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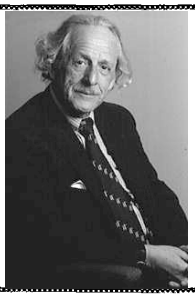

Current Comments®

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Research and Immunotherapy Are Taking the Bite out of Venom

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Poisonous organisms and the toxic effects of their venom have long been objects of both fear and fascination. Using ISI® data to identify the field's most active research fronts, the essay discusses the development of the interests of venom researchers. Basic research was originally concerned with physical descriptions of venom, venomous organisms, and the mechanics of envenomation. Research now focuses heavily on antivenins, immunotherapy against venom toxins, and the potential applications of venom and venom extracts in the treatment of disease.

Poisonous organisms — especially snakes—have exerted a powerful hold on human imagination "since the dawn of human thought."[1] (p. vii) Herpetologists Sherman A. Minton, Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, and Madge Rutherford Minton also note that cobras have been worshiped for centuries throughout the Indian subcontinent.[1] (p. 131) Fantastic, plumed rattlesnakes were carved into Mayan and Aztec temple walls,[1] (p. 173-4) and vipers figure prominently in the myths and symbology of the ancient Greeks and Romans.[1] (p. 158-62) The term "viper" is properly applied only to venomous snakes of the family Viperidae, but it is often used to describe any actually, or presumably, venomous snake.[1] (p. 14-9)

Snakes have long been associated with fertility and guardianship.[1] (p. 131-97) In fact, the role of guardian is one of many symbolic functions attached to snakes in Asian art. In a previous essay,[2] I discussed a sculpture that depicts a snake coiled around a turtle. We believe this symbolizes the serpent's role of protecting the world from malignant influences, but we have been unable to document this.

Among Christians, however, snakes have become linked with evil and duplicity. In the biblical account Satan, in the form of a serpent, caused the expulsion of Adam and Eve from the Garden of Eden. Indeed, snake-handling became a test of faith in certain Christian sects in some parts of the southeastern US.[1] (p. 181-7) Other poisonous animals, notably spiders and scorpions, have also inspired tales, fear, and respect in humans as far back as the earliest written records.[3]

Owing to their worldwide distribution, snakes are among the most familiar poisonous animals. But numerous other organisms on land and sea are equipped with venomous fangs, spines, barbs, crests, or tentacles for purposes of aggression or defense. As noted by Wolfgang Bücherl, Butantan Institute, São Paulo, Brazil, among these are some species of moths, beetles, caterpillars, centipedes, ticks, toads, frogs, salamanders, lizards, and certain bony fish. Other animals that carry venom include scorpions and many ants; most bees and wasps; jellyfish; octopuses, rays, skates, and sea snakes; anemones, sea urchins, and starfish; some snails; and even a few mammals, such as duckbill platypuses and certain shrews.[4]

Obviously, some of the most interesting features of these animals, from a scientific standpoint, are their venoms: their composition, effects, and the means with which they are delivered to the victim. The word "venom" comes from the Middle English

word *venim*, which, in turn, is derived from the Latin *venenum*—a "magic charm," "drug," or "poison."[5]

Venoms vary widely in their chemical makeup and in their toxic effects. They can provide a means of self-defense, or, in some cases, they help subdue prey. Venomous animals differ widely in how they deliver poison to victims. Most inject poison by stinging or biting, but some, such as toads and frogs, secrete venom from glands in the skin and require direct body contact to poison victims. However, even within the same species there are variations. For instance, only adult female honeybees are venomous. And while both males and females of certain species of spider are poisonous, the females usually are far more dangerous because of their larger size.[4] An important exception to this generalization, however, is the Australian funnel-web spider (*Atrax*), in which the venom of the male is more lethal.[6]

Our discussion of current research will cover the particularly exciting, newer developments concerning snake venom. We'll also look at research on members of the Hymenoptera order, a classification that includes bees, hornets, wasps, yellow jackets, ants, sawflies, and ichneumon flies. ("Ichneumon," incidentally, is a Greek word meaning "tracker"; ichneumon flies are members of the family Ichneumonoidea, whose larvae are generally internal parasites of the larvae of other insects.[7])

Development of Venom Research

My old friend and mentor, the late Chauncey D. Leake,[8,9] was among the contributors to a comprehensive, three-volume work entitled *Venomous Animals and Their Venoms*, edited by Bücherl; Eleanor E. Buckley, Wyeth Laboratories, Philadelphia; and Venancio Deulofeu, University of Buenos Aires, Argentina.[10] Data from the *Science Citation Index®* (*SCI®*) indicate that this collection has been cited in 72 publications since its appearance in 1968.

