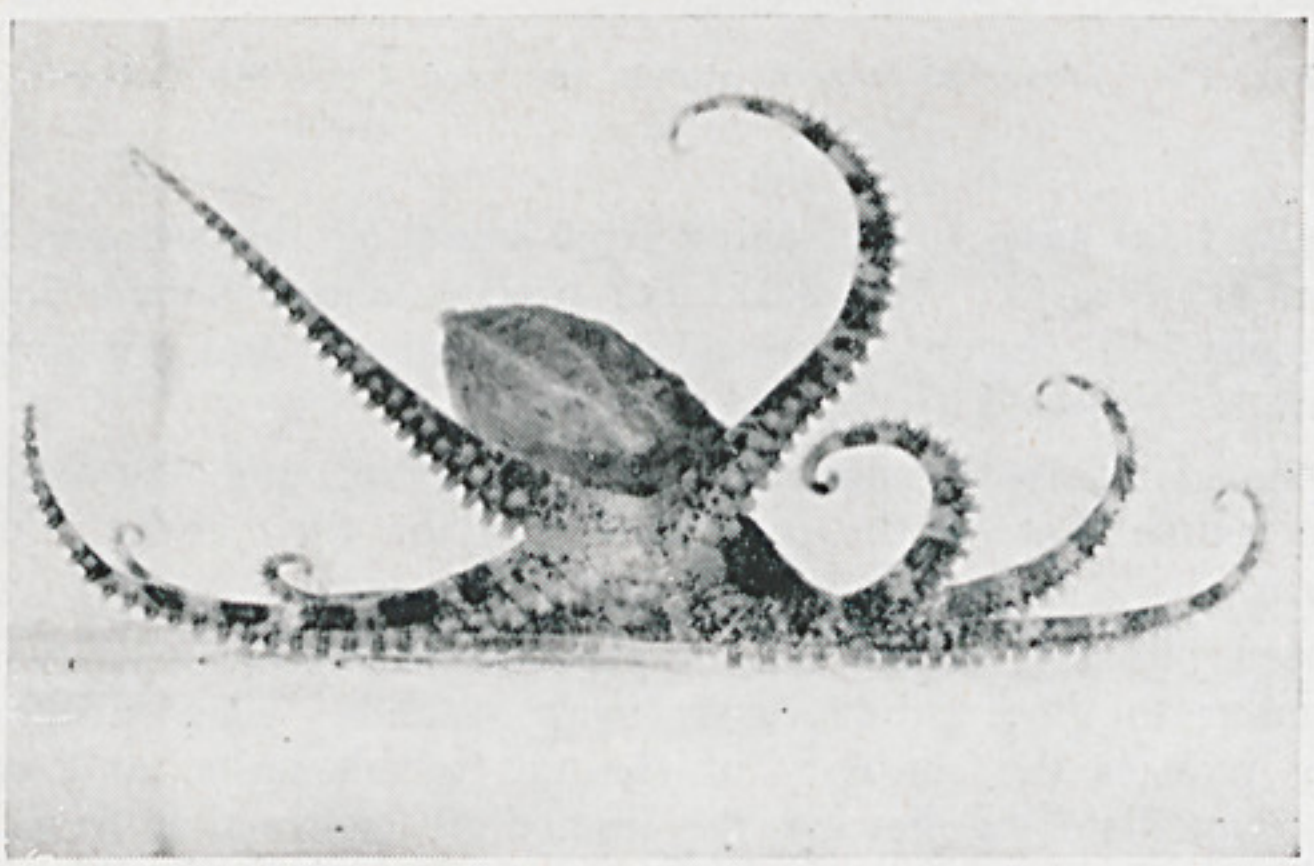

Fig. 3 — View of Octopus showing banding on tentacle.

