EXPERIMENTAL AND CLINICAL STUDY OF COBRA VENOM AS AN ANALGESIC

BY DAVID I. MACHT

PHARMACOLOGICAL RESEARCH LABORATORY, HYNSON, WESTCOTT & DUNNING, INC., BALTIMORE, MARYLAND

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Introduction.—Reptiles were used empirically in the primitive medicine of the ancients. Eminent physicians of the Middle Ages used different portions of various snakes as medicinal agents. Thus, for instance, Moses Maimonides, the Osler of medieval Hebrew and Arabic medicine, states in his treatise entitled, *Pirqué Mosheh*,[1] that certain parts of poisonous snakes were useful in the treatment of leprosy and *cancer*.[2] Even in the old English dispensatories of modern times, reptiles, including serpents, are classified under materia medica as, for instance, in the fascinating *Pharmacopoeia Londinensis*[3] of William Salmon. Parenteral administration of snake venom for medicinal purposes, however, is an achievement of recent years. Venoms or poisons of various species of snakes have thus been introduced into therapeutics in largely an empirical way within the last decade or two. Thus *Crotalus* or rattlesnake venom has been empirically employed in the treatment of epilepsy by Mays,[4] Fackenheim,[5] Prévost,[6] Jenkins and Pendleton,[7] Thom[8] and others; and the venom of the moccasin, *Ancistrodon piscivorus*, has been recommended for treatment of certain hemorrhagic conditions.[9] The most interesting and important contributions regarding snake venom, however, are those which have lately been written in France on *cobra* venom, which has been therapeutically employed on a rational and experimental basis. Calmette,[10] Taguet and Monaelesser,[11] Laignel-Lavastine and Koressios[12] have reported remarkable effects produced by injections of cobra venom in cases of malignant tumor, particularly the relief of the severe pains so common among patients affected with such diseases. These carefully controlled scientific medical researches of French writers prompted the present investigation. The four-fold objective of the writer was (1) to study the general pharmacology and toxicology of cobra venom according to the latest technical methods; (2) to prepare and assay biologically a sterile solution of cobra venom for therapeutic use in human patients; (3) to carry out a carefully controlled clinical investigation in order to ascertain the action of cobra venom injections on patients affected with malignant tumors causing severe pains; and (4) to analyze the more intimate pharmacodynamic action of cobra venom.

Snake venoms are general protoplasmic poisons which, however, exert a specially toxic action on two physiological systems, the blood and central

nervous systems, some venoms affecting the blood and others, the nerve elements. The constituents of snake venoms producing blood changes are variously named hemorrhagins, hemolysins, cytotoxins, precipitins, agglutinins, etc., according to the effect they produce. That constituent of snake venom having a predilection for nerve tissue is usually spoken of as neurotoxin,[13] the chemical nature of which is still unknown. Cobra venom contains a neurotoxin *par excellence.*

The action of cobra venom as a general protoplasmic poison can easily be demonstrated on protozoa and other animalcules, and on blood cells. It has recently been even more strikingly demonstrated by the author's phytopharmacological studies on living seedlings. Such tests proved that solutions of 1:25,000, and of even greater dilution, definitely inhibited the growth of roots of *Lupinus albus* seedlings.[14] Inasmuch as the small therapeutic dosage employed in clinical practice does not appreciably affect the blood elements, the writer's attention was devoted chiefly to the pharmacological effect of cobra venom on the nervous system and on the vital organs—heart, lungs and kidneys.

Pharmacology and Toxicology.—Dried crystalline secretion, or, more accurately speaking, scales of venom from three species of cobra, *Naia naia, Naia haji* and *Naia tripudians,* were used in this investigation. The specimens were procured through the courtesy and generosity of the author's colleagues in India and Egypt, to whom a lasting gratitude is hereby expressed. The dried secretion was dissolved in physiological sodium chloride solution, 0.9 per cent, which was used as the starting point for animal and clinical experiments.