As I mentioned in the essay marking Chauncey's death in 1978, he was a man of many talents who authored works in pharmacology, chemistry, and philosophy.[9] Also an avid historian, he wrote a chapter outlining some of the major historical developments in venom research.[11]

According to Leake, the oldest writings on venom come from Egyptian papyri from around 1600 BC.[11] Ancient Egyptian and Greco-Roman interest in venom centered on treatments for bites. Transmitted through Byzantine and Arabic writings, the ideas of these civilizations persisted through the Middle Ages until the Renaissance.[11]

Early Work on Snake Venom

Detailed descriptions of venomous animals began to be written in the 1500s, but the first systematic studies of venoms were not made until the 1600s. According to the Mintons, some of the liveliest controversies in late seventeenth-century Europe "revolved about the bite of the viper."[1] (p. 28) A French physician and chemist, Moyse Charas (1619-1698), attributed the characteristic effects of a snakebite to the animal's "enraged spirits," but it was Italian physician Francisco Redi (1621-1697) who correctly ascribed them to the yellowish fluid that flowed from the snake's fangs.[1] (p. 28)

Redi wrote the first methodical work on snake venoms,[11] demonstrating that in order for the poison to work, it must be injected through the skin; merely swallowing it did not produce its characteristic effects.[12] This helps explain why the emergency remedy of sucking the site of a snake bite can safely remove some of the toxins from the tissue around the wound.[1] (p. 105-6) Redi's studies were considerably extended by Felice Fontana (1720-1805),[13] whose investigations into snake poisons and other toxic substances are the first in systematic toxicology and represent the beginning of the modern scientific study of these substances.[11]

In the latter part of the nineteenth century, the great Philadelphia neurologist Silas Weir Mitchell (1829-1914) published "carefully devised and significant studies"[11] on rattlesnake and other venoms.[14] Among other pioneers was another American scientist, E.T. Reichert.[15] These researchers showed that snake venoms contain toxic proteins that affect nerve tissue and blood cells.

The Rabies Connection

Venom immunization studies began toward the end of the nineteenth century. At the time, the secretions of rabid dogs were considered venomous because of their horrifying—and fatal—effects. Suspecting an infectious agent as the cause, Louis Pasteur (1822-1895) managed to devise a vaccine against rabies (known then as "hydrophobia") in spite of his failure to actually isolate the rabies virus.[16,17] Pasteur's advance was internationally acclaimed and helped focus attention on immunological research in general and on the development of antivenins—antidotes for the effects of venoms.[11]

The first example of a successful immunization against venom came in 1887, when Henry Sewall, University of Michigan, Ann Arbor, showed that pigeons could be immunized against rattlesnake venom.[18] This is a marvelous example of the impact that basic research can have on the efforts to combat disease. It is also a useful lesson to remember whenever proposals to reduce budgets for basic research are made. Whenever there is mounting pressure to find treatments for the most immediate, intractable diseases—such as AIDS—quick, practical solutions are demanded. But recall that it was basic research that yielded the vaccine for polio; without support for such work, we might now be mass-producing artificial lungs for polio victims.[19,20]

Current Venom Research

In the twentieth century, the interests of venom researchers began to extend beyond snakes to other poisonous animals as well, especially venomous invertebrates and marine life. A comprehensive symposium, the first International Conference on Venoms, was sponsored by the American Association for the Advancement of Science (AAAS) in 1954.[21] (Not coincidentally, Leake once served as president of the AAAS.) Today the venom research community is a relatively small but growing branch of the life sciences; its scope is illustrated by the founding in 1962 of the International Society on Toxinology, which is based in Tokyo, Japan, and publishes the journal *Toxicon*.