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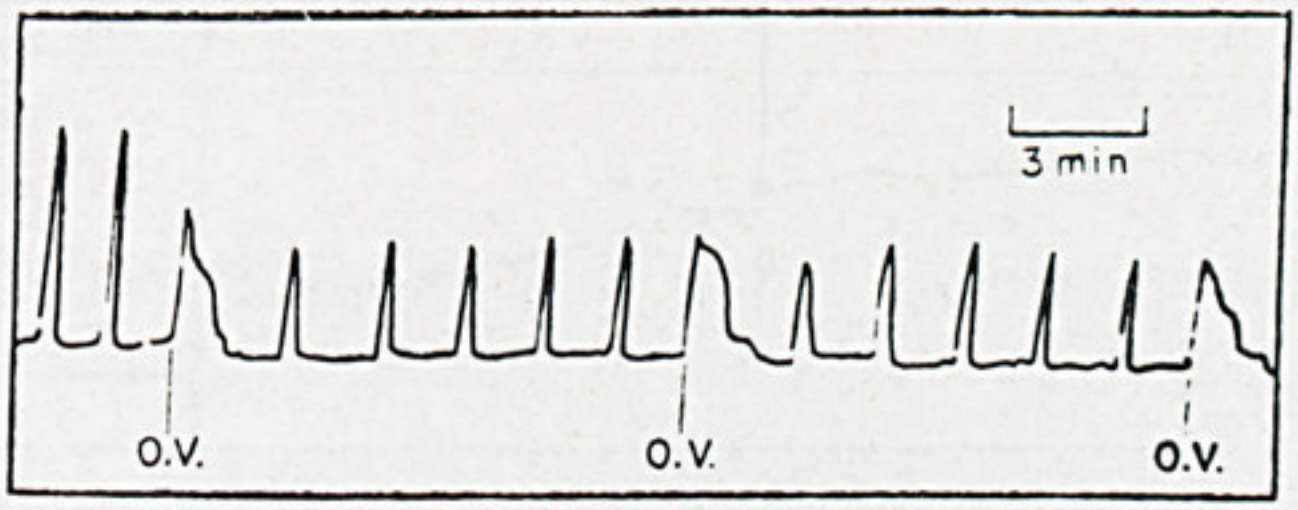

Fig. 4 — Responses of isolated jejunum of guinea-pig O.V. 4.5 mg Venom extract showing immediate contraction followed by delayed relaxation. Unlettered contractions to 0.1 μg histamine. Halving of responses after venom injection.

When we perfuse the isolated heart of the cat we find that venom in doses quite effective on the gut produce very little effect on the heart. The amplitude of contraction falls off only slightly more rapidly than that of control hearts. The coronary flow is also little affected even when the venom is recirculated with the perfusion. The rate of the heart is slowed immediately following injection of venom but this recovers rapidly. The ECG under the Langendorf type perfusion with Tyrode normally soon shows block in contra distinction to that of the blood perfused heart which is normal. We were not able therefore to determine with this technique whether heart block could occur from a direct effect of the venom and its appearance in the intact animal follows probably from anoxia.

Fig. 5 — Contraction of the isolated perfused heart of the cat. At arrow, intracoronary injection of venom (18 mg). There is little fall off of amplitude over 40 minutes. Time S = 1 min, R = 1 sec, M = 10 sec intervals.

In the intact cat following the injection of gland extract intravenously the respiration slows and the blood pressure declines slightly. Sometimes respiration stops, returns temporarily, and finally ceases a few minutes later. Large doses of gland extract lower the blood pressure significantly and this is coincidental with failure of respiration. Artificial respiration and cardiac massage have not been adequate to restore the animal in acute experiments.

The rat diaphragm preparation is very sensitive to venom extract. The response to indirect stimulation is rapidly abolished. At a later stage the response to indirect stimulation fails and recovery on repeatedly washing out the bath occurs in reverse order; but the response to nerve stimulation remains impaired for a very long time.

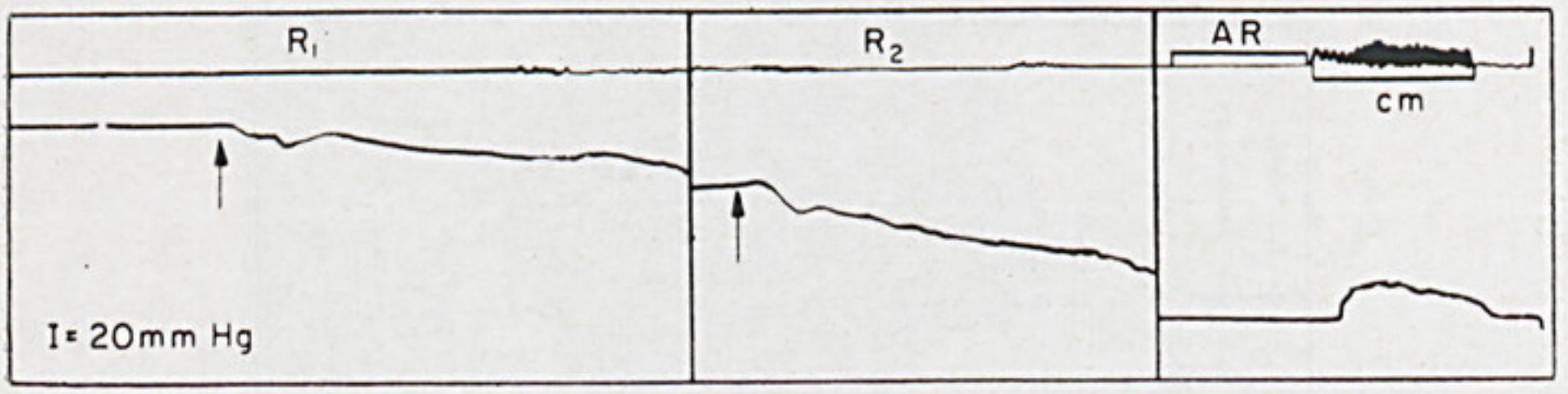

Fig. 6 — Upper tracing — respiration. Lower tracing — blood pressure, in the intact cat. At the arrows, venom extract injected, 18,50 mg gland extract. Respiration after temporary increase soon fails. Blood pressure slowly declines with temporary depression from extract. Respiration fails completely before heart beat fails.

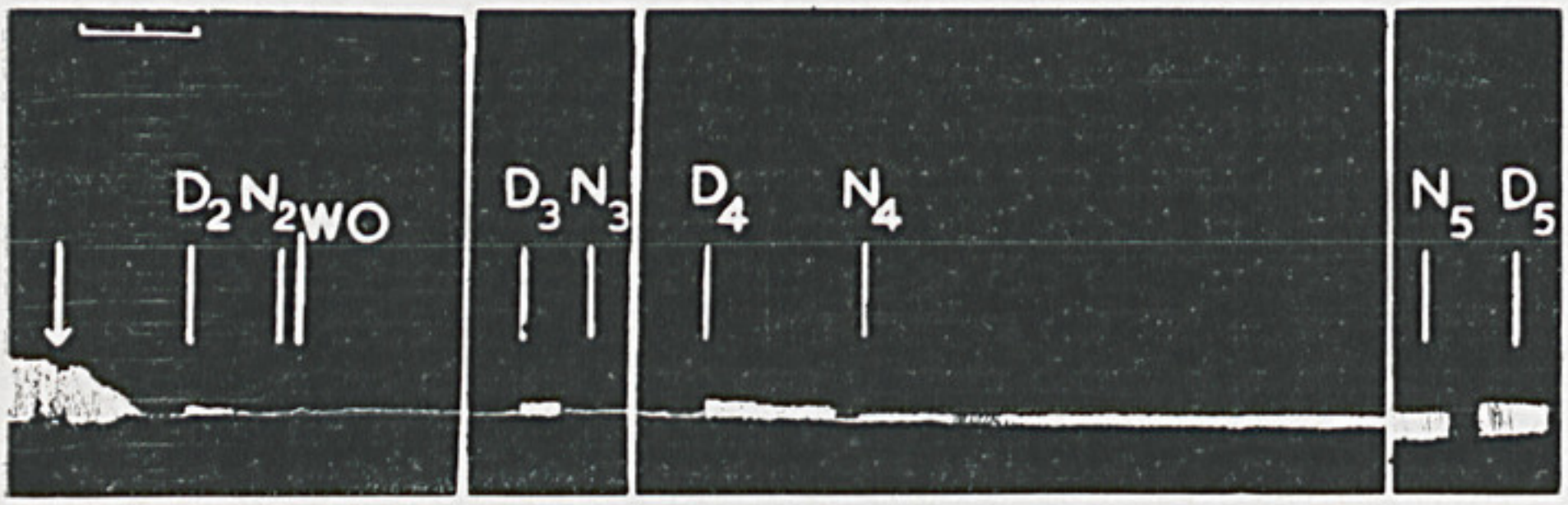

Fig. 7 — Responses of rat diaphragm to (D) direct and (N) indirect (phrenic nerve) stimulation. Failure to direct stimulation is not complete nor as severe as that to indirect stimulation, and recovers much more rapidly.

It is apparent that the main effect of the venom is respiratory paralysis. Cardiac effects are largely secondary, probably due to anoxia, and appear in the intact animal but to no marked degree in the isolated heart. Respiration fails before the blood pressure falls significantly. One would expect the blood pressure to rise with the failure of respiration from asphyxia unless the venom has a similar effect on the vaso-motor centre or peripheral arteriolar inervation as it has on the rat diaphragm. It may well be that there is a central effect on respiration also and we shall investigate this possibility later. The temporary slowing of the heart but without impaired amplitude of beat suggests some direct cardiac effect similar to that of the venom on the muscle of the diaphragm and the gut.

The isolated diaphragm progressively shows failure of transmission of the nerve impulse as well as less evident direct muscle depression and since this effect is rapid and marked in relation to quantity of gland compared with any cardiac effect it would appear that the main effect of the venom is in blocking nerve conduction and so causing death. It would therefore appear advisable in man in addition to applying artificial respiration to administer prostigmin, and thereby enhancing transmission.

Chromatographic studies indicate there are two muscular toxins.