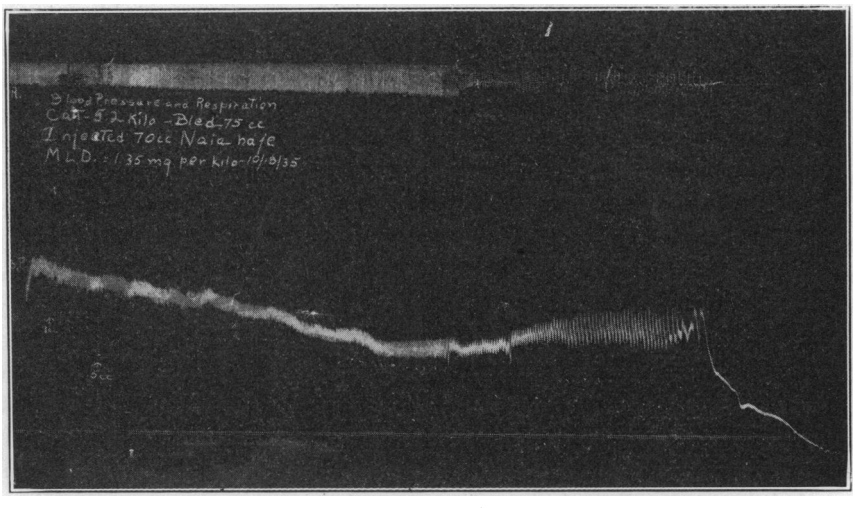
Zoopharmacological experiments were made on mice, rats, guinea pigs, rabbits, cats and dogs. The pharmacological action of dilute solutions of cobra venom on the respiration and circulation is best demonstrated by tests on cats or rabbits. The subjoined figure illustrates such an experiment. The carotid artery of a cat kept under ether anesthesia is cannulated and blood tracings are made while respiratory movements are recorded by a device which the author describes elsewhere.[15] A solution of cobra venom, 1:10,000, in physiological saline is slowly injected through cannula into the femoral vein at one-minute intervals. Such an experiment reveals that cobra venom first exerts a primary stimulating effect on both circulation and respiration. As the injections proceed, however, the respiratory center in the medulla is slowly depressed and finally paralyzed. In the last stages of medullary paralysis, the toxic effect on the heart is noted; but death occurs primarily through paralysis of the medulla, and the heart as a rule is brought to a standstill shortly afterward. Similar effects were produced in blood pressure experiments on rabbits and dogs.

The lethal dose of dilute solutions of cobra venom for cats, injected intravenously as described above, is 1.35 mg. per kilo weight, but varies

more or less according to the preparation tested. The lethal dose of the most potent preparation examined was 1.04 mg. while that of other solutions ran as high as 2.6 mg. per kilo weight of cat.

The Rowntree-Geraghty method[16] was used in studying the effect of cobra venom on the kidney function of rabbits intravenously injected with the drug. Injections of 5 mouse units in rabbits weighing 2 kilos produced no appreciable deterioration of kidney function.

The action of cobra venom was also studied by parenteral injection in guinea pigs, rats and mice. Mice afforded the most useful and economical means of assaying the venom. All that is necessary is to prepare a solution or colloidal suspension of the venom in physiological saline and to determine the minimal dose required to kill a mouse (20 to 22 gm.) within twenty



Effect of cobra venom (*Naia haji*), 1:10,000, on respiration and circulation of cat.

hours after intraperitoneal injection. This toxic dose is designated as a *mouse unit.* The mouse unit corresponds approximately to 0.01 mg. of venom, but some specimens give lower while others give higher ratings. For this reason it is not practical to express the therapeutic dosage of cobra venom in milligrams; the biological standard, expressed in mouse units, is usually employed instead.

The venom of the cobra is much more stable than that of other snakes, e.g., *Crotalus.* Whereas solutions of rattlesnake and moccasin venom deteriorate rapidly at room temperature, cobra venom decomposes but slowly below 70°C. This is a most fortunate circumstance when dealing with the preparation of a solution for use in human therapeutics. Higher temperatures and ultra-violet radiations, however, produce deterioration

of cobra venom solutions. The writer has described elsewhere the effect of light on cobra venom *in vitro* and *in vivo*.[17]

Preparation of Therapeutic Solutions.—Although solutions of cobra venom for laboratory use on animals and plants can be readily made, the preparation of a solution suitable for clinical administration is not a simple matter. The chief difficulty lies in securing a sterile solution free from bacteria and other microörganisms. After considerable experimentation, a method of preparing such a solution was developed. Dried scales of cobra venom were dissolved in physiological salt solution. The preparation was then put up in hard-glass ampules, sterilized by a special method at a temperature not exceeding 60°C., and assayed by the mouse method. Repeated tests proved that such ampules, when kept in the dark ice-chest, remained sterile and potent for many months.

Clinical Experiences.—Having succeeded in preparing a stable, sterile solution of cobra venom, the potency of which was accurately assayed by physiological methods, the writer in collaboration with several medical colleagues cautiously undertook a clinical study of cobra venom injections in a series of patients suffering from severe and uncontrollable pain. Such a clinical study could not have been successfully carried out had it not been for the keen interest and whole-hearted coöperation of two distinguished colleagues, Professor Joseph Çolt Bloodgood,* of the Johns Hopkins Medical School, and Dr. Curtis F. Burnam, radiologist and surgeon of the Howard A. Kelly Hospital, Baltimore. The great majority of cases treated with cobra came to the writer through one or other of these colleagues and their associates. It was found that the average effective therapeutic dose of cobra venom for relieving pain in human beings was five mouse units. In a few cases a double quantity of the drug was injected at one time but in no instance was it necessary to give such large doses as those recommended by some French investigators. Injections were usually given intramuscularly and sometimes subcutaneously. In one case, intravenous injections were employed with no untoward effect. The usual therapeutic procedure was as follows: A dose of 2 or 3 mouse units was first administered to ascertain whether the patient had any idiosyncrasy to the drug. If no undesirable effect was noted, a full dose of 5 mouse units was injected the following day. The same amount was injected several successive days until a definite physiological effect (i.e., relief of pain) was noted. The dosage was then cut down in frequency, injections being given on alternate days. Later patients could be kept comfortable with one or two injections a week. In this respect cobra venom was strikingly different from morphine which usually leads rapidly to habituation requiring increasingly frequent dosage.

The majority of cases treated were patients suffering from carcinoma and other malignant tumors in which surgical operation had been contra-

indicated or proved to be unsuccessful in eradicating the lesion. Many of these patients had also been treated with deep x-rays and radium, and most of them had run the gamut of such pain-relieving drugs as antipyretics and narcotics. A few cases of intractable neuralgia and non-malignant diseases were also studied. Table 1 exhibits the variety and number of cases treated.

TABLE 1

PATHOLOGICAL CLASSIFICATION OF DISEASES TREATED

Cancer of breast	14	Cancer of ovary	4	Cancer of fallopian tubes	1
Cancer of cervix	14	Cancer of tongue	4	Cancer of intestine	1
Cancer of uterus	4	Cancer of floor of mouth	3	Cancer of larynx	1
Cancer of rectum	10	Cancer of glands (primary)	2	Myxolipoma	1
Cancer of jaw	8	Cancer of prostate	2	Cancer of orbit	1
Cancer of bladder	7	Cancer of spine	2	Cancer of penis	1
Cancer of retroperitoneal tissues	6	Cancer of thyroid	2	Cancer of stomach	1
Cancer of lungs and mediastinum	5	Cancer of tonsils	2	Arthritis	1
Cancer of bone	5	Cancer of antrum	1	Neuralgia	7
Epithelioma	4			Raynaud's disease	1

It will be noted that the largest number of cancer patients suffered from tumors of the uterine body or cervix. Next in number were tumors of the breast, cancers of the rectum, tumors of the lungs, cancer of the jaw, sarcoma of the bones and malignant diseases of the spine.

TABLE 2

SUMMARY OF CASES AND RESULTS

Total number of cases treated		115
Cases with incomplete histories		10
Number of cases analyzed		105
Doubtful results in	5 cases	4.7%
No relief in	9 cases	8.6%
Slight relief in	23 cases	21.9%
Definite relief in	30 cases	28.6%
Marked relief	38 cases	36.2%
		100.0%

Table 2 shows the results obtained in the 115 patients studied up to the time of this writing. Ten of the histories being incomplete were not included in an analysis of the therapeutic results, and 105 cases remained for analytic study. Of the 105 patients, nine obtained no relief and five cases gave doubtful results, which may be regarded as negative. Of the remaining patients, 23 cases, or 27.9 per cent, gave evidence of slight relief

after receiving several injections of cobra venom. Thirty cases, or 28.6 per cent, gave histories of definite and more lasting relief, while 38 cases, or 36.2 per cent, were markedly benefited. Not only was relief from pain effected in these patients but their general condition was improved and treatment with narcotics was temporarily suspended. If we disregard the 23 cases obtaining slight relief and add together only those patients who have obtained definite and marked relief, we find 64.8 per cent of them belonging to this group. If all the patients be counted, irrespective of the degree of relief they experienced, the percentage of more or less favorable results amounts to 86.7, as compared with 13.3 per cent or the group of patients in whom the results obtained were doubtful or negative. These figures compare very favorably with those given the writer by Professor A. Saenz of the Institut Pasteur in a personal communication in which he states, "Il a une réelle action anesthésiante dans 70% cas traités." Fortunately, not a single case under the care of the writer and his colleagues showed any toxic reaction after the cobra venom injections. This was not surprising, however, in view of the conservative dosage employed. Doses of 4 or 5 mouse units were followed by no untoward effect whatever when injected in the writer himself and his laboratory staff in connection with studies on the pain threshold which will presently be described. Even nausea was surprisingly absent in all but two or three cases and in only one instance did a patient state that his pains, instead of being relieved, became more acute after the injection of cobra venom. These clinical data, while not numerous, certainly seem to warrant further experimentation with the drug.

A powerful analgesic or pain-relieving effect was undoubtedly produced in a large number of cases. Such an analgesic action was noted in some of the most intractable conditions as, for instance, in malignant tumors of the jaw, spine and pelvic bones. A number of the patients treated were morphine addicts. In such cases the writer and his colleagues were able to reduce the amount of narcotic to a minimum by substituting cobra venom injections and in a few instances opiates were dispensed with temporarily.

Pharmacodynamic Analysis.—The pain-relieving or analgesic property of cobra venom is of great interest from a purely pharmacodynamic point of view. It has been the general impression of earlier writers that such an analgesia is due to a local action of cobra venom. This was a fallacious deduction from the fact that the bite of a cobra caused numbness of the affected member. When injected at one time, such a massive dose of cobra venom will undoubtedly act as general protoplasmic poison, producing local paralysis and necrosis. The writer's systematic pharmacological analysis of the effects of dilute solutions of cobra venom on various organs and tissues, and particularly on nerve tissues, however, throws an entirely different light on the action of cobra venom in relieving pain. In the first

place, dilute solutions of cobra venom, tested by standard procedures (such as the frog method, rabbit's eye method and "wheal" method) for their local anesthetic effect on sensory nerve endings, produce no local anesthesia. In the second place, similar negative results were obtained with applications of cobra venom to ascending or descending nerve fibres of the sciatic and pneumogastric nerves. In the third place, studies on isolated surviving smooth muscle preparations (such as those of the small intestine, uterus, vas deferens and bladder) revealed that even considerable doses of cobra venom, 5 to 10 mouse units, introduced into 50 cc. of Locke solution, in which the surviving organs were suspended, affected the myoneural junctions and nerve terminals in such segments either not at all or to but slight extent. This was evidenced by their subsequent normal response to parasympathetic or sympathetic drugs, respectively—pilocarpine, atropine, ergotoxin and epinephrine.