The historiograph in Figure 1 shows the research fronts explicitly concerned with venom research that we've identified over the last few years. The discussion of these research fronts on the following pages focuses on their core papers, unless otherwise stated. An active 1986 front, "Immunological histamine release and Hymenoptera venom immunotherapy" (#86-5954), involves 11 core and 79 published (citing) papers. The multidimensionally scaled map in Figure 2 illustrates the co-citation connections, or "semantic" relationships, between the core papers.

Hymenoptera Venom Immunotherapy

Front #86-5954 focuses on allergic reactions to the venom of hornets, honeybees, and yellow jackets; methods of treating stings in individuals who are hypersensitive to bee venom; and the effectiveness of procedures for immunizing hypersensitive individuals. A study of human hypersensitivity to the venom of honeybees, yellow jackets, and yellow- and white-faced hornets was published in the *New England Journal of Medicine* (*NEJM*) by Kevin J. Hunt and colleagues, Department of Medicine, Division of Clinical Immunology, Johns Hopkins University School of Medicine, Good Samaritan Hospital, Baltimore, Maryland, and Pennsylvania State University, University Park.[22]

This paper cited a study by H.M. Parrish, University of Missouri School of Medicine, Columbia, which reported that severe allergic reactions to Hymenoptera stings result in more than 50 deaths annually in the US alone;[23] about 0.4 percent of the US population shows clinical allergy to insect venom.[24] The treatment for allergic responses to insect venom has historically been injections with extracts of crushed, whole insect bodies. But Hunt and colleagues found that whole-body extracts failed to increase patients' antibody responses to the active proteins in venom. They reported that after immunization with the proteins in Hymenop-

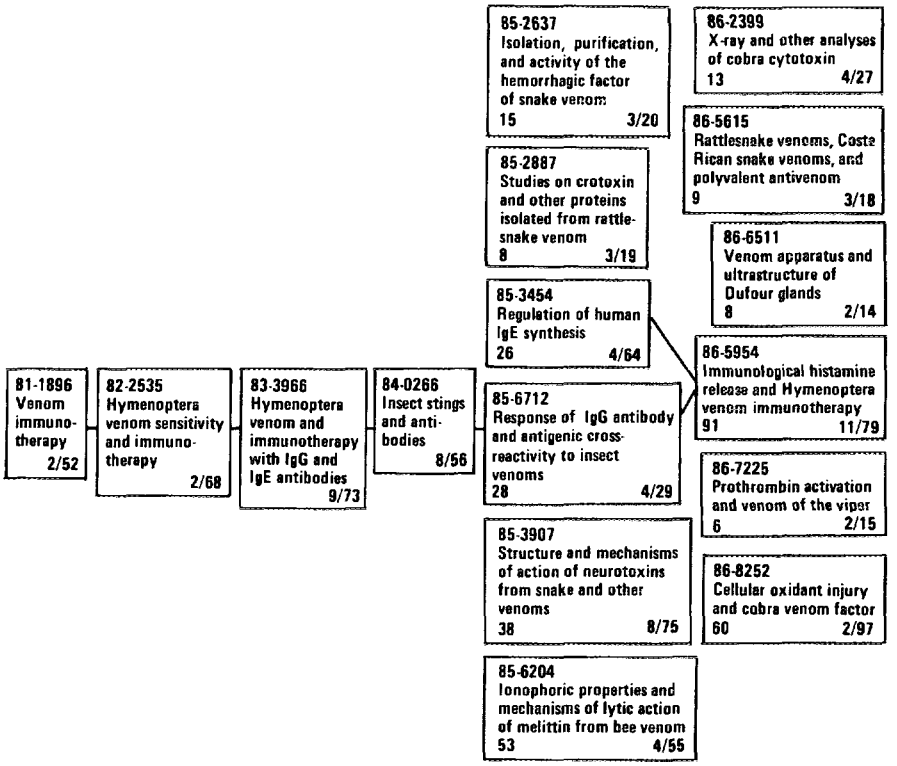

Figure 1: Historiograph highlighting research in venom immunotherapy and other recent research activity. Numbers of core/citing papers are indicated at the bottom right-hand corner of each box. Number of papers published in 1987 citing into the 1985 and 1986 research fronts is indicated in the bottom left-hand corner of each box.

