INTRODUCTION

Man has encountered snakes since the beginning of time. Our fascination with snakes has been manifested by their being both loathed and worshipped. This report will document the progress in medical treatment of victims of pit viper envenomation over time (Table 1). I will refer to medicalization as the process of a human condition progressing from one that essentially did not involve the medical profession to that of a high involvement with modern clinical science. Many human conditions that we accept as having medical implications have not always been so. Two hundred years ago, childbirth was the sole purview of midwives and there were practically no recognized medical aspects of this event and certainly no specialty of obstetrics. More recently, we have seen medicalization of alcoholism, drug addiction, obesity, personality disorders, and a host of environmental and occupational aspects of medicine.

That man and snakes have had a stressed relationship is alluded to in the Bible. It is only seventeen verses after the creation of man and two verses after the creation of woman that mankind in the Garden of Eden had the first encounter with “the most subtle of all beasts” [Genesis 3:1]. This confrontation with the reptile was the original sin, a mere three chapters into the Bible.

For every ancient representation of snakes as evil there is at least an equal depiction of snakes as highly revered. One of the first cultures to do this was that of the ancient Egyptians. Their principal deity, Ra, was adorned with a hoop-like device depicting a snake. The Romans used a snake in the form of the caduceus which was the serpent-staff of Mercury. Similarly, the symbol of medicine, the staff of Aesculapius, consists of a snake intertwined around the staff. Of interest this staff-snake motif may reflect the magical staff that Moses used in the wilderness in Exodus. Moses was commanded to “make a poisonous serpent and set it on a pole; everyone who was bitten shall look at it.
TABLE 1.
Milestones in Therapeutic Approach to Pit Viper Envenomation

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<th>Era</th>
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<td>Post-Columbian</td>
<td>EtOH, politex, parts of snakes</td>
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<td>19th Century</td>
<td>EtOH, cathartics, purges</td>
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<td>Early 20th Century</td>
<td>Stimulants—EtOH, strychnine</td>
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<td>Keep venom local—ligatures</td>
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<td>Neutralize venom—ice therapy, KMnO₄</td>
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<td></td>
<td>Rid venom—incision and suction, surgical exploration</td>
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<td>Early antivenom experimentation in Saigon and Sao Paulo</td>
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<td>Late 20th Century</td>
<td>Large clinical series with accurate observation</td>
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<td>Understanding venom—toxinology</td>
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<td>Antivenom with rapid IV usage</td>
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<td>Routine surgical exploration revisited (rebuffed)</td>
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<td>Electroshock with DC current (rebuffed)</td>
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<td>21st Century</td>
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and live” [Numbers 21:8]. Many Asian and Hindu myths employed snakes in a magical or divine manner.

A great deal of mythology involves pre-Columbian civilizations in the Americas. The American Indians revered nature and animals in their ceremonial life more than most other civilizations. Their adoration of snakes, and particularly rattlesnakes, is noteworthy. The ancient May- ans and Aztecs frequently used images of rattlesnakes with almost all the rattlesnakes displaying thirteen rattles, thirteen being a sacred number. Early colonists in the Americas noted the strong sense of reverence if not awe that the American Indians had for rattlesnakes. Rattlesnakes were honored and protected by most Indian tribes. Russell states that American Indians went out of their way to not bother, offend or let alone kill rattlesnakes (1). To do so may invite a bad consequence. Regarding the Seminole Indians’ practices and beliefs, the 18th century naturalist William Bartram noted: “These people never kill the rattle snake or any other serpent, saying if they do so, the spirit of the killed snake will excite or influence his living kindred or relatives to revenge the injury or violence done to him when alive” (2).

Of interest, American Indians also perceived parallel imagery between lightning strikes and rattlesnakes, presumably because of the random, rapid, and dangerous actions of each. It has been alleged that the Indians’ respect and reverence for snakes led to their being envenomated less often than the curious, inquisitive, and venturesome early white settlers (1).

Some of our earliest proposals of treatment of snakebites comes from the pre-Columbian American Indians. Treatment at that time was
often performed by shamans, members of the Indian tribes who were not only medicine men-priests but as often as not assumed this role because they had survived a snakebite themselves. Tribal rituals and ceremonies were often used more than direct manipulation of the patient in attempts to ward off effects of snake venom poisoning once an envenomation had occurred. A variety of plants have been referred to as “snakeroot” or “snakeweed” and all of these, particularly the roots thereof, were thought to have magical powers in treatment and prevention of snake venom poisoning. A variety of roots or leaves were chewed and spit into the wound. Alternatively, these leaves could also be chewed and spit on their hands and feet to prevent snake bite if they were off on a hunting party. Chewed tobacco was similarly used. Russell catalogues at least two dozen American plants which were employed as snakeroot or snakeweed (1).

