Venomous Animals and Their Venoms

EDITED BY W. BÜCHERL, E. BUCKLEY, AND V. DEULOFEU

Volume I
Venomous Vertebrates

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VOLUME I Venomous Vertebrates

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Preface

The modern trend in the study of the wide field of venomous animals and their venoms is directed toward basic research that emphasizes zoological ecology, biochemistry, pharmacology, and immunobiology. The increasing importance of this development, stimulated also by the political and industrial expansion into the undeveloped areas of the tropics, is reflected by the great number of publications on venoms of animal origin. Every year about 10,000 papers are published on this subject, scattered in hundreds of journals in many languages, thus making it impossible for the individual scientist to keep abreast of new developments.

The present treatise is an attempt to offer, for the first time, a comprehensive presentation of the entire field of the venomous members of the animal kingdom, of the chemistry and biochemistry of the venoms, of their pharmacological actions and their antigenic properties. The medical aspects, both symptomatology and therapy, are included. The work is the result of close cooperation of fifty-three scientists from thirty-two countries on all continents. The authors are highly qualified specialists in their specific areas of research; their concerted efforts made this book one of unusual scope and depth.

This first volume of the three volume work is devoted to venomous mammals and begins the extensive section on snakes. Volume II will complete the discussion on snakes and include the saurians, batrachians, and fishes. The venomous invertebrates, such as insects, centipedes, spiders, and scorpions, venomous molluscs, and marine animals, will be considered in Volume III.

The interdisciplinary aspects of the subject necessitated assigning several chapters to a single group of animals and offering separate sections covering the zoological, chemical, and biomedical points of view.

It is hoped that these volumes will be valuable reference works and stimulating guides for future research to all investigators in the field; they will also serve the needs of physicians and veterinarians seeking information on the injuries caused by venomous animals. The volumes should also facilitate the teaching of this important topic and should prove a welcome source of instruction to students and to the large group of laymen interested in this fascinating field of natural science.

The editors wish to thank the authors for their cooperation and for generously contributing the results of their work and experience.

Our thanks are also due to the staff of Academic Press for helpful advice, patience, and understanding.

We cannot conclude this preface without expressing our gratitude to Professor Dionysio de Klobusitzky who conceived the idea of this book and outlined its initial organization.

WOLFGANG BÜCHERL
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October 1967

Introduction

The so-called venomous animals described in these volumes possess at least one or more venom glands and mechanism for excretion or extrusion of the venom, as well as apparatus with which to inflict wounds. The venom may be injected at will. These animals have been characterized by several authors as being "actively venomous." The "passively venomous" species have venom glands and venom-excreting ducts, but lack adequate apparatus for inflicting wounds.

In their struggle for life, all venomous animals seem to be rigorously extroverted. Their energies are directed against the other animal and vegetable organisms in their environment. All the venom glands of these animals are of the exocrine type. Their venoms, produced by special epithelial cells and stored in the lumina of glands, are always extruded to the outer world, generally by biting or stinging such as is the case with shrews, serpents, saurians, stinging insects, scolopendrids, spiders, scorpions, some fishes, molluscs, some echinoderms, and worms. Other animals envenomate the victim by direct bodily contact such as is true of caterpillars, certain echinoderms, sea anemones, jellyfishes, and hydroids. All venomous animals possess characteristics which distinguish them from other members of the animal kingdom. Often venomous animals are hunters, predators, solitaries, and also enemies of other members of the animal kingdom. There are exceptions, of course, such as the social Hymenoptera.

The wounding apparatus is located on the head, on the hind portion, or over the entire exposed surface of the animal. In shrews, serpents, and Gila monsters, the venom apparatus is inside the mouth. The venom glands are in fact salivary glands; the bite is inflicted by modified teeth equipped with venom canals. In scolopendrids and spiders, the venom system is situated outside the mouth, but is in close proximity to it, and is designed for protection and acquisition of food. A strange situation is present in the scorpion: the venomous mechanism is found in the last segment of the body, the "cauda venenum." In fact, the scorpion sting must be considered "peribuccal." The scorpion is able to move its tail sufficiently far in front of its head to kill its prey before eating it.

In the venomous Hymenoptera, such as ants, bees, wasps, and hornets, the wounding apparatus and the venom glands are also situated in the

last segments of the abdomen, far from the mouth. The stinging mechanism may function primarily as an ovipositor, having no connection with the mouth, and its venom-injecting function may only be secondary.

