

cent. of cases. And some results obtained so far suggest that this method of treatment may prove of value as a postoperative procedure in diminishing the number of recurrences, and that in a certain number of cases it might limit the necessity for amputation of the limb in cases of sarcoma of the long bones. As to its mode of action, nothing definite can be stated, but it is likely that the toxins themselves, as well as the local and general reactions they produce, frequently affect the life of the sarcoma cells unfavorably.

ABSTRACT OF DISCUSSION

DR. B. A. THOMAS, Philadelphia: Dr. Loeb's paper has recalled to my mind a very interesting case which was brought to my attention a year since. The patient had been suffering for several weeks from an inoperable malignant tumor of the mouth and was being treated at the time by one of Philadelphia's most eminent internists, whose word I think would substantiate the diagnosis of a definite neoplasm. After several weeks of treatment the patient was told that nothing further could be done and was advised to arrange his estate. A few days later he was taken ill with a severe infection of grippe. He was confined to bed for several days. A few weeks after he recovered he called to see the physician again and was informed that, beyond a doubt, there had been a considerable decrease in the size of the tumor and there was evidence of healing. In the course of a few weeks the growth had entirely disappeared and the patient died subsequently of other intercurrent condition. It seems to me advisable to report this case, in the belief that toxins of bacteria or infections other than those caused by *Streptococcus* or *B. prodigiosus* may at times be instrumental in the cure or treatment of inoperable sarcoma.

DR. W. DUFFIELD ROBINSON, Philadelphia: I employed Coley's serum in a case of extraperitoneal sarcoma and had tried everything else I could think of and all had failed absolutely in doing anything, but the Coley serum had the most remarkable control of pain. The young man required 1 1/2 grains of morphin every hour or two; on the second day after beginning the treatment the morphin was reduced to 1/4, at the end of two weeks 1/12 grain three times a day. He was made much more comfortable and improved in many ways, but eventually died. Coley changed the serum at different times according to his ideas of the condition present. The entire treatment was under Coley's supervision. The other case was sarcoma of the neck and jaw. This patient was taken to the hospital and treated under Dr. Coley's supervision without result, except for controlling of pain. It failed entirely, although the serum was crowded to the maximum dose. Operation was done and the man has a recurrence now.

DR. O. P. JOHNSTONE, Pittsburg, Pa.: I have used Coley's fluid in two cases of sarcoma; one, a typical large spindle-celled sarcoma of the palate, had been operated on three times the previous year, with recurrences. After the third operation I recommended a trial of Coley's fluid, and it was given every day for three months. It is now a year since the last operation and there has been no recurrence. In the second case, a spindle-celled sarcoma of the skin, operated on a year ago, could not be completely removed, sections from the edge of the portion removed still showing tumor tissue. Coley's fluid was given daily for eight months, and twice a week for the following four months. The wound healed nicely, and the skin around the wound where the sarcoma tissue was left appears normal. The girl has increased in weight and appears perfectly well a year after the operation.

Plague Infected Wood Rat.—The discovery of a wood rat (*Neotoma fuscipes annectens*, Elliot), from Alameda county, California, on Oct. 17, 1909, infected with bubonic plague, adds a new link to the chain of plague, as it is believed this is the first plague-infected wood rat ever discovered. The wood rat may act as an intermediary in the transmission of disease to other mammals. The infection was found by Passed Assistant Surgeon G. W. McCoy of the laboratory in San Francisco (*Public Health Reports*, Jan. 7, 1910).

ANTIVENINS*

HIDEYO NOGUCHI, M.D.

NEW YORK

In order to understand the proper administration of antivenins we must first consider several fundamental facts concerning the main properties of snake venoms and their antitoxins.

PROPERTIES OF VENOMS

1. *Constituents.*—There are three principal groups of death-dealing constituents in snake venoms, namely, the neurotoxins, hemorrhagins and fibrin ferments. In the venoms of colubrine snakes the neurotoxins are the most important constituents, while the hemorrhagins constitute the chief toxins of all the viperine venoms. The fibrin ferments are present in the colubrine as well as the viperine venoms and vary somewhat with the species. These three groups of toxins may in most venoms be present in varying quantities, but some venoms contain almost exclusively the neurotoxins, or neurotoxins and fibrin ferments with but little hemorrhagin. Thus the venoms of the Australian snakes—*Pseudechis* and *Notechis*—contain all three constituents in fairly even quantity, those of the marine snakes only the neurotoxins, those of the Indian and African colubrine snakes chiefly the neurotoxins with a negligible amount of hemorrhagins. The venoms of crotaline snakes, including the rattlesnakes and pit-vipers of America and Asia, contain chiefly hemorrhagins, with secondary amounts of the neurotoxins and fibrin-ferments. The real vipers owe their poisonousness to hemorrhagins, and sometimes to powerful fibrin ferments in their venoms. The most deadly of all the true vipers are the Indian *Daboia* and *Echis*. The *Elaps* of America has a venom rich in neurotoxins.

2. *The Causes of Death.*—Death from snake-poisoning is due to various causes, according to the varieties of venoms introduced. The death from the cobras, *Elaps*, *Bungarus* and marine snake-bite is due to the paralysis of respiratory center. The fatal issue from the poisoning by the daboia, *Echis*, and Australian snakes is due either to a rapid intravascular thrombosis or to secondary poisoning or infection resulting in marasmus. In cases of rattlesnake or any other crotaline snake-bite death is caused by occasional hemorrhages in vital organs or by a setting in of secondary poisoning resulting in cachexia or septicemia. In excessive absorption of these venoms death may result from the effects of neurotoxins also. The most distinctive of venom toxication in the crotaline bite is the extensive local disturbances produced by the hemorrhagins; this local effect is highly important in considering all the viperine and crotaline poisoning.

3. *Fatal Dosage.*—The minimal fatal doses of different venoms can be accurately determined by animal experimentation. But this is influenced by the mode of introduction of snake venom into the animal body. Thus in case of neurotoxic venom there is but little difference in the final result whether it is introduced directly into the circulation or under the skin. On the other hand, the minimal lethal dose of fibrin ferment containing venoms is very much smaller when injected into the circulation than when introduced subcutaneously, the greater part of the toxic ferment being absorbed in the neighborhood of the injection site. This is also true

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of the hemorrhagin-containing venoms. The minimal fatal dose of crotalus venom, for example, is several times smaller when given intraperitoneally or intravenously.

4. *Hemolytic Properties*.—Hemolytic principles of venom play no important rôle in the fatal issue.

5. *Specificity of Toxins*.—Specificity of toxic constituents of venoms of various species of snakes is very important in considering the questions of antivenins. It has been established since the investigations of Mitchell and Reichert that different venoms are different in their pharmacologic and chemical properties.

VARIETIES AND PROPERTIES OF ANTIVENINS

But the knowledge of specificity has recently gone much further mainly through the aids of antivenins. The recent studies demonstrate that not only the venom as a whole, but also the apparently similar toxic constituents of different venoms, are not identical. Thus, the neurotoxins of the cobra are not the same as those of *Bungarus* or *Pseudechis*. The hemorrhagins of the rattlesnake is different from those of *Ancistrodon* or *Lachesis*. The fibrin ferment of the daboia venom is entirely different from that contained in other species of snakes. Hemolysins are also specific. This fact is extremely vital in employing antivenins as therapeutic agents.

6. *Varieties*.—There are seven different specific antivenins produced.

Cobra antivenin (Calmette, Lamb).
Crotalus antivenin (Flexner and Noguchi, McFarland).
Moccasin antivenin (Noguchi).
Lachesis antivenin (Brazil).
Crotalus terrificus antivenin (Brazil).
Trimeresurus antivenin (Kitashima, Ishizaka).
Daboia antivenin (Lamb).

Calmette's antivenin is produced by using several venoms and is a polyvalent one, although its action on other than cobra venom is rather feeble. McFarland's antivenin was also a polyvalent one, though not very strong.

7. *Specificity of Antivenins*.—Antivenins contain multiple antibodies or antitoxins corresponding to the number and varieties of toxic constituents contained in a given venom. There may be present antineurotoxins, antihemorrhagins, antifibrin ferments, antihemolysins, etc. But their action is highly specific—that is, the antineurotoxin of cobra antivenin cannot neutralize any other neurotoxins but the cobra neurotoxin. The antihemorrhagin of lachesis antivenin is effective only in neutralizing the corresponding hemorrhagin. The hemolysis or fibrin ferment of daboia venom are not affected by the antifibrin ferment or antihemolysin of other antivenins.

8. *Standardization of Antivenins*.—In the therapeutic application of antivenins their specificity must first be respected. The methods of standardization of antivenins are different according to different investigators. With cobra antivenins the only reliable method is to resort to animal experiments. Calmette chose the rabbit, giving the antivenin and venom simultaneously into the marginal vein. Myers preferred the mouse, giving a mixture of the venom and antivenin which had been left in contact for a few hours, administered intraperitoneally.

With crotalus antivenin Flexner and Noguchi and Madsen and Noguchi used intraperitoneal injection of the venom and antivenin mixture into guinea-pig and rabbit.

With daboia antivenin Lamb employed rabbits and monkeys. The daboia venom cannot be used or tested

in the same manner as in cases of other antivenins, as it contains powerful fibrin ferments. The strength is estimated by using the mixture of the antivenin and venom (*in vitro*) or by observing the anticoagulating power on the citrated blood plasma *in vitro*.

With trimeresurus antivenin Kitashima employed several laboratory animals.

9. *Therapeutic Dosage of Antivenins*.—This depends on the quantity of venom that may be introduced by the bite. We require that quantity of antivenin which neutralizes a maximum quantity that a snake can inject. Three important snakes can yield at one time the following doses:

Naja tripudians (Cobra) 0.2 —0.35 gm. (dried)
Crotalus adamanteus 0.2 —0.3 gm. (dried)
Daboia 0.15—0.25 gm. (dried)

The cobra antivenin prepared by Lamb requires 200 to 350 c.c., that of Calmette twice as much (Martin and Lamb).

The crotalus antivenin prepared by Flexner and Noguchi requires about 100 to 150 c.c.

The daboia antivenin prepared by Lamb requires about 150 to 250 c.c.

These quantities of antivenins appear enormous, but here come in some important factors to alter the matter. The resistance of man to these venoms, and the possibility of unfavorable conditions that may prevent snakes from injecting the maximum quantity of venom are the chief ones.

From animal experiments we can approximately estimate the minimal lethal dose of different venoms for man. Thus, according to several authors, one obtains the following data:

Cobra 0.015—0.0175 gm. (Lamb)
0.01 (Calmette).
0.031 (Frazer).
Daboia 0.06 (Lamb).
Crotalus 0.15—0.20 (Noguchi).

Under favorable conditions only the maximum quantity of venom may be injected by a snake, but this is not always the case. Especially the bite of *Crotalus* seldom destroys human life (Mitchell).

Supposing that a bite is inflicted by a cobra or any other venomous snake and the person receives a quantity of the venom little over the human tolerance. This excess may be so small that a few vials of antivenin may neutralize it and save the victim from death. This is very important in encouraging the use of antivenins whenever available. From animal experiments we know that the animals which survive acute poisoning with cobra or daboia recover rapidly without sequelæ. This is also true in human cases. The persons who escape death within the first few days usually recover soon.

Another factor is the favorable effect of a ligature in case of the daboia bite. The venom causes a quick intravenous thrombosis and prevents the absorption of the rest of the venom into the general circulation. Here we have ample chance to derive benefit from the administration of antivenin.

In crotalus poisoning death never occurs so rapidly and we also may expect much benefit from its antivenin.

All the antivenins should be administered intravenously or intramuscularly. In case of crotalus poisoning by *Crotalus* it is advisable to inject the antivenin both around the wound and intravenously.

In the future we must strive to produce much stronger preