EXPERIENTIA

Vol. 29 – Fasc. 11 Pag. 1317–1452 15. 11. 1973

Notes on Toxinology

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Introduction

Many more species of the Animal Kingdom are toxic than is usually assumed[1,2]. Laypeople often refer to animals as being either venomous or poisonous when these are known to be harmful to man only. Even today toxinology suffers from being studied from a rather anthropocentric viewpoint. In fact, until the 1950s, most scientific papers on toxic animals were written by representatives of the medical profession, the practitioners being, of course, concerned with the various envenomations or intoxications of patients. One notable exception has been the zoologist J. STROHL[3], who, in 1926, pointed out that toxicity in animals was a subject mainly of biological range. Even the outstanding oeuvres by PHISALIX[4] and by PAWLOWSKY[5] are characterized by their anthropocentrism. Nonetheless, these two workers layed the actual basis for a more comprehensive toxinology in that they gave much more information on toxic animals than would be necessary for purely medical aims. It was not before 1958 that two scientists, KAISER and MICHL[6], published their remarkable review on the biochemistry of animal toxins. Since that time much progress has been achieved in the field of toxinology, mainly with respect to chemistry, immunology and, more recently, pharmacology. The few fields mentionned, adjacent to toxinology, indicate how plurivalent toxinology is. Also, the existence of the International Society on Toxinology and the publication of its Journal Toxicon, since 1962, demonstrate that toxinology belongs to the most modern branches of the sciences.

However, whilst the results of current research may help to solve more of the problems encountered by physicians, chemists, immunologists and pharmacologists, the biological aspects of the phenomenon of toxicity in the Animal Kingdom must not be neglected. Toxinology is not only of medical relevance; it is to be considered mainly as a biological science. In order to avoid a onesided view, biased by medical concern, one has to bear in mind that man is always in the role of a potential enemy when meeting toxic animals. In order to reach a deeper understanding, in a broader context, we feel, that toxic animals must be studied as entities, i.e. including their natural environment and their behaviour.

Terminology

In the field of toxinology not all terms are generally accepted. Some of them are used without being clearly defined; others are used in different ways. Hence, it may be beneficial to briefly define a few terms which are to be discussed later in this paper. For a more explicit characterization of terms, reference is made to a previous paper by one of us[1].

We consider 'toxin' to be the more general term for substances potentially noxious to living organisms, in the sense of KAISER and MICHL[6]. With reference to the Animal Kingdom, toxins may be subdivided into 'venoms' and 'poisons'. *Poisons* may be considered as metabolic by-products, either produced or stocked in various animal organs. Under natural conditions all poisons act upon ingestion. As far as we know, under artificial conditions, poisons may also act by parenteral route. It may be pointed out here that the term 'poisonous' applies almost exclusively to the effect on man and some domestic animals since virtually no experiments were conducted with other animals, e.g. natural enemies. Furthermore, it is presumably correct to distinguish between 'primary poisonous' and 'secondary poisonous' animals. 'Primary poisonous' are those animals in which the poison is actually produced, e.g. dinoflagellates, certain fish (roe) and

[1] T. A. FREYVOGEL, Acta trop. *29*, 401 (1972).

[2] W. BÜCHERL, E.E. BUCKLEY and V. DEULOFEU, *Venomous Animals and Their Venoms*, 3 vols. (Academic Press, New York, London 1968).

[3] J. STROHL, *Die Giftproduktion bei den Tieren* (Georg Thieme, Leipzig 1926).

[4] M. PHISALIX, *Animaux venimeux et venins* (Masson, Paris 1922).

[5] E.N. PAWLOWSKY, *Gifttiere und ihre Giftigkeit* (Gustav Fischer, Jena 1927).

[6] E. KAISER and H. MICHL, *Die Biochemie der tierischen Gifte* (Franz Deuticke, Wien 1958).

newts (*Taricha spec.*); 'secondary poisonous' are animals which acquire poison by feeding on 'primary poisonous' animals, e.g. clams, mussels, fish and possibly others. (This definition applies equally well to animals feeding on 'primary poisonous' micro-organisms or plants.)

Venoms are produced in specialized glands. All venoms act either upon parenteral application or else, upon contact. Upon oral ingestion by mammals, many of them are destroyed. They are needed by the animals concerned, either exclusively for self-defense ('VD-animals'), e.g. scorpionfish, or primarily for the obtainment of prey ('VP-animals'), e.g. snakes or spiders. In lower Hymenopterans, (e.g. several species among the Terebrantes), venoms serve the obtainment of 'prey' for the progeniture. Furthermore, most VP-animals may apply their venoms for self-defense. In the group of VP-animals all venom apparatus are complete, i.e. they are composed of glands, excretory ducts and a means of application such as fangs, cheliceres, dart, etc. VD-animals, on the other hand, may show incomplete venom apparatus, without means of application, e.g. in amphibians or the boxfish, or in rare instances without an excretory duct, e.g. lionfish (*Pterois spec.*).

Requirements

In order to come to a clearer conception of the role of toxins in animal life it may be useful to observe the requirements which are necessary for either poisons or venoms and their apparatus.

As was mentioned above 'VP-venoms' serve in the obtainment of prey or the care of the progeniture. In either case the prey has first to be immobilized. For that, the animal must be capable of applying its venom in an efficient way; the venom then must induce almost instant paralysis or shock. When prey is concerned, it may be killed by the same immobilizing action and also pre-digested by enzymes contained in the venom. If food for progeniture is concerned, in a number of instances, it has to be preserved for the developing offspring and is neither killed nor pre-digested. (Some of the following papers in the coming issues of this Journal will discuss chemistry and pharmacological action of venoms, particularly of neurotoxins.)

Secondarily, many VP-animals may use their venom apparatus for self-defense. Some animals however, although possessing a venom apparatus and being capable of using it for self-defense, have evolved defense mechanisms independent of their venom apparatus. Before biting, various snakes often warn, e.g. 'puff'-adders and 'rattle'-snakes. Centipedes frighten an enemy by suddenly raising their anal legs; they bite only if the enemy insists. Some mygalomorph spiders may scratch spiny hair off the abdomen, which irritate the enemy's mucous membranes and skin. Other animals do use their VP-apparatus more readily for self-defense, but as a rule, apply only enough venom needed to deter the enemy and not to kill him. One particularly good example of this are the 'spitting cobras'[7]. The same phenomenon may explain why in 2–3, out of 4 cases of bites by potentially dangerous snakes, patients suffer from no severe consequences of envenomation[8]. Finally, it may be pointed out that some animals apparently did not evolve a behaviour which enables them to use their VP-apparatus for self-defense. For example, such might be the case with worm-feeding Conid snails, e.g. *Conus chaldeus*[9]; it may also apply, though to a lesser extent, to many scorpion species as well as to a number of Heterophaga (Terebrantes) among the Hymenopterans. It is interesting to note that the animals mentioned, produce venoms which affect man only mildly and which, in some cases, might be highly 'prey-specific'.

With regard to VD-animals the requirement is that they are in a position to get rid of enemies. This may be accomplished by a simple determent or in extreme cases, by a killing action. Determent may be achieved by a surprise, in combination with unpleasant odours such as with bombardier beetles and some other Coleopterans; it may also be achieved by causing pain, as experienced from dermatitis, blister formation, etc. More dangerous action may be observed where highly toxic substances are available and where parenteral application is rendered possible by a complete venom apparatus. This is the case particularly with various venomous fish, and possibly, with the starfish *Acanthaster planci*[10].

It may be considered peculiar that there are animals which produce rather toxic substances in specialized dermal glands, which they have no means to apply parenterally and which, therefore, have a limited effect where man is concerned. This situation applies to the majority of amphibians and, perhaps, to many more animals.