The rattlesnake itself, even more so if it were the exact snake that inflicted the wound, had magical powers in reversing the effects of the snakebite. American Indians would pulverize the head of a rattlesnake, mix it with human saliva and then apply it to the wound. Either fresh or dried rattlesnake and particularly rattlesnake heart could be used externally or taken internally. Also rattlesnake skin and rattlesnake fat were held as having curative properties as did its blood. Alternatively, one could eat the entire snake. Other tribes used the rattlesnake liver. Some tribes found that primitive forms of alcohol worked but with the coming of the white man and his liquor, alcohol rapidly became the favored remedy.

Other agents having curative properties have been listed by Russell and as many as 300 have been used to include rain, seawater, hearts of turtles and gunpowder (1). A more recent favorite was soaking the bitten extremity in kerosene which has been used until extremely recently as kerosene was thought to “draw out” a variety of poisons to include snake venom. Some shamans were used simply to prognosticate without actually employing therapy. Such a shaman would produce a prognosis and if they thought that the case was for certain fatal, they did not spend much effort in trying to intervene on behalf of the patient.

During the 18th and 19th century, state-of-the-art medicine at that time did not involve treatment of snakebites. Mention is not made of snakebite in Osler’s monumental textbook (3) nor in Austin Flint’s competing textbook (4). Usually if doctors were employed, it was simply to amputate a gangrenous limb.

As the then new twentieth century began, clinical medicine was on the verge of breathtaking discoveries based on excellent clinical obser-
vation, clinical investigations, and laboratory investigation, all of which had roles in the development of modern treatment of pit viper envenomation.

Clinical Observation

In the 18th and 19th centuries in the United States there was no meaningful collection of clinical experiences regarding either the natural course of snakebites or proposed treatment thereof. Most physicians, with the majority of better-trained pre-Flexnerian physicians who consulted and practiced in larger cities, saw few, if any, victims. Those victims who were encountered by these physicians would more likely than not have been in the latter stages of their injury. Ironically those physicians have had little chance to observe the natural history of either the infrequent fatal injuries or the mild or trivial nature characteristic of the majority of wounds. Rather, they would have encountered late manifestations such as large edematous wounds, mostly infected and gangrenous, and many requiring amputations. These services were typically surgical in nature.

In 1908, in the initial volume of Archives of Internal Medicine, Willson presented a collection of observations regarding snake bites made from reviewing various publications and experiences he had gathered throughout the United States (5). This may well be the first systemic review of the subject and is, even now, surprisingly accurate given the resources available at that time. Willson opined that “knowledge concerning snake poisoning in the United States is decidedly meager” citing frequent “misstatements”, “impression”, and “conjectures”. He stated that most cases were not treated by physicians owing to “the laity being well aware of the uniformly good prognosis” of snakebites. His review, at a time of essentially no meaningful available therapy cited an 8–10% mortality rate for those patients seeing a physician. Regarding touted therapies he concluded “the mere length of the list of drugs and other therapeutic procedures recommended as specific in the treatment of these cases is proof positive of their utter worthlessness”. Alcohol as a stimulant, he concluded, was “much worse than useless” deducing that acute alcohol poisoning was the most likely cause of several deaths, especially in bitten children.

Willson cataloged three approaches to therapy: 1) maneuvers to keep the venom deposit local rather than systemic even if this worsened local damage (ligatures, amputations, excisions, ethyl chloride freezing, or cutting the wound with kneading and massage to work out accessible venom); 2) attempts to destroy the potency of the venom
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(local injections of calcium chloride, packing the wound with crystals of potassium permanganate, or topical chromic acid); 3) general support of the patient (using what we would now call the Trendelenburg position and stimulation with ammonia or strychnine but not alcohol). Of interest, he noted that the circulatory collapse seen with severe envenomation could be successfully treated with the then newly described procedure of saline injection administered either intravascularly or by clysis. Although some experiments in animals had indicated that inoculation therapy (see below) and either active or passive immunity was a laboratory possibility, Willson prognosticated that such therapy would never be clinically available or practical.

Little clinical improvement immediately followed that 1908 report. Progress would depend on more basic knowledge regarding snake venom. There was an explosion of knowledge from the early 1900s to now regarding that science, namely venom toxinology. The history of this exciting science has been thoroughly reviewed by Russell (1), a source to which the interested reader is referred for its breadth and for its primary references and from which this author gathered most of the following information.

Pit viper venom is an extremely complex mix of proteins most of which are enzymes. The similarity of many of these enzymes to digestive enzymes cannot help but be noticed and has led many to conclude that the primary purpose of the pit viper venom is actually early digestion of its prey. There are 20–30 enzymes in pit viper venom which are designed to digest fat, protein, nucleic acids, collagen and other connective tissues. These enzymes in concert cause the hemorrhagic necrosis and lysis of tissues characteristic of pit viper envenomation. Other proteins may initiate directly or indirectly autonomic system manifestations such as tachycardia, hypotension, diaphoresis, and greatly enhanced gastrointestinal mobility (vomiting and diarrhea) that are other characteristics of pit viper envenomation.

The variety of proteins in snake venom is extreme. Not only does the spectrum of components in the venom and their relative concentration vary from species to species but also from locality to locality and even with the age of the reptile. Because each component is thought to result in actions and damage specific to that protein, pit viper poisoning should be expected to be variable, complex, and difficult to predict. Even with comparatively fixed variables using a known amount of venom injected into laboratory animals, the LD\textsubscript{50} is highly variable and even more so when one varies the species of experimental animals into which the venom is injected.

As a hematologist, the author is drawn to the effects of venom on
plasma. That rattlesnake venom clots plasma in vitro has been known for at least a century. However in vivo one usually finds incoagulable blood in the victims of Eastern Diamondback rattlesnake (Crotalus adamanteus) envenomation (6). Markland and Pirkle (7) described a thrombin-like principle in the venom of Eastern Diamondback rattlesnakes that they termed crotalase. Crotalase, like thrombin, appears to clot fibrinogen to fibrin. However, further investigation has shown that only fibrinopeptide A is cleaved from fibrinogen by crotalase. This results in the formation of a clot in vitro but in vivo, animals were found anticoagulated by virtue of defibrinogenation. The partial fibrin (termed DesAAfibrinogen) produced by crotalase is sufficient to cause an imperfect soft clot yet is capable of briskly releasing tissue plasminogen activator (tPA) from endothelium leading to rapid clearance of any clot, massive production of circulating fibrin degradation products (FDP) and depletion of plasma plasminogen and alpha-2 plasmin inhibitor (8). Whereas thrombin completely cleaves both fibrinopeptide A and B from fibrinogen, activates factor XIII to covalently cross-link strands of fibrin (thus greatly increasing resistance to fibrinolysis) and activates platelets, crotalase has none of these actions. Crotalase also is not inhibited by heparin, antithrombin III, or hirudin whereas thrombin is (9). These facts differentiate crotalase infusion or Eastern Diamondback rattlesnake envenomation from disseminated intravascular coagulation (DIC) and explain the fact that Eastern Diamondback rattlesnake defibrinogenation is more benign than DIC.

In Eastern Diamondback rattlesnake envenomation, hemostasis is maintained as the hemostatic system (i.e., physiologic production of thrombin) is preserved as are platelet numbers and platelet function. Interestingly, despite near complete defibrinogenation, hemostasis remains intact even proving adequate for the rare patient requiring fasciotomy (9). In victims of Eastern Diamondback rattlesnake envenomation, fibrinogen levels remained low enough such that the partial thromboplastin time (PTT), prothrombin time (PT) and thrombin time (TT) remained unclottable for up to 2–3 days in patients who do not receive antivenom whereas in victims treated with antivenom, the fibrinogen level concentration returns to levels adequate (i.e., levels greater than 50 mg/dL) to result in normalization of the PT, PTT and TT within 24 hours of antivenom therapy (6). These observations force one to conclude that the commercially available antivenom contains an antibody fraction that is highly effective against crotalase. In summary, the venom of Eastern Diamondback rattlesnakes contains an activity (crotalase) that readily clots blood in vitro but actually results in anticoagulation in vivo.
Of interest, DIC is characteristic of envenomation by Echis carinatus and Vipera russelli envenomation as their venom directly activates prothrombin and factor X respectively thus resulting in in vivo production and circulation of thrombin, the defining and central feature of DIC (10). Lethality from these reptiles is much higher than Eastern Diamondback rattlesnake envenomation with thrombosis playing a major role.

A principal in the venom of Western Diamondback rattlesnake (Crotalus atrox) directly activates plasminogen to plasmin and thus its venom has direct in vivo and in vitro anticoagulant properties.

Another example of “signature effect” of a species of pit viper venom is the recently described action of the venom of the canebrake rattlesnake (Crotalus horridus atricaudatus) on type B skeletal muscle fibers that result in massive, dose-dependent release of creatinine kinase (CK) with elevated MB fractions but normal troponin levels (11). Envenomation by these snakes does not result in defibrination and likewise, envenomation by the Eastern Diamondback rattlesnake does not result in the myonecrosis typical of the canebrake rattlesnake.

CLINICAL INVESTIGATION

Remarkable progress in management of snakebite envenomation was made in the decades following World War II. This progress was enabled primarily by adroit observations of snakebites, its natural history, its response to either effective or ineffective therapy, and compilation of a vast clinical experience coupled with the employment of the scientific method in clinical investigators using an open mind. Most of these observations were made by and catalogued by a small number of investigators whose experience negated the long true fact that most previous experience was the result of vocal expression of physicians who had actually seen less than a handful of pit viper bites. Additionally, these practitioners practiced in the era of modern laboratory studies, the development of intensive care units, tremendous advances in emergency medical transport and treatment, and modern advances in resuscitative medicine and the development of antivenom, none of which was available to Willson 60 years earlier (5). We owe a great debt to these early, progressive if not often loquacious clinical investigators. Three physicians, F.E. Russell in 1975 (12), L.H.S. Van-Mierop in 1976 (13) and C.H. Watt in 1978 (14) published comprehensive, up-to-date reviews based on critical analysis of the available literature and their own considerable experience. Their papers remain highly readable and of interest to the practicing physician. Despite
differences in these three physicians’ locality of practice, their individual experiences, and their training, their degree of agreement in this heretofore bewildered area is remarkable. These experts all agreed that for cases of moderate and especially severe envenomation that the available antivenom (Wyeth polyvalent Crotalidae) should be intravenously administered in large quantities as soon as possible. They likewise denounced the use of cryotherapy, extensive use of ligatures, and routine surgical exploration. In 1980, two books were published providing exhaustive information regarding statistics, anatomy, toxicology, pharmacology, history, folklore, and related facts concerning snakes, their venom, and the treatment of snakebites. These remain as encyclopedic references to this day and this author has heavily relied on these books as a data base and for in-depth information (1,15).

Parrish and colleagues (16) were among the first to gather large amounts of clinical data and devise a grading system. It has been argued whether the grading system was an advance or step backwards in evaluation of snakebite. It is the opinion of this author that having the concept is better than not having the system in judging the degree of pit viper envenomation if one avoids two serious pitfalls.

The grading system primarily involves one that is based on local damage from the snakebite. The first of the two pitfalls is that as many as 25–30% of snakebites by known pit vipers result in no envenomation. Several reasons have been proffered but this results from failure of the snake, despite puncture of the skin by their fangs, to envenomate the victim. Signs for this include failure to develop the classic triad of swelling, pain, and discoloration typically within two hours of the accident. We however suggest observation overnight for nearly all snakebite victims. These patients, if they have no other symptoms besides a bit of understandable anxiety, have not been poisoned and therefore should not be administered antivenom.

Grade I or minimal envenomation is a minimal amount of swelling that does not progress rapidly (i.e. hours rather than minutes) and the victim does not display systemic symptoms. In Grade II or moderate envenomation the swelling may initially be mild but progresses rather rapidly (such as doubling the amount of swelling in 1–2 hours). Often some mild signs of systemic envenomation (fasciculation or diaphoresis) develop depending on the species of snake involved. The rarest is Grade III or severe envenomation. These are the patients who have autonomic manifestations such as tachycardia, hypotension and intense diaphoresis as well as nausea, vomiting, diarrhea, and often a woozy, slightly disoriented-type feeling.

The second pitfall regarding the grading system is that unfortu-
nately some victims with the worst bites, i.e. Grade III, actually have very few local signs and symptoms. The best explanation for this paradox is that patients so bitten often do not manifest local signs because the venom has so rapidly gained access into the vascular system that systemic poisoning overshadows local poisoning. Such bites typically occur in muscular areas and not in the relatively avascular parts of the hands, toes, fingers and feet. Common areas include bites in the thenar or hypothenar eminences, arms or legs, areas which are quite vascular because of their muscle bulk. Accordingly intramuscular injection (roughly 10% of all bites) is typically worse than subcutaneous or intraconnective tissue bites (approximately 90% of all bites). Factors favoring intramuscular injection of venom not only include the bite site but the fact that large rattlesnakes such as Eastern and Western Diamondback rattlesnakes by virtue of having longer fangs are in a position to more deeply inject their venom. Smaller snakes lack that ability.

Parrish and colleagues (16) were among the first to stratify severity of snakebites that they encountered. They found that 26% were so-called Grade 0, i.e. without envenomation; 38% were Grade I or minimal; 22% were Grade II or moderate; and 14% were Grade III or severe. They lamented that 64% of the patients who clearly had Grade 0 envenomation received antivenom showing that many physicians tend to overtreat these lucky patients. One could argue, as is also our experience, that the combination of Grade 0 and Grade I bites is over 50% and therefore at least 50% of patients are not prime candidates for antivenom administration. One should also counter this statement with the fact that approximately half of Grade III or severe snakebite envenomations are underestimated by practitioners because these victims have so few local signs and symptoms that a feeling of complacency is generated on the part of the practitioner while the patient is actually seriously systemically ill based on systemic symptoms rather than local pain, swelling and discoloration. Most of our Grade I envenomations are from the almost nuisance bites of the pigmy rattlesnake (Sistrurus miliaris). The majority of our Grade II envenomations occur from water moccasins (Agkistrodon piscivorus) and small rattlesnakes whereas the vast majority of Grade III or severe occur from bites by the Eastern Diamondback rattlesnake and occasionally the canebrake rattlesnake. Be advised that this grading system does not pertain to bites from coral snakes (Micrurus fulvius) (17).

In defense of the grading system, this author's opinion is that it is of assistance to patients and practitioners who are not used to treating and evaluating a large number of snakebite victims. Actually more
useful is the first derivative of the clinical situation over time, viz., progression of symptoms. It is very clear that prognosis and therefore treatment are direct functions of the grading system if the grading system is successfully carried out and one is aware of the two above pitfalls.

LABORATORY INVESTIGATION

Biomedical and laboratory technology exploded in the 1960s and since playing a major role in focusing on scientific discussion in this area. Using newer methods, newer information could clarify misunderstood topics and settle disagreements among differing treatment methods. Using laboratory animals and in certain instances human victims, trials clearly pointed out effective therapies while at the same time serving to prove the worthlessness of other therapies.

As early as 1887, Sewall (18) performed experiments that he termed inoculation which involved serial injection of pigeons with rattlesnake venom. He quite clearly demonstrated that with repetitive small but progressive inoculations of rattlesnake venom, pigeons could be given up to seven times a lethal dose without any apparent effect. He also showed that with time without further inoculation resistance was lost and that a late subsequent injection of rattlesnake venom in the same pigeon would cause death of the bird. Sewall clearly described what we would now believe to be induction of progressive antibodies against these foreign proteins.

B.J. Hawgood chronicles extremely well in two manuscripts, the contributions of Calmette (19) and Brazil (20) in the early history of antivenom production. Hawgood credits Sewall with initial experiments in these two reviews to which the interested reader is referred. In France, Dr. Calmette was instrumental in the establishment of the Pasteur Institute and then moved to Saigon in then French Indochina. He had been impressed by antitoxin therapy that had been developed against diphtheria. He then set out to produce a serum to protect against cobra bites which were then common in that part of the world. He did develop a partially effective anti-cobra venom and thus in 1895 was the first to actually open the door to widespread therapeutics for snakebite. He went on also to become quite famous in the prevention of tuberculosis and the establishment of the Bacille Calmette-Guerin (BCG) vaccine. If any one individual was actually most responsible for the medicalization of snakebite treatment it would have to be Dr. Vitil Brazil. This man in the last decade of the 19th century and first decade of the 20th century became aware of Dr. Calmette’s work. While work-
ing in Sao Paulo, Brazil, he demonstrated that Calmette's anti-cobra antivenom was not effective against South American snakes. He then set out to develop his own antivenom and did so by progressively injecting small amounts of raw venom into dogs and goats, the serum of which provided protection following Bothrops jararaca and Crotalus durissus terrificus envenomation. He also discredited local charlatans and magicians showing that their treatment to include a variety of natural plants and the like were not efficacious using the scientific method whereas his antivenom was therapeutic. Brazil established the Institute Butantan. By this time, but not in the United States, antivenom therapy was becoming established and credited by these scientific studies.

Schottler (21) in 1952 showed that an early preparation of antivenom when given quickly to mice gave greatly superior results than no antivenom and also showed that the intravenous injection was much more efficacious in these mice than if the antivenom were given subcutaneously.

Minton (20) in 1954 showed that an early preparation of polyvalent antivenom worked in mice but also found that this early antivenom had a poor ability to neutralize the venom of the Western diamondback, Eastern diamondback, cottonmouth water moccasin (Agkistrodon piscivorus), or the copperhead (Agkistrodon contortrix). This was explained by the types of venoms which were injected into the animals raising this early antivenom. It should be noted however that the failure of this early antivenom to work well arguably retarded the employment of the newer antivenoms which came on the market in the late 50s and early 60s, namely the Wyeth product which is still available.

The early Wyeth antivenom was studied in 1963 by McCollough and Gennaro (23). They showed that radiolabeled antivenom was highly effective therapy and that efficacy was a function of whether the antivenom traveled to the bite site. When antivenom was given intravenously, 85% of it could be found by scanning at the bite site in dogs two hours after the administration of the antivenom. If it was given intramuscularly, only 1% got to the site and only 6% traveled to the bite site if the antivenom was given subcutaneously. This led to early but not often heeded advice to administer antivenom intravenously and not to give it intramuscularly, subcutaneously or certainly not intralesionally. This latter route was associated with development of extremely high local pressures in bitten fingers and toes. Additionally there was failure of the antivenom to mobilize from the intralesional deposition site to the systemic circulation. Russell and colleagues (24)
showed quite clearly in experimental rats that the efficacy of the new Wyeth product was a function of how soon the antivenom was administered. There was a much better prognosis with less death and less tissue destruction in experimental rats given lethal doses of rattlesnake venom if antivenom is given quite early. This has led to the now unchallenged concept that essentially all antivenom should be given before 12 hours, and certainly before 24 hours by the intravenous route.

That argument that antivenom was effective was markedly strengthened by the studies of Parrish and colleagues (25). By reviewing the literature available in 1965, they showed that morbidity and mortality in humans decreased with antivenom administration. Although clinical studies done in that era are subject to criticism as they failed to account for multiple variables and were not randomized, the trend is inescapable. They (25) quoted a 1926 review by Amarol and a 1929 review by Hutchinson claiming that patients who received a early antivenom preparation experienced a death rate of 6% and 3% respectively whereas those patients who did not receive the available antivenom died at a rate of 34% and 11% respectively. Despite the nature of patients presented, the lack of other supporting therapy available in the mid-20s, and the early crude antivenom then available, antivenom administration did appear to reduce mortality by approximately four or fivefold. Their own data from the late 1950s demonstrated, at a time when medical and other supportive care was much improved, a mortality rate without antivenom of 2.6% dropping tenfold to 0.3% in patients who received the modern preparation of antivenom (25).

Mechanical devices have been used for some time with the notion of decreasing the escape of venom from the envenomation site into the systemic circulation. One may try to retard flow out of the bitten extremity or attempt to get the venom out of the wound directly. One of the earliest studies testing this idea was that of Jackson and Harrison in 1928 (26) when they conclusively showed that dogs in an experimental setting administered highly lethal doses of rattlesnake venom lived if the wounds were incised and suction was applied within a short period of time. Additionally if a second dog were injected with the fluid that was extracted from the first dog, the second dog died in a manner expected from snakebite.

This experience was essentially duplicated by Russell and Emery in 1961 (27) using rabbits instead of dogs. The incision and suction method did save envenomated rabbits. If the removed fluid were injected into yet another rabbit, that rabbit displayed severe toxicity consistent with rattlesnake envenomation. In 1963 and using labeled
pit viper venom, McCollough and Gennaro (23) showed that the incision and suction method could remove up to 40–50% of labeled venom if this was done very early (30 minutes or less) and if the bite were shallow (meaning subcutaneous as opposed to intramuscular). However this method proved to be inferior to that of antivenom administration. Although they and the earlier investigators had proved the incision and suction method worked, it was agreed it should not be performed if this treatment meant postponement of travel promptly to a medical facility. If done improperly, major adverse effects (laceration of nerves, tendons, and vessels as well as infectious potential) can occur and therefore this method is not held currently in high regard.

Another mechanical method used is that of the loose ligature in which a band at least an inch in width is placed loosely around the bitten extremity proximal to the bite. The rationale is to sequester the venom in the bitten extremity as opposed to its gaining entry into the general circulation. Burgess and colleagues (28) demonstrated that labeled Western Diamondback venom was successfully retained by ligature for several hours in pigs. Most clinicians investigating this field think that this ligature method should not be used if it slows transportation to a medical facility. It should be cautioned that this method is not by definition a tourniquet blocking blood flow but uses pressure sufficient to block only the superficial lymphatic flow, namely around 20 mmHg pressure.

The administration of ice, otherwise known as cryotherapy, has been suggested by many with the dual notion that its use would both decrease the circulation of blood into and subsequently out of the bitten extremity thereby postponing systemic entry of venom and also that the enzymatic activities that are present in the venom would be slowed by cooling down the bitten extremity. Snyder and colleagues (29) studied this maneuver again using labeled venom in experimental dogs. They were able to show that if a dog’s leg was left in its natural state following administration of a fixed amount of venom that 22% of the venom gained systemic access within one hour, and that this could be decreased to 9% by using a tourniquet and down to 2% if the limb was packed in ice. However, they did not endorse this method because of a net increase in tissue loss from frostbite using cryotherapy. Of interest these same investigators showed that alcohol and/or exercising the limb (such as running for help) actually enhanced mobilization of venom from the bitten extremity.

McCollough and Gennaro (23) showed that cryotherapy was closely associated with worse necrosis presumably from frostbite and that cryotherapy resulted in an increase in loss of limbs.
In summary, the preponderance of medical and experimental evidence would on the one hand support that the incision and suction method is rational and, if performed properly and within a very few minutes from the bite, can remove venom but this should never be done at the expense of transportation to an emergency facility. Use of ice and cryotherapy are not supported.

Another proposed method of snakebite treatment was the aggressive surgical approach to the wound. This method, to include prompt preemptive amputation, had been advocated off and on for hundreds of years. Because of legitimate concern of immunologic reactions, especially to early preparations of antivenom, some investigators decided to again approach the wounds surgically. The leading proponent of this approach was Glass (30) who advocated that snakebite wounds should be acutely, radically and aggressively explored surgically in order to relieve pressure on the wound, to control swelling of the extremity, to debride necrotic tissue and hopefully to remove venom. This method gained a significant amount of popularity.

More recent studies have shown that the notion of routine surgical exploration is probably ill-advised. Using an experimental laboratory method, Garfin and colleagues (31) studied dogs which were envenomed in both legs with rattlesnake venom and then systemically injected with antivenom. If one leg were subjected to immediate surgical exploration and the other leg served as its control, it was impossible to distinguish differences in the outcome 48 hours later when the legs were examined macroscopically and microscopically. Fasciotomy did not prevent muscle necrosis. This study negated the notion that opening a wound would decrease damage by decreasing pressure in the affected limb. Stewart and colleagues (32) used rabbits injected with Western diamondback venom and randomized them to undergo fasciotomy and debridement alone vs. antivenom alone vs. a combination of the two methods. They showed that superior survival and preservation of muscle resulted when animals were treated with antivenom alone. This study served not only to show the experimental utility of antivenom but actually the addition of routine surgical procedures decreased overall viability and function of the limb. Doing a retrospective chart review, Derlet and Silva (33) showed that humans had a longer hospital stay and no increase in functional outcome if they were treated primarily by surgical methods.

Kitchens and colleagues (34) studied muscle damage in a fatal case of human envenomation by canebrake rattlesnake. This victim had massive systemic muscle necrosis as evidenced by serum CK levels of 2.8 million units/dL. At autopsy the thenar eminence in which he was
bitten on one hand was examined and compared to the thenar eminence on the other (control) side as well as the psoas muscles, arguably quite distant from the bite site. Microscopically, it was impossible to distinguish among the samples of origin of the muscles. The bitten thenar eminence, despite extreme pressure that was present in the wound was indistinguishable from the psoas muscle focusing on the fact the damage appears more likely due to chemical necrosis rather than pressure necrosis.

Most authorities now do not suggest routine surgical exploration of wounds. Theoretically, this approach also is additionally ill-advised as during the surgical procedure in the operative suite it is likely that submaximal attention will be paid to both resuscitation of the victim by administration of antivenom and close observation of the patient and his laboratory results.

There appears to be an infrequent (approximately 1%) need for fasciotomy. These are justified in cases where there is a true compartment syndrome and/or such pressure on adjacent nerves that there is extreme danger to viability of underlying tissues. Most of these cases have in common that antivenom was administered rather late; therefore, tissue had the opportunity to swell enormously to invoke a compartment syndrome. Most such compartments that have been attended by this author have been in the palm of the hand, the volar component of the arm (median nerve) or the anterolateral compartment of the leg. These patients however should not be sent to surgery prior to resuscitation with fluids and substantial amounts of antivenom. Only at that time should a simple fasciotomy with not much attention paid to debridement be considered. Viability of the muscle should be ascertained. Muscle that is directly injected with venom may be extremely hemorrhagic appearing but, if viable, should not be routinely debrided.

The most recent highly touted “new treatment” for snakebite involves electric shock therapy. Apparently the original notion of this started when some observers had noticed that clinical manifestations of bee stings may be altered if a direct electric current was passed through tissue that had been stung. The first report of electric therapy for snakebite apparently was in 1986 by Guderian and colleagues (35). These investigators in the Amazon jungle area of Ecuador noticed that if natives bitten by poisonous snakes (chiefly Bothrops atrox) were treated by these medical missionaries with electric current passed through the bitten area that they achieved strikingly successful results. This was even more so dramatic because the morbidity and mortality expectations among these Ecuadorian Indians was very high. These physicians apparently initially used electric shock therapy
generated by outboard motors and, at times, lawnmowers. They then refined their method using a hand-held “stun gun” with some modifications. These successes were reported at least three times in *Outdoor Life*.

In the laboratory, Johnson et al (36) studied the effects of electric shock on lethality of rattlesnake venom in mice and found that there was no positive effect whatsoever. A similar experiment was then done by Howe and Meisenheimer (37) when they injected the venom of Bothrops atrhox in increasing doses in rats and were unable to demonstrate any efficacy of electric shock.

Dart and Gustafson (38) reported experience in a human who, after being bitten in the face by a rattlesnake, was hooked up to a highly revved car with an electrode being placed on the patient’s face and the other at a distant site. This caused not only no apparent salubrious benefit to the patient but caused massive swelling and substantial burning of the face.

This experience demonstrates once again that if expectations of morbidity and mortality are high in situations where they are actually low, a high success rate independent of the therapy provided will appear to result. Not only has experimental experience been neutral at best and bad at worst, there appears to be no rationale for electric therapy.

The Wyeth antivenom has been available for nearly a half century. It is very efficacious, particularly when given rapidly and in large enough quantities neutralizes systemic and local manifestations of envenomation. It is associated with a certain background rate of immune reactions (see Table 2) and the length of time it takes for the product to go into solution, particularly facing an ill patient in the emergency room, is bothersome. Over the last few years a new product has been developed and is nearing FDA release. This product is pre-

| Table 2. Qualities of Antivenoms Available in the United States |
|------------------|-----------------|-----------------|
| Wyeth            | Crotab          |
| Source           | Horse           | Sheep           |
| Product          | Serum immunoglobulins | Fab fragment of IgG |
| Solubility       | Slow            | Rapid           |
| Incidence of     |                 |                 |
| 1) anaphylaxis   | 1:100–1:1000    | Extremely low   |
| 2) other rapid allergic reactions | 20–25% | 14% |
| 3) serum sickness| 30–60%          | 15%             |
| t₁/₂             | Days            | 12–30 hours     |
| Efficacy         | Good            | Good            |
pared from flocks of sheep which have been immunized against four species of American crotalids. The ovine plasma is then fractionated into the immunoglobulin fraction, immunoglobulins then papain cleaved with isolation of the Fab fragments which are then further purified and lyophilized. This results in a smaller amount of foreign protein injected and also results in a product that goes into solution much faster than the Wyeth product. This production is very similar to Fab fragments that are used as antibodies against digitalis for digitalis intoxication (Digibind; Burroughs-Wellcome). This new antivenom has gone through several trials (39,40) and has been shown to be quite efficacious. Advantages of the ovine antivenom compared to the equine antivenom are shown in Table 2. The product appears to be as efficacious as the Wyeth product but it has several advantages. It should be noted the Fab fragment opposed to the native intact IgG immunoglobulin has a shorter half-life so periodic retreatment appears to be more commonly indicated than with the equine product because of this difference.

As the product is safer one may confidently predict that the therapeutic threshold for treating snakebites with antivenom will be somewhat lowered because there is less fear of risks, chiefly from immunologic reactions.

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DISCUSSION

Atkinson, St. Louis: About a decade ago I looked into the circumstances surrounding snakebites in the state of Missouri. About one-half of the cases also involved “snake fanciers” and excessive alcohol. After a Saturday night of partying, the inebriated individual would return home and “play with the snake” and get bitten in the process. The other common circumstance in Missouri was also interesting. Beginning in the 1970’s, the many camping places for vans, trucks, and RVs in the Ozarks were covered with asphalt. Due to a prostate condition and/or too much imbibing, the victim would go to the edge of the asphalt, usually barefooted, half asleep and in the dark, to urinate. The copperhead was also sitting on the asphalt edge taking advantage of the heat retained by this material. Naturally, the snake would bite as it was stepped on.

Wolf, Chestnut Hill: I was surprised you didn’t mention a very famous quote in the field. In the last Road movie as Bob Hope was going off in the jungle he meets with Peter Sellers, who is an Indian Shaman to get instructions about snake bites. He’s told to put a little “x” over the bite and suck out the venom. Bob Hope thinks for a second, and looks at his nether region and says “What if you can’t reach the area of the bite?” Peter Sellers says “That’s when you find out who your friends are.”

Kitchens, Gainesville: I was aware of that, but my sense of southern propriety said don’t put it in.

Sergent, Nashville: Just a little more epidemiology. In our state one of the biggest causes of death from snakebites is actually among religious sects. There’s one sect called the Holiness Church of God in Jesus’ Name where people advertise openly that they handle and have been bitten hundreds of times, and almost invariably the ministers do die eventually after enough snakebites, so I guess they come up against your odds of 1000:1.

Kitchens: Well, if you get bitten enough times I guess something will happen. If you don’t wear your seat belt enough times, something will happen.