tera venom, especially phospholipase A, only 1 of 18 patients suffered a systemic reaction to a bee sting, while 7 of 12 immunized with whole-body extracts had such reactions.[22]

The Immuno-Allergy Connection

Several papers that are core to front #86-5954 underscore the importance of work in immunology and allergy to this area of venom research. One is a classic paper by L. Noon, St. Mary's Hospital, University of London, UK, on immunizing patients against hay fever.[25] Published in 1911 in the *Lancet*, Noon's paper has accumulated over 200 explicit citations since 1955. We'll know more about its influence when we publish the 1945-1954 *SCI* later this year.

Two additional papers were written by Gerald J. Gleich, Allergic Diseases Research Laboratory, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, and colleagues. The first, published in 1971 and cited over 370 times, concerns a method of measuring serum antibody levels via radioimmunoassay techniques;[26] the second, published three years later and cited over 130 times, reports a method of measuring the potency of the response to a specific allergen.[27] Another paper of interest to venom researchers because of the immunization techniques it discusses was written in 1977 by P. Stahl Skov and S. Norn, Department of Pharmacology, University of Copenhagen, Denmark. They describe a method for measuring histamine release and serum antibody levels in hay-fever patients.[28] We published a three-part essay on allergies that

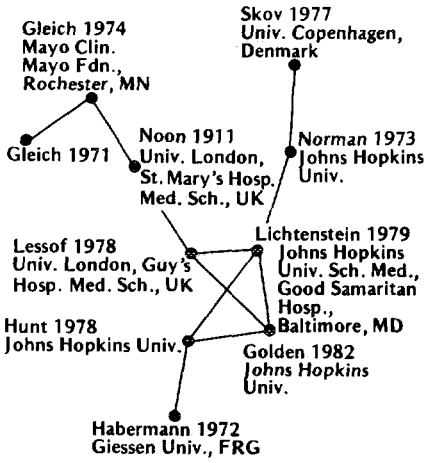

Figure 2: Multidimensionally scaled map of the 1986 *SCI®/SSCI®* research front entitled "Immunological histamine release and Hymenoptera venom immunotherapy" (#86-5954), showing links between core papers. Complete bibliographic citations appear in the reference section of this essay.

included a discussion of life-threatening reactions a few years ago.[29]

Lawrence M. Lichtenstein, Martin D. Valentine, and Anne Kagey-Sobotka, Johns Hopkins and Penn State, were among the authors of the *NEJM* paper cited above.[22] They report that, of the three venomous proteins found in Hymenoptera venom (melittin, phospholipase A, and hyaluronidase), the major cause of allergic response is phospholipase A.[30] Published in 1979 in the *Journal of Allergy and Clinical Immunology*, this paper has been cited over 140 times.

Along with Valentine and Kagey-Sobotka, Lichtenstein was also among the authors of a core paper with first author David B.K. Golden, also of Johns Hopkins.[31] The paper relates the severity of allergic reaction to blood levels of the IgG antibody. Lichtenstein and Kagey-Sobotka are also among the authors on two other core papers,[32,33] and Lichtenstein is an author on yet another.[34]

The Toxic Constituents of Bee Venom

A 1972 paper by E. Habermann and K.L. Hardt, Pharmacology Institute, Giessen University, Federal Republic of Germany, describes a method of quantifying the amount of phospholipase A in samples of bee venom.[35] Incidentally, Habermann has written a *Citation Classic®* commentary[36] on his review of bee and wasp venoms, also published in 1972 (in *Science*), and cited in more than 400 publications.[37] The article contains a complete analysis—both biochemical and pharmacological—of bee venom and represents "the zenith" of Habermann's work; his interest later shifted to bacterial toxins. Habermann notes that the paper distills 20 years of work that was "largely unnoticed" in English-speaking countries, since it was originally published in German.[36]