In some venomous fishes, molluscs, and bristleworms, the venomous organs may be distributed over certain exposed portions of the body or may cover more or less the entire body surface, as in caterpillars, some echinoderms, and coelenterates, with no relation to the mouth.

The location of the venom system and the transformation of certain organs into venom-conducting channels may lead us to theorize on the significance of venom in the animal kingdom. Why do venomous animals exist? What is the primary function of venom? Are venoms present principally for digestion of food, and is the wounding apparatus intended for self-defense and even attack in the never-ending struggle for survival? Is the stinging function designed mainly for oviposition, or for defense and attack, and is it combined with the mechanism for obtaining food and provision for offspring, as is true for all the solitary wasps? Thus, the role of venoms immediately appears very complex.

Shrews, serpents, scolopendrids, spiders, scorpions, solitary wasps, and some coelenterates are exclusively *carnivorous,* but they never feed on an animal that is already dead. They are predators and active hunters, and they capture and kill their prey. The social wasps, bees, hornets, and caterpillars are exclusively *herbivorous;* other venomous animals may be *omnivorous,* i.e., they will feed on creatures that have died of other causes.

The venom and wounding apparatus must also be considered in relation to *sex,* particularly in venomous adult insects such as bees, wasps, and hornets. Only the adult female Hymenoptera are poisonous, not the adult males. In all other venomous animals both sexes may be equally poisonous, or the males, which are much smaller, may do less serious harm, as is true of most spider species.

Consideration of the localization of the venom apparatus, the mode with which these animals take their prey or their food, and the fact that often only one sex bears a venom-conducting apparatus may guide us to another very important question: For what purpose is the venom used?

Toads, venomous frogs, salamanders, and other "passively" venomous animals certainly may use their toxic products for self-defense. Often these animals may not rely entirely on their venomous power, but may prefer to use other protective methods such as mimicry, flight, and concealment. Caterpillars and other Lepidoptera larvae are also in this category. They procure food only from plants, and desire peace from other animals.

One habit of several solitary wasps is rather curious: They use their

stinging apparatus to paralyze spiders and other insects. Then they bring the prey to the nest, deposit an egg over the body of it, and close the orifice of the nest. The wasp larva, hatched a few weeks later, thus is provided with fresh food. These wasps possess a nerve- or muscle-paralyzing venom with long-lasting effect and they may attack in order to protect their offspring. The social Hymenoptera, such as the bee, wasp, and hornet, may use the venom apparatus primarily for defense against enemies, even against other groups of the same family. Also, they may attack and kill, e.g., the females of bees kill the males after fertilization of the new queen. A newly hatched queen bee kills all the other queens present in the hive. Thus the stinging apparatus and venom have both defensive and offensive functions. The venomous fishes, coelenterates, and echinoderms, as well as the bristleworms, use the wounding mechanism for self-defense.

It is curious that in all these animals—toads, salamanders, bees, wasps, hornets, caterpillars, some fishes, molluscs, sea cucumbers, urchins, starfishes, sea anemones, jellyfishes, and the like—the venom and the biting or stinging system have nothing to do with the acquisition of food. In the aggressive predators, such as the solitary wasp and the social bee, under certain circumstances, the venom system may be transformed to provide food for the young. Consequently, the venom apparatus will have nothing in common with the digestive or salivary organs.

In scolopendrids, spiders, scorpions, venomous snakes, Gila monsters, and venomous shrews, the venoms, venom apparatus, and the wounding system are designed primarily for food acquisition, and not so much for the predigestion of food. This is especially true of scorpions. Their venoms are paralyzing, not digestive agents. They use the sting only when the prey is large and vigorous in defending itself, as spiders. Small animals are captured directly with the pedipalps, and immediately killed and eaten; the sting is not needed. Scolopendrids and spiders use the wounding apparatus in two ways: to hold the prey and introduce it into the mouth, or, when resistance is offered, to inject and kill the prey with the venom. The salivary function of venom in scolopendrids, spiders, and especially in scorpions may be questionable.

The situation appears to differ with snakes, venomous saurians, and Insectivora. Since the venom glands and the venom-injecting apparatus are found in the mouth, with phylogenetic transformation of a few teeth, and the venom glands may be true salivary glands, with or without digestive ferments and enzymes, one might think that the main purposes of the venom mechanism are the capture of prey and the partial breakdown of body tissues. On the other hand, it is also true that venomous snakes may be force-fed with rats, birds, and other small animals, which they

do not envenomate but which they digest very well. Without the venom apparatus it may be very difficult or even impossible for them to obtain their food. Venom may also activate the digestive processes in some manner, but, probably, it is not necessary for this purpose. Scolopendrids, scorpions, spiders, snakes, venomous saurians, and shrews may be considered primarily of the offensive type, their venom-apparatus being used for the capturing of food; secondarily, of course, they use such apparatus for self-defense.

Exact knowledge of the biological habits of venomous animals would provide more accurate answers as to the real purpose of venoms. Too little is known about this broad subject.

Another very important issue to be clarified concerns the intensity of action of the venoms of all species. For example, a venom of one species of snake may be several times more active in rats, mice, and birds than in other animals. Human beings are extremely sensitive to certain animal venoms. One-tenth of one milligram of *Loxosceles* venom may seriously endanger human life. It is conservatively estimated that 40,000 to 50,000 people throughout the world may be killed every year by accidental contact with venomous animals. Every scientific effort must be directed toward the prevention of this tragedy.

WOLFGANG BÜCHERL

Contents

CHAPTER 3. Chemistry and Pharmacology of Insectivore Venoms

MICHALINA PUCEK

VENOMOUS SNAKES

General Information

CHAPTER 4. Karyotypes, Sex Chromosomes, and Chromosomal Evolution in Snakes

WILLY BEÇAK

CHAPTER 5. Extraction and Quantities of Venom Obtained from Some Brazilian Snakes

HELIO EMERSON BELLUOMINI

CHAPTER 6. The Protein and Nonprotein Constituents of Snake Venoms

ANIMA DEVI

CHAPTER 7. Enzymes in Snake Venoms

N. K. Sarkar and Anima Devi

CHAPTER 8. Bradykinin Formation by Snake Venoms

Carlos R. Diniz

CHAPTER 9. Coagulant, Proteolytic, and Hemolytic Properties of Some Snake Venoms

G. Rosenfeld, L. Nahas, and E. M. A. Kelen

Venomous Snakes of the World

CHAPTER 10. Methods of Classification of Venomous Snakes

Konrad Klemmer

CHAPTER 11. Venomous Sea Snakes (Hydrophiidae)

MICHEL BARME

Venomous Snakes of Central and South Africa

CHAPTER 12. Classification and Distribution of European, North African, and North and West Asiatic Venomous Snakes

KONRAD KLEMMER

CHAPTER 13A. Chemistry and Biochemistry of the Snake Venoms of Europe and the Mediterranean Regions

P. BOQUET

CHAPTER 13B. Pharmacology and Toxicology of Snake Venoms of Europe and the Mediterranean Regions

P. BOQUET

Venomous Snakes of East Asia, India, Malaya, and Indonesia

CONTENTS OF VOLUME II (Tentative)

CONTENTS OF VOLUME III (Tentative)

VENOMOUS INVERTEBRATES

VENOMOUS INSECTS

Venomous Animals and Their Venoms

VOLUME I
Venomous Vertebrates

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Development of Knowledge about Venoms

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From earliest times, people have been aware of the possible dangers of bites and stings from insects, snakes, fishes, and other animals. Everyone has a natural fear of hostile living things, and people must have learned early of the possible pain, distress, and often death, that result from bites or scratches of poisonous animals. For thousands of years, there has been general ignorance and fear about the possible effects of such bites. The very word "venom" has a sinister sound, and may partially reflect the fear aroused by the thought of being bitten.

Accumulation of knowledge from observation of and experience with venomous bites has been slow. Nevertheless, there has been steady increase in such knowledge, and records persist, even from remotest antiquity, of attempts to treat and prevent venomous bites.

The oldest medical writings are the ancient papyri from Old Egypt, dating from around 1600 B.C. In addition to the great Smith Surgical Papyrus, there are several that deal with medical matters. In fact these are formularies for various prescriptions to be used to treat injuries or disease. Some of these, such as the Ebers Medical Papyrus (formerly at Leipzig, but apparently destroyed in World War II), a great teaching text, contained prescriptions for treating various kinds of bites. The Hearst Medical Papyrus, which is at the University of California in Berkeley, is a general practitioner's formulary, probably copied from several organized teaching texts. Although the document is mutilated, it nevertheless contains some 260 prescriptions, many of which are for treating "a bite on people."