Regarding poisons, it is difficult to define the requirements. For, little is known about their biological functions. They afford no individual protection. They could be important for the protection of whole species. Provided specimens are easily recognized they will be avoided by potential enemies. Many poisonous fish, especially reef-fish, catch the eye (of man!) by bizarre shapes and/or bright colours. The efficiency of the combination of poison and a striking appearance is

[7] T. A. FREYVOGEL and C. G. HONEGGER, Acta trop. *22*, 289 (1965).
[8] H. A. REID, Trop. Doctor *2*, 155 (1972).
[9] H. MARSH, Toxicon *8*, 271 (1970).
[10] B. W. HALSTEAD, *Poisonous and Venomous Marine Animals of the World*, 3 vols. (U.S. Government Printing Office, Washington D.C. 1965–1970).

thought to increase with the learning capacity of the predator and his ability to communicate this information. If cases of mimicry could be demonstrated in this context, these would present a strong indication for the protective and selective value of poisons.

There is a further group of toxic animals for which the value of toxicity is not yet understood. They are classified as 'ichthyocrinotoxic'[10] e.g. boxfish (*Ostracion spec.*), which show dermal glands at the bases of the tail and fins, and in connection with the buccal orifice. The presence of dermal glands, producing toxins, without means of application, is similar to the situation in amphibians. It is questionable if a special term, like 'ichthyocrinotoxic', is necessary and justifiable. Even if it is, the term would seem somewhat misleading, in that it appears to place the fish concerned into the context of 'ichthyosarco'- 'ichthyohaemo-' and 'ichthyootoxic', i.e. poisonous fish. The production of toxic substances in special glands, the contents of which are excreted into the outside world, however, clearly demonstrates the venomous (as opposed to poisonous) character of the animals concerned.

As to the functions of the venom apparatus it has been suggested[10] that it is used for self-defense as well as for the control of population dynamics. The venom might serve as a repellent to other fish and even to its own species. Its application may be seen in the context of the solitary mode of life of the boxfish. Further to this, the idea has been put forward that the venom might serve for the control of ectoparasites[10]. If these assumptions should prove correct, new dimensions would be added to the field of toxinology.

Conclusions

Some of the papers to follow in the present series of communications on toxinology will show that in the field of chemistry, physiology, pharmacology and immunology, as well as molecular biology, animal venoms provide us with some particularly useful models. Obviously, this is one of the main reasons for the growing interest shown by numerous scientists in animal toxins.

With reference to medicine, more research is needed in the field just mentioned with the aim of improving medical care. In addition, however, it is postulated that research on the behaviour of venomous animals towards man, and research into the quantities of venom actually applied to man, be intensified. Also, on the basis of results in this context, people most exposed could be provided with more and better information about prevention.

Work of this sort requests the collaboration of biologists, who observe toxic animals in their natural habitat and who investigate in particular when, and under what prerogatives, the animals make use of toxins in their natural surroundings. Thus we end up with what has been said in the introduction to these notes: toxic animals are to be studied as entities and toxicity has to be looked at from all aspects essential for life, possibly including parasite and population control.

Should the very last point prove valid, fascinating links could be established between toxinology and ecology and in turn migt become important for nature conservation. Thus, toxinology is but a budding field, the limits of which, can yet only be assumed.

Chemistry of Some Potent Animal Toxins

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Introduction

My theme is to give a short review of the present knowledge of animal poisons, especially neurotoxins. The subject is a vast one, as there are thousands of poisonous animals with many different types of toxins. I have therefore chosen to limit myself to discussing only the most active toxins, which are almost exclusively neurotoxins. This selection is perhaps more justifiable on psychological rather than on scientific grounds, since the primeval interest in poisonous animals and their toxins inherently involves the attitude: the more poisonous – the more interesting. It is suitable to begin with a description of snake venom neurotoxins, since no animal has played such a role in religion and superstition as the snake, and the snake is still today the most feared animal[1]. There are, however, also other reasons to give snake venoms priority in this article: we know more about snake venom neurotoxins than about any other group of animal poisons.

[1] R. Morris and D. Morris, *Men and Snakes* (Hutchinson and Co. Ltd, London 1965).