All the pharmacodynamic evidence which the writer has gathered from extensive and intensive experimentation point to the higher nerve centers in the cerebrum as the seat of the analgesic action affected by cobra venom. In support of this conclusion, the following experimental data are adduced:

(1) Experiments made on mice, rats and guinea pigs revealed that injections of cobra venom are antagonistic to the pharmacological action of such so-called "cerebral convulsants" as camphor. This anticonvulsant action of cobra venom may perhaps explain its alleged usefulness in the treatment of epilepsy. (2) Even small doses of cobra venom, injected in guinea pigs and rats, produced a definite antipyretic effect, as may be illustrated by the following protocol:

EXPERIMENT ON GUINEA PIG WEIGHING 200 GRAMS

9:54 A.M.	Temperature, 100.2°F.
9:56 A.M.	Injected 2 mouse units of cobra venom
10:35 A.M.	Temperature, 98.6°F. Slight depression
12:00 M.	Temperature, 100.0°F.

This fall in temperature, considered with other experimental data, seems to indicate an effect on the temperature-regulating center in the brain. (3) Extremely interesting findings regarding the cerebral action of cobra-venom injections were obtained in psychological experiments on the behavior of white rats trained in the circular maze, employed extensively by the writer for the study of the cerebral effects of various drugs and chemicals. Under the drive of hunger, white rats were trained to run from the periphery to the center of a circular maze. After the animals had learned to find their way to the dish of food placed in the center quickly and without making any mistake, they were injected with small doses of the cobra venom, and their running time, number of errors, neuromuscular co-

TABLE 3

THRESHOLD OF PAIN BEFORE AND AFTER INJECTION OF COBRA VENOM IN HUMAN SUBJECTS

SUBJECT	SOLUTION INJECTED	MOUSE UNITS INJECTED	THRESHOLD OF PAIN BEFORE INJECTION AT	THRESHOLD OF PAIN AFTER INJECTION AT						
C.K.	Naia naia	5	10:00 A.M.	10:23 A.M.	10:48 A.M.	11:10 A.M.	11:30 A.M.	12:30 A.M.	2:30 P.M.	4:30 P.M.
			5.0 cm.	4.0 cm.	4.5 cm.	4.4 cm.	4.1 cm.	4.3 cm.	4.2 cm.	4.8 cm.
M.M.	Naia naia	4	9:50 A.M.	10:10 A.M.	10:25 A.M.	10:45 A.M.	11:20 A.M.	11:45 A.M.	12:10 P.M.	12:30 P.M.
			5.0 cm.	4.4 cm.	4.2 cm.	4.1 cm.	3.8 cm.	4.0 cm.	4.2 cm.	4.4 cm.
S.P.	Naia haji	3	10:25 A.M.	10:45 A.M.	11:00 A.M.	11:15 A.M.	11:30 A.M.	12:00 M.	12:30 P.M.	3:40 P.M.
			5.0 cm.	4.3 cm.	4.0 cm.	4.0 cm.	3.0 cm.	4.0 cm.	4.5 cm.	4.9 cm.
R.M.	Naia haji	2	2:15 P.M.	2:30 P.M.	2:50 P.M.	3:00 P.M.	3:30 P.M.	4:00 P.M.	4:30 P.M.	4:45 P.M.
			5.9 cm.	5.4 cm.	5.3 cm.	5.0 cm.	5.2 cm.	5.0 cm.	5.4 cm.	5.5 cm.
N.G.	Naia haji	3	10:10 A.M.	10:35 A.M.	11:00 A.M.	11:40 A.M.	11:55 A.M.	12:30 P.M.	2:00 P.M.	3:30 P.M.
			5.5 cm.	5.2 cm.	5.0 cm.	5.0 cm.	5.0 cm.	5.6 cm.	5.0 cm.	5.3 cm
S.M.	Naia tripudians	3	10:28 A.M.	10:50 A.M.	11:05 A.M.	11:25 A.M.	11:48 A.M.	12:10 P.M.	1:00 P.M.	
			5.4 cm.	5.0 cm.	3.9 cm.	4.3 cm.	4.2 cm.	4.5 cm.	5.0 cm.	
H.B.	Naia tripudians	4	2:30 P.M.	2:53 P.M.	3:35 P.M.	3:55 P.M.	4:10 P.M.	4:34 P.M.	9:15 A.M.	11:45 A.M.
			7.1 cm.	6.5 cm.	6.6 cm.	6.4 cm.	6.4 cm.	6.5 cm.	6.8 cm.	7.0 cm.
M.M.	Naia tripudians	4	2:25 P.M.	2:55 P.M.	3:15 P.M.	3:35 P.M.	4:00 P.M.	4:35 P.M.	9:10 A.M.	
			6.0 cm.	5.0 cm.	5.2 cm.	5.0 cm.	4.9 cm.	5.2 cm.	6.2 cm.	
K.C.	Naia tripudians	4	2:30 P.M.	2:50 P.M.	3:35 P.M.	3:55 P.M.	4:15 P.M.	4:30 P.M.	10:00 A.M.	
			5.8 cm.	3.2 cm.	5.0 cm.	4.6 cm.	4.5 cm.	5.0 cm.	5.8 cm.	
D.M.	Naia tripudians	4	2:30 P.M.	2:45 P.M.	3:10 P.M.	3:35 P.M.	3:55 P.M.	4:20 P.M.	10:10 A.M.	
			6.5 cm.	4.8 cm.	6.2 cm.	5.2 cm.	5.3 cm.	5.5 cm.	6.5 cm.	
K.C.	Saline control—pH 4.6	2 cc.	2:15 P.M.	3:00 P.M.	3:35 P.M.	3:50 P.M.	4:10 P.M.			
			5.4 cm.	5.5 cm.	5.8 cm.	5.7 cm.	5.6 cm.			
B.M.	Saline control—pH 6.8	2 cc.	10:10 A.M.	10:35 A.M.	10:50 A.M.	11:10 A.M.	11:30 A.M.	12:00 M.	12:40 P.M.	
			4.9 cm.	4.9 cm.	5.0 cm.	5.0 cm.	5.0 cm.	5.0 cm.	5.0 cm.	

ordination and general behavior were studied. It was found that such a small dose as 0.5 mouse unit produced a primary stimulation of the cerebral and neuromuscular responses. The primary stimulation was followed by depression. The results of such experiments, described elsewhere in detail,[18] were strikingly similar to those obtained by Macht and Mora in studies on the effect of opium alkaloids.[19] The following protocols illustrate the findings:

Rat C, weighing 250 grams, injected with 0.5 mouse unit of cobra venom
Running time for three consecutive trips in maze:
(1) Just before injection: 31 seconds—no error
(2) 1 hr. after injection: 16 seconds—no error
(3) 2 hrs. after injection: 16 seconds—no error

Rat D, weighing 210 grams, injected with 3.0 mouse units of cobra venom
Running time for three consecutive trips in maze:
(1) Just before injection 18 seconds—no error
(2) 1 hr. after injection: stalled completely
(3) 13 hrs. after injection: 23 seconds—1 error

(4) Further and more direct evidence as to the central effect of cobra venom on relieving pain is furnished by the writer's experiments on the threshold of pain, as studied in both human beings and guinea pigs. In these tests, of which a detailed description is given elsewhere,[20] the threshold of pain marked on some specific point in the skin by the graduating induction current is determined before and after injection of the drug to be studied by a method detailed some years ago in these PROCEEDINGS in connection with a quantitative study of analgesia affected by opium alkaloids.[21] It was found that even as little as 3 mouse units of cobra venom, injected subcutaneously or intramuscularly in human beings, produced a definite depression of the pain threshold as compared with the result obtained in control experiments with injections of normal physiological saline solutions of different hydrogen-ion concentration. These results are strikingly illustrated by the subjoined table (table 3).

Discussion.—The results of the present investigation may be briefly restated as follows: A toxicological study of solutions of cobra venom in physiological saline reveals that lethal doses produce death primarily through a paralysis of vital centers in the medulla. Such paralysis is rapidly followed by arrest of the heart and fall of the blood pressure to dead level. The lethal dosage of the venom in great dilution injected continuously, while very small, is not as potent as that of some other powerful poisons which the writer has studied by similar methods. Thus, for instance, when tested by continuous intravenous injection in cats, cobra venom was usually found to be no more poisonous than nicotine and was certainly far less toxic than a solution of aconitin hydrochloride. The

potency of cobra venom for therapeutic administration is more conveniently expressed in mouse units than in milligrams. Standard solutions of cobra venom in saline were prepared for clinical use and sterilized by appropriate methods, and the average therapeutic dose of such a biologically standardized solution was found to be 5 mouse units, a dose which, if indicated, could be injected at regular intervals for long periods of time. Such solutions of cobra venom were employed in treatment of intractable pains of a series of 115 clinical cases, and extraordinarily favorable results, as far as relief of pain was concerned, were noted in a large percentage of the patients. This pain-relieving or analgesic effect of cobra venom on pharmacodynamic analysis seems to be a central one and points to the cerebrum as the seat of action. It is not a local anesthetic effect. When compared with the analgesia produced by morphine, the effects of cobra venom were found to supervene more slowly but proved, on the other hand, to be more lasting. While the action of cobra venom on the central nervous system in some respects is not unlike that of morphine, it differs from the latter in that it does not bring about the addiction and other undesirable features consequent upon injection of opiates and cocaine. The reason for the longer duration of the cobra venom effect is not quite clear but studies which the writer is making on the relation of this toxin and morphine to oxidative processes in brain tissue may help to throw more light on the phenomenon.

While the present paper is confined to a discussion of the analgesic or pain-relieving properties of cobra venom, it may not be irrelevant to mention that certain French investigators, notably Calmette, Saenz and Costil,[22] have found that cobra venom exerts a depressant or inhibitory effect on experimental tumors in mice. Such experiments are also being carried on by the writer but the data obtained so far are inconclusive.

Summary.—(1) An experimental study of cobra venom was undertaken with the four-fold objective (*a*) of determining its toxicological and therapeutic dosage, (*b*) or preparing a stable, sterile and biologically assayed solution for clinical administration, (*c*) of making a carefully controlled clinical study concerning the effect of injections of cobra venom in a series of cases suffering from intractable pain and (*d*) of ascertaining as far as possible its mechanism of action as a pain-relieving drug.

(2) A series of 115 clinical cases, treated with injections of cobra venom, revealed that such injections produced definite and marked relief of pain in nearly 65 per cent of the patients and a slight relief in even a larger number.

(3) Pharmacodynamic analysis of cobra venom action points to the higher nerve centers as the seat of the analgesia, resembling in this respect the action of morphine but differing from the opiate in that it does not produce addiction and other disagreeable and dangerous by-effects.

* Deceased October 22, 1935.

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STRUCTURAL AGE DETERMINATION OF PIEDMONT INTRUSIVES IN MARYLAND

BY ERNST CLOOS AND H. GARLAND HERSHEY

DEPARTMENT OF GEOLOGY, THE JOHNS HOPKINS UNIVERSITY

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Problems and Method.—Most of the intrusives of the Piedmont region of Maryland and Pennsylvania are considered to be pre-Cambrian by many workers.[1] Port Deposit granite and Baltimore gabbro are intrusive into the Glenarm series, which is also considered pre-Cambrian.

A direct age determination, based on intrusive relations, is not possible because the intrusives are separated from known Paleozoic sediments by a wide belt of rocks of the Glenarm series (Fig. 1). A gap of approximately 20–30 miles must be bridged by other means. Persistent structures which can be recognized over a large territory and which transect formational boundaries regardless of their trend serve the purpose. Two such structures were utilized: flow cleavage and fracture cleavage. Hitherto