In the earlier attempts to translate the Ebers and Hearst papyri, the prescriptions, which make good sense when translated for the purpose of

treating "a bite *on* people," were often translated as being for the purpose of treating "a bite of people." The point is that in ancient Egyptian grammar there was no clear distinction between the genitive and ablative case. In general, people do not bite one another, and the character of the prescriptions is such as to indicate that they are more logically concerned with bites that may occur on people, such as bites from insects.

Three such prescriptions in the Hearst Medical Papyrus, occurring on the second sheet of the papyrus, recommend leek, garlic, onion juice, salt, bile, and incense, to be applied locally or bandaged into place where the bite occurs. These prescriptions are similar to another series of three prescriptions in the Ebers Medical Papyrus. Both papyri contain other prescriptions for soothing the skin after experiencing bites that most likely would have come from insects. Certainly insects must have abounded in Old Egypt, even as they do now. In addition, the Ebers and Hearst papyri contain prescriptions for treating the bites of specific animals, such as crocodiles, pigs, and lions.

It is interesting that the agents recommended for treating bites in the Ebers and Hearst papyri should persist through the formal medical writings of the Greco-Roman world and well into the Medieval period. This is further evidence of the many instances of transmission of Egyptian culture into the Greco-Roman world, and its subsequent persistence into the Middle Ages.

There is much evidence that the relatively sound empirical medical lore of the old Egyptians was taken over almost literally by the ancient Greeks. Many of the same prescriptions in Greek medical writings are to be found in the old Egyptian medical papyri. In addition, there must have been a verbal tradition, which may have been continued in various special families, who may have had a local reputation for being good healers or good physicians.

Apparently in this way the cult of Aesklepios developed in ancient Greece, which took over many aspects of the worship of Imhotep from ancient Egypt. Imhotep had actually lived during the fourth millennium B.C. So great was his reputation as a healer that at his death people came to his tomb to supplicate his spirit to aid them in treating their injuries or diseases. Soon the number of pilgrims became so large that attendants were needed to care for them, and inevitably priests arose to mediate the supplications between the people and the spirit of Imhotep. After the passage of about fifteen hundred years, he was a demigod; the apotheosis was complete by the first millennium when other temples sacred to him had been established in other parts of Egypt. In each of these temples, there was the ritual of the "temple sleep," in which the supplicants, after being bathed and fed, would sleep and dream that the god had

visited them and advised them on the regimen to be followed. The temples also had pits sacred to snakes. This is interesting in view of the high probability of venomous snakes in Egypt. There was also the custom of leaving ex-votos at the temple when patients would leave. Patients were always discharged before death, so that the temple would never suffer from an adverse reputation. These ex-votos could be obtained, according to the circumstances of the patient, in terra-cotta, gold, or ivory. They would be hung on the temple walls for a while, and then taken down and resold by the priests to subsequent patients. In this manner, the finances of the temples were maintained.

The features of the worship of Imhotep in Egypt became characteristic of the worship of Aesklepios in the old Greek world. It is remarkable that snakes should have played such a dominant role in the symbolism of the Aesklepian cult. There were probably no poisonous snakes in Greece proper, but there certainly were in Egypt, and probably in Asia Minor as well.

The snakes in the worship of Aesklepios were supposed to symbolize the healing power of nature, being close and living within Mother Earth, as it were. Since they were usually found around springs of water, which were scarce in the ancient eastern Mediterranean, snakes were thought to be the closest to that from which human life and health came. Accordingly, the snake became the symbol of the healing cult.

On the other hand, some element of fear may have been associated with the good care taken of the snakes which were found around the healing springs, near which the temples of Aesklepios arose. The snakes may have excited interest by the peculiarity of their ways, as judged by the projective emotional rationalizations of the people who watched them. Considerable folklore developed regarding snakes and their ambivalent possibilities for both good and evil. Usually, a sacred snake was kept in every major household and was tended rather carefully.

Meanwhile, a great deal of experience must have accumulated with various kinds of poisonous sea animals, with poisonous spiders, and with other insects and animals whose bites might cause pain, distress, or even death. Experience was also obtained with animals and plants that might cause skin irritation on contact. An extensive lore developed early regarding the possible poisonous character of certain plants. This could have come about as a result of the continuous search for food. In this process, the effects of various biologically active plant materials must have been noticed, and consequently those that caused purgation came to be used as purgatives, whereas those that caused irritation to the stomach were used in medicine for the purpose of inducing vomiting.

The practical aspects of using plant and animal material as food or as medicine required some means of recognizing and identifying not only those which might be useful, but also those which might be dangerous. This observational effort led gradually to methods of classification. Poisonous plant and animal materials were early set apart and were discussed separately from those used for food or drugs.

Possibly, the extensive expeditions of Alexander the Great brought knowledge to the Greek world of the amazing rare and exotic plants and animals from the East. It may have been as a result of the Alexandrian expeditions that the Greek people became familiar with the venomous action of many kinds of snakes, fish, and other animals. Some of this lore may have been preserved by word of mouth and passed on by the soldiers who took part in the expeditions. It may very well have been that these tales were recited in a sing-song manner, and gradually became a sort of versification.

This may explain the origin of the first important work on toxicology, the famed "Theriaca" of Nikandros of Kolophon (275–130 B.C.). Nicander, to use the anglicized version of his name, lived at Klaros, and may have been associated with a family of priests of Aesklepios. He was friendly with a famed physician, Appolodorus of Lemnos. He wrote in hexameter verse, and his first work on "Theriaca" was followed by a later poem, "Alexipharmaca." These books deal respectively with the actions of various kinds of venoms and poisons, from both animals and plants, and they provide methods of treating cases of poisoning.

The writings of Nicander must have been highly regarded as they persisted in manuscript throughout the Greco-Roman and Medieval periods. They were first published in a Latin translation in Venice in 1499, and the Greek text with a Latin translation was published in Paris in 1549. Although originally written in Greek, several Latin translations are to be found.

Nicander also wrote prose works, one of which was a glossary on the writings of the Hippocratic School at Cos. The best translation and commentary on Nicander was given by J. C. Schneider (1792). Nicander's work has also been translated into German by M. Brenning (1904).

There is nothing in the extant writings of the Hippocratic physicians that indicates an interest on their part in poisonous animals or plants. This is not particularly surprising since these physicians were not especially interested in treatment with drugs. On the contrary, they were more concerned with aiding nature to restore health during sickness, or in treating injuries. Nevertheless, they must have been acquainted with the extensive drug lore of antiquity, particularly that which came from ancient Egypt. Furthermore, patients must have come to them who had

been poisoned either by venomous animals or by poisonous plants, and they must have had some empirical methods for treatment. It may simply be that we do not now have the writings they may have left.

The tradition established by Nicander's versifications long persisted. Through Roman times it had much influence. Poisonous plants and animals were described by the great Roman encyclopedist, Celsus, who flourished at the beginning of our era. The fifth book of his writings deals with poisonous animals and follows the descriptions given by Nicander.

One of the most important Roman medical authorities was Dioscorides, the surgeon associated with the armies of Nero. He made an extremely important scientific contribution in his analysis of the various plant, animal, and mineral materials used from antiquity as drugs. The information transmitted in the formularies from antiquity, such as in the prescriptions of the Ebers and Hearst Medical Papyri, were analyzed with respect to the individual ingredients. After general classification into various types, each separate agent was discussed in a systematic manner, giving names, sources, identification, its physiological actions, and medical use.

The basic writings of Dioscorides refer chiefly to the animal, plant, and mineral ingredients of the ancient formularies. Nevertheless, the later Latin annotators included a *Liber de Venenis.* Dioscorides, being a Greek, of course wrote in his native language, but his writings seem to have been translated into Latin quite early. The book on poisons may not have been written by Dioscorides, but may have simply been a prose adaptation of Nicander, appended to the basic work of Dioscorides. Sprengel, who was one of the chief scholars on Dioscorides, doubts the authenticity of the book on venoms. Nevertheless, it is important, and it contains a great deal of information regarding venomous animals, most of which was taken from Nicander.

The writings of Dioscorides were popular throughout the Medieval period and were widely used in the early days of the Renaissance. His work was first printed in Latin translation in 1478, and was published in the original Greek by Aldus in 1499 in Venice. In the great Matthioli edition of Dioscorides, published in Venice in 1554, there is the full text of the *Liber de Venenis.* This begins with a description of the terror inspired by the bites of mad dogs and then goes on to considerable discussion about the way in which this might best be handled. Sucking on the wound was recommended, as well as the application of a tourniquet above the bite, to prevent the venom from getting into the body, and the application of various materials such as salt and juices of onions or garlic was advised. The section given by Matthioli proceeded to a commentary on venoms, including consideration of bites inflicted by vipers and

other kinds of snakes, as well as to bites by scorpions and even shrews. The asp, an African species, was already famous in legend in connection with the death of Cleopatra.

It is interesting that this commentary contains many pictures to aid in the identification of the venomous animals described in the text. These seem to be conventionalized representations derived from some early Greek manuscript now lost. They are similar to those in the Juliana Codex of Dioscorides of the 5th century A.D. The plant representations in this beautiful manuscript probably came, as Charles Singer suggested, from earlier manuscripts that contained illustrations from drawings made by the Greek artist Kratius which may have illustrated Nicander's verses. These illustrations remained traditionally conventional for many years.

The greatest Roman physician was Galen (131–201 A.D.), who received his early training in the renowned Aesklepian temple at Pergamon. After extensive travel, he became the outstanding physician in Rome, and served the Emperor Marcus Aurelius. Galen was an extraordinary writer, and brought together all of the major medical and surgical ideas of antiquity. His commentaries were extensive, and his medical learning and experience were obviously great. He gave many case reports from his own experience and indicated the experimental studies he made regarding the functions of various parts of the body.

In his work on "The Natural Faculties," he refers to ". . . certain medicaments . . . which attract the poison of the viper, others that of the stingray, and others of some other animals: we can, in fact, plainly observe these poisons deposited on the medicaments." He speaks further of certain drugs for drawing out inflammation and for bringing out embedded substances (Brock, 1916). These references may have been to various kinds of astringents. They indicate that it was thought that the poisons were specific physical materials that might be adsorbed in some way on astringent materials and drawn out of wounds.

Galen wrote a specific article on poisons. This again was in Greek, but was early translated into Latin. This was "De Theriaca ad Pisonen." This important work has been translated into Italian with a critical introduction by E. Coturri (1959). This writing of Galen, like similar writings on poisons in the Roman period, seems again to have been based largely on Nicander. There is careful description of various types of venomous animals including snakes, spiders, scorpions, marine forms, and even small mammals such as shrews. The method of treatment recommended again was to suck the venomous material from the bite, to apply a cautery above the bite so as to prevent absorption of the venom into the body, and then to place various astringent agents on the bite. Sometimes actual excision of the bite was recommended. Remedies to be taken by

mouth were supposed to be relaxing and quieting. It was recognized that animal venoms are not poisonous when ingested orally.

These same conventional and more or less traditional descriptions of venoms were repeated in the writings of Aetius (480–556 A.D.) and Oribasius (325–403 A.D.), the famed physician to Julian the Apostate. Oribasius gave some commentary on venoms, but clearly based his account on the writings of Galen. Paul of Aegina (625–690) also followed the conventional pattern established by Nicander.

The best summary of classical Greco-Roman and Islamic medicine was given by Francis Adams (1846) in his translation and commentary of "The Seven Books of Paulus Aegineta." The first twenty-five sections of Book V, in the second volume, dealt with venomous animals, and included a general statement with indications for the treatment of persons bitten or stung, and then a detailed consideration of the different kinds of animals whose bite may have been venomous. The general treatment included immediate sucking of the bitten area, to be followed by cupping, and then, as introduced later by the Islamic physicians, by cautery. Various local applications were suggested, including onions, wine, hot vinegar, with various internal remedies comprising "theriacs." These in general were mild stimulating materials, and again they were transmitted from the time of Nicander.

The detailed description given by Paulus included bites from mad dogs, bees, spiders, wasps, scorpions, lizards, scolopendra, shrew-mice, vipers, various snakes, some of which were specifically described, asps, eels, stingrays, stingballs, sea scorpions, crocodiles, mammals, and even men. Some legendary venomous creatures had names that are unfamiliar to us now, such as "basilisks," but they may have been species of cobra.

The importance of the commentary by Francis Adams on the writings of Paulus consists of his references not only to the writers of antiquity who may have preceded Paulus, but also to those who followed him, especially the Islamic physicians, Rhazes (860–932) and the great codifier, Avicenna (980–1037).

After transmission through Byzantine and Arabic writings, the general discussions on venomous animals by Greco-Roman medical writers persisted through Medieval Europe to the Renaissance. Especially interesting was the long popularity of a work entitled "Antidotarium," written by Nicolaus of Salerno. He taught at the famed Salernitan Medical Center during the first half of the 12th century. Most of his source material seems to have come from Arabic writers, probably through the translations made by Constantine the African. The book was first printed in Venice in 1471, and within a century went through more than a dozen editions.

The great French surgeon Ambroise Paré (1510–1590) offered an extended discussion of bites by mad dogs and other poisonous creatures. It is illustrated by the same sort of representations given by Matthioli. This is available in quaint English translation in the collection of writings by Thomas Johnson, "The Workes of that famous Chirurgion Ambroise Paré" (Paré, 1634). In Paré's discussion, the bites of mad dogs, as well as of other "venomous beasts," were considered, with interesting illustrations of vipers, stingrays, and other poisonous animals. This account also included a description of poisonous plants.

A detailed account of venoms was prepared by a contemporary of Paré—the Parisian, Jacques Grévin (1538–1570). This was issued in the vernacular as "Deux livres des venins" (Grévin, 1568). The first part dealt with venomous animals, and the second part considered poisonous plants. Again there were the interesting conventionalized illustrations, which were meant to aid in identifying the various snakes and other poisonous animals that were described. This work offered an excellent summary of classical ideas regarding venoms, and included much of the folklore transmitted by Pliny (23–77 A.D.). Poisonous marine animals and venomous fish were discussed. The "torpedo" was fully considered, as well as poisonous spiny fish. Rabid dogs were discussed in detail.

It was not until the 17th century that systematic studies of venoms were made in a manner that may be regarded as scientific. In 1664, Francesco Redi (1621–1697) wrote the first methodical work on snake poisons (Redi, 1664). Redi demonstrated that in order for the snake poisons known at that time to produce their characteristic effects, they must be injected under the skin. When taken by mouth, certain venoms were clearly recognized as harmless.

These studies were considerably extended by Felice Fontana (1720–1805), who investigated snake poisons, and many other toxic materials. Fontana's study is one of the first in systematic toxicology. His investigations of snake venoms was the beginning of the modern scientific study of these widespread poisons (Fontana, 1767).

It is rather remarkable that the studies of Redi and Fontana were not followed by anything particularly significant for many years. It may well be that John Hunter (1728–1793) made observations on venomous animals, but if he did, his notes seem to have been among those destroyed by his nephew Sir Everad Home. It was not until the latter part of the 19th century that Silas Weir Mitchell (1829–1914), the great Philadelphia neurologist, published his carefully devised and significant studies on rattlesnake venom and on other serpent venoms (Mitchell, 1860).

These investigations were continued with E. T. Reichert (1886). It

was shown by these pioneering American scientists that snake venoms are proteins and that some of them contain toxic albumins. These students also demonstrated that many of the characteristic toxic effects of snake venoms were to be noted on nerve tissue and on blood.

Meanwhile, the ancient fear of mad dogs and the horrible effects of their bites, in the "hydrophobia" that had been well described by the ancient writers, was dramatically allayed by the insight of Louis Pasteur (1822–1895). Suspecting an infectious agent, he was lucky in being able to devise a protective antibody preparation without being able to isolate or identify the virus (Pasteur, 1885, 1886). Pasteur's brilliant success was internationally acclaimed and led to the establishment of Pasteur Institutes throughout the world for the preparation of antirabies vaccines and antivenins, and for immunological research in general.

With the modern development of taxonomy, it became possible satisfactorily to begin the classification of poisonous animals. The first systematic description of venomous snakes from any one part of the world was made by Sir Joseph Fayrer (1824–1907). He already had extensive experience with many poisonous snakes of India, and he wrote fully and well on the subject (Fayrer, 1872). This important book made it possible readily to identify the various venomous snakes of India and to begin a systematic survey of the characteristic secretions of their poison glands.

Studies on immunization against serpent venom began toward the end of the 19th century. The pioneer investigations of Henry Sewall, at the University of Michigan, ushered in an entirely new concept in the treatment of snake envenomation. He showed that the experimental animal (pigeon) could be immunized against rattlesnake venom (Sewall, 1887). These studies led to investigations by Calmette (1891–1892; 1892; 1892–1893), who obtained immunity in the experimental animal and inaugurated studies on the immunization of animals to venoms Calmette (1894, 1895, 1898). Meanwhile, Sir Thomas R. Fraser (1841–1919), the well-known Edinburgh toxicologist, investigated immunization against cobra venom and obtained a specific immune serum (Fraser, 1895). In 1896, Calmette had published a small volume on the venom of serpents which served to give the background for immunization, and as a result Pasteur Institutes throughout the world undertook to supply "antivenoms," or antivenins.