In his commentary, he writes that "the contents of the publication survived my interest in insect venoms, and even my name. Such uncoupling is the ultimate proof for acceptance of one's work by the scientific community. Nevertheless, I have to admit my mixed feelings at a conference about 10 years ago, when I was just 51 years old. A young scientist had spotted my name in the list of participants just before he started his talk about bee-venom peptides. He commenced, 'I am particularly happy that Dr. Habermann is still among us.' I thoroughly shared his opinion."[36] The full commentary can be found elsewhere in this issue of the *Life Sciences* and *Agriculture, Biology & Environmental Sciences* editions of *Current Contents®*.

The historiograph in Figure 1 shows that in 1985 we identified the then-current front #85-6712. Four core papers are associated with this front, entitled "Response of IgG antibody and antigenic cross-reactivity to insect venoms." Three of them, described above,[22,31,33] carried over into the 1986 front #86-5954. The fourth, by R.E. Reisman and colleagues, Departments of Medicine and Biochemistry, State University of New York, Buffalo, compares the immunologic properties of yellow-jacket and hornet venoms.[38] We use carry-over linkages to construct these historiographs. But since the appropriate thresholds may not occur every year, we may have to fill in the linkages subjectively. So we have simply shown all the relevant fronts (subtopics) we identified in each year.

Mechanics of Envenomation in Hymenoptera

A small research front that concerns the venom of bees and other hymenopterous insects is "Venom apparatus and ultrastructure of Dufour glands" (#86-6511). This topic deals with the physiology of the glands that produce venom in insects and the organs that deliver the venom. These include the Dufour glands, which are part of the stinging organs in bees, wasps, and ants. A simple, tube-like organ, the Dufour gland acts as an accessory to the venom-producing glands in these insects, secreting and storing the alkaline component of venom. In fact, the Dufour gland is sometimes called the alkaline gland.

Two review papers helped identify this area of research. In 1974 Charles Noirot and André Quennedey, Laboratory of Zoology, Dijon University, France, reviewed the structure and functional relationships of exocrine glands found in the epidermis of insects.[39] Seven years later, in another review, Henry R. Hermann and Murray S. Blum, Department of Entomology, University of Georgia, Athens, discussed the behavioral and physical defense mechanisms of the highly social Hymenoptera. Secretions from the Dufour glands act as repellents.[40]

Defensive behaviors can include passive, or nonaggressive, components, such as escape, rigorous territoriality, and even apparently "altruistic" behavior. For instance, some ants barricade the entrances to their nests with their own bodies. Of course, more aggressive defense mechanisms include stinging and biting. Bees and wasps that have flown away from their nests or colonies are generally not easily provoked into stinging, according to Hermann and Blum. However, in defense of their nests, they can be highly aggressive and attack intruders in swarms; yellow jackets and hornets are notoriously aggressive in this respect.[40] Incidentally, ants are generally considered relatively inoffensive. But many species not only have powerful jaws that can inflict painful bites but also have venomous stingers in their tails.

The Biochemistry of Snake Venoms

Snake venom is a complex substance composed of numerous substances, including neurotoxins, cardiotoxins, myotoxins, hemorrhagic toxins, coagulants, anticoagulants, enzymes, enzyme inhibitors, nerve growth factors, and many other components that have not yet been characterized.[41] Two kinds of growth factors were discovered by Rita Levi-Montalcini, Institute of Cell Biology, Rome, Italy, and Stanley Cohen, Vanderbilt University School of Medicine, Nashville, Tennessee, who shared the 1986 Nobel Prize.[42] Among their many classic works, we cited their 1956 paper in the *Proceedings of the National Academy of Sciences of the USA*, which deals specifically with the isolation of nerve growth factor from snake venom.[43]

One might say that snake venom research is a foray in biochemistry. Indeed, the literature is heavily represented in biochemistry journals. One 1986 front, "Rattlesnake venoms, Costa Rican snake venoms, and polyvalent antivenom" (#86-5615), clustered around three core papers. About 18 papers were published on the characterization of the constituent chemicals in snake venom and methods of countering their toxic effects. Two core papers were published by Charlotte L. Ownby and colleagues, Oklahoma State University, Stillwater.[44,45]

One was published in *Toxicon* with George V. Odell, Biochemistry Department, and William M. Woods and Terry R. Colberg, Department of Physiological Sciences.[44] It was an investigation into the ability of an antivenin to neutralize both the localized and the lethal effects of myotoxin *a*, a component of prairie-rattlesnake (*Crotalus viridis viridis*) venom that causes myonecrosis, the death of individual muscle fibers. The other, published in 1976 with David Cameron and Anthony T. Tu, of the same group, discusses the isolation of a myotoxic component of the prairie rattlesnake's venom and the mechanism by which it damages the muscle cells of victims.[45] Tu was also among the authors of a 1979 paper, published in *Biochemistry*, in which the structure of myotoxin *a* is detailed.[46]

Although some snake venoms prevent the victim's blood from clotting normally, others actually promote clotting action. The biochemistry of the interaction between coagulant-promoting enzymes in venom and those in the victim's blood is covered in 15 published papers in "Prothrombin activation and venom of the viper" (#86-7225). The two core papers include a 1976 paper by Takashi Morita, Sadaaki Iwanaga, and Tomoji Suzuki, Division of Plasma Proteins, Institute for Protein Research, Osaka University, Japan. They discuss the process by which an enzyme in the venom of the vicious and deadly saw-scaled viper, the Indian phoorsa (*Echis carinatus*), activates prothrombin. As a precursor of the enzyme thrombin, prothrombin catalyzes the conversion of fibrinogen to fibrin and thus facilitates blood clotting.[47] In a 1975 core paper, F. Kornalik, Institute of Pathophysiology, Charles University, Prague, Czechoslovakia, and B. Blombäck, Department of Blood Coagulation Research, Karolinska Institute, Stockholm, Sweden, discuss similar effects caused by the venom of such snakes as the Australian tiger snake (*Notechis scutatus scutatus*) and the Indian phoorsa.[48]

Table 1: Selected list of journals reporting on animal venoms. A=title, editor, and publisher. B=1986 *SCI®/SSCI®* impact factor.

A	B
Annals of Allergy J.A. Bellanti, ed. American College of Allergists McLean, VA	0.94
Insect Biochemistry L.I. Gilbert, ed. Pergamon Journals, Ltd. Oxford, United Kingdom	1.80
Journal of Allergy and Clinical Immunology A.L. Sheffer & A.S. Buist, eds. C.V. Mosby Co. St. Louis, MO	3.17
Pharmacology & Therapeutics A.C. Sartorelli, ed. Pergamon Journals, Ltd. Oxford, United Kingdom	1.85
Thrombosis and Haemostasis J.J. Sixma, ed. F.K. Schattauer Verlag GmbH Stuttgart, Federal Republic of Germany	3.37
Toxicon P. Rosenberg & G. Habermehl, eds. Pergamon Journals, Ltd. Oxford, United Kingdom	1.23

Cobra Venom

A front entitled "Cellular oxidant injury and cobra venom factor" (#86-8252), with 2 core and 97 published papers, deals with the effects of the toxic constituents of cobra venom on cells and ways of minimizing the damage. These two papers were originally published in the *Journal of Clinical Investigation* in 1978 and 1981. This co-cited pair beautifully illustrates how research-front identification proceeds independently of the nomenclature of the cited and citing works.

The core papers by Thomas Sacks and colleagues, Department of Medicine, School of Medicine, University of Minnesota, Minneapolis,[49] and by Stephen J. Weiss and colleagues, Simpson Memorial Institute, University of Michigan,[50] discuss the conditions under which components of the human immune system attack the body's own cells and cause them to rupture. One such condition is the presence of a component of cobra venom, called cobra venom factor. Various studies have found that this factor, upon interaction with one of the proteins found in serum, produces a complex that stimulates the complement system, which participates in the immunological destruction of invading organisms.[51-53] The cobra venom, however, causes the complement system to attack other components of the serum, notably red blood cells.

Interestingly, cobra venom is a topic of intense research by Soviet scientists. A substantial number of both the core and citing papers on "X-ray and other analyses of cobra cytotoxin" (#86-2399) consist of Soviet works. Three recent articles were published by T.F. Aripov and colleagues, Institute of Bioorganic Chemistry, Tashkent. They studied the interaction of cytotoxins from bees and central Asiatic cobras with phospholipids, the major form of lipid in all cell membranes.[54-56]

Some of the key journals reporting venom research are listed in Table 1, a list indicating that venom research is a multidisci-

Table 2: Selected list of institutes and research centers engaged in studies on biotoxicity, biotoxins, immunotherapy, and antivenins.

Alistair Reid Snake Venom Research Unit
Liverpool School of Tropical Medicine
University of Liverpool
Liverpool L3 5QA, United Kingdom

Butantan Institute
Av. Vital Brazil 1500
CP 65
05504 Sao Paulo, Brazil

Cardiopulmonary/Venom Research Laboratory
Department of Medicine
School of Medicine
Wayne State University
540 East Canfield
Detroit, MI 48201

Clodomiro Picado Institute
Costa Rica University
San Jose, Costa Rica

Department of Immunology Research
Commonwealth Serum Laboratories Commission
Parkville, Victoria 3052, Australia

Hungarian Herpetological Society
Division of Toxinology
P.O. Box 274
Szeged 6701, Hungary

International Biotoxicological Center
World Life Research Institute
23000 Grand Terrace Road
Colton, CA 92324

International Consortium for Jellyfish Stings
Division of Dermatology
University of Maryland Hospital
22 South Greene Street
Baltimore, MD 21201

International Society on Toxinology
c/o Dr. Philip Rosenberg
Department of Pharmacology and Toxicology
University of Connecticut
Storrs, CT 06268

Japan Snake Institute
Yabuzuka-honmachi
Nitta-gun
Gunma Prefecture 370-23
Japan

Laboratory of Entomology and Venomous Animals
Hebrew University of Jerusalem
Jerusalem, Israel

Venom Research Center
Faculty of Medicine
Ain Shams University
Cairo, Egypt

Venom Research Laboratory
Departments of Physiological Sciences and Biochemistry
Oklahoma State University
Stillwater, OK 74078

Venom Research Laboratory
Veterans Administration Medical Center
Salt Lake City, UT 84148

Venom Unit
Pasteur Associate Unit/INSERM #285
Pasteur Institute
28 rue de Dr. Roux
75724 Paris, France

plinary field. Relevant articles appear in immunobiology, biochemistry, pharmacology, and medical journals as well as zoology and ecology journals. A selected list of research centers and institutions engaged in the study of biotoxins and biotoxicity, immunotherapy, and antivenins is shown in Table 2.

Future Directions in Venom Research

Immunization will continue to be a major area of interest within the venom research community. New methods of detecting the presence of venom and antibodies to venom in body fluids (such as serum and urine) are being developed and are becoming increasingly useful in the clinical study and diagnosis of snakebite. As noted by Minton, such methods, pioneered in Australia in the early 1970s, make use of radioimmunoassay techniques. One such technique, known as ELISA (enzyme-linked immunosorbent assay), has already been used in the clinical diagnosis of snakebite. It has also been used to monitor and evaluate first-aid techniques, to study clinical syndromes associated with snakebite, and to detect and identify venom in forensic cases.[57]

Another area that is expected to grow concerns the uses of venom and venom extracts in the treatment of diseases, such as feline leukemia and other types of cancer, arthritis, and lupus.[58,59] The latter is a chronic, often fatal condition that kills thousands of people each year—predominantly young women. We will discuss lupus in a future essay.

As we have seen, early venom research concentrated on describing the physical and

chemical characteristics of venom. Although much remains to be done in this area, researchers are learning how to combat the effects of venom. Antivenin and immunological research has ironically led to potential uses of venom in fighting disease. Substances that, until now, posed an unmitigated threat to humanity may prove to also be of benefit.

* * * * *

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