Subsequent systematic studies on the biological action of snake venoms were undertaken by Simon Flexner (1863–1954) and Hideyo Noguchi (1876–1928) at the Rockefeller Institute in New York. The reports from these studies described in detail the effects of various snake venoms in producing hemolysis and other toxic effects on blood. The reports also showed that snake venoms could cause bacteriolysis (Flexner and

Noguchi, 1902). Noguchi (1909) later summarized the information then available in a book entitled "Snake Venoms." At about this time, Preston Keyes (1875–1944) investigated cobra venom and showed that lecithin is a complement for cobra hemolysin (Keyes, 1902, 1903).

Careful and detailed studies on immunization and treatment of snake venom toxicity were made by Vital Brazil (1865–1946), of São Paulo. He founded the great Instituto Butantan of São Paulo, which is one of the most important centers for study of snake venoms in the world. His book, "A Defensa contra o Ophidismo" (Brazil, 1911), deserves wide appreciation and recognition. From the Instituto Butantan have subsequently come, under the leadership of its distinguished Director, Professor Do Amaral, many hundreds of outstanding publications on snake venoms.

A short but quite comprehensive review on poisonous marine animals was prepared by Charles H. Taft (1941) with a rather extensive bibliography. This was later expanded in association with George A. Emerson, in a comprehensive summary and extensive bibliography (Taft and Emerson, 1945).

With the advent of skin diving and with extensive interest in underwater exploration, an important review of "Dangerous Marine Animals" has been prepared by B. W. Halstead (1959). This volume is well illustrated with photographs and scientific drawings, so that identification of the various types of poisonous marine animals may readily be made. This includes dangerous marine animals that bite, that sting, and that are poisonous to eat. There is a selected bibliography, which gives some indication of the world-wide interest in poisonous animals from the sea. This bibliography includes references to E. N. Pawlowsky (1927) and M. Phisalix (1922).

The American Association for the Advancement of Science, in 1954, sponsored the first International Conference on Venoms. The Proceedings of this conference were edited by Eleanor E. Buckley and Nandor Porges (1956) of Philadelphia, and published as No. 44 in the Symposium Series of AAAS under the title of "Venoms." This is an extremely comprehensive symposium and gives clear indication of the wide interest of research studies on venoms in current scientific interest. Modern methods of analysis are making it possible to separate the components of important venoms and to characterize them in a reasonably satisfactory chemical manner. From this information, it is certain that effective methods of protection may be developed. This symposium well illustrated the worldwide interest in and the study of venoms. Reports were made by scientists from all major areas in the world, including India, Australia, South Africa, as well as Europe and Asia.

Current popular interest in venoms is well illustrated by the ten-column article in *The Times Science Review,* Autumn, 1963, by F. E. Russell of Cambridge. This characterizes fifteen kinds of poisonous snakes, with indications of venom yields and toxic doses, and sixteen kinds of venomous marine animals from Coelenterata such as *Physalia* (Portuguese man-of-war), through Mollusca as the geographer cone and octopi, and echinoderms such as Diaema (sea-urchins), to fishes such as stingrays, scorpion fishes, weever fishes and toadfishes. The venoms from these sources contain many enzymes and nonenzymatic proteins of high molecular weight. These proteins liberate bradykinin and histamine from punctured cells and these substances contribute greatly to the pain and tissue damage. Slotta and H. Fraenkel-Conrat isolated "crotoxin," in 1938, from the venom of *Crotalus terrificus,* with a molecular weight of 30,000. Subsequently it has been shown that most snake venoms contain as many as a dozen nonenzymatic proteins with varying activities.

Much scientific study remains to be done on animal venoms, and research in this subject may be expected to expand for a long time. The history of our knowledge of venoms is contemporaneous with our interest and curiosity of the world around us, and this history reflects our effort at understanding one of the dangerous features of the organisms in our environment. It is significant that, while some imaginative misinformation was early involved in the writings on poisonous animals, there was relatively little superstitious irrationality. Nicander's early work served as a reasonably satisfactory base for knowledge of venoms until modern methodology could clarify the matter. Our knowledge and thus our control of venomous animals and their secretions is expanding with amazing rapidity, along with all other scientific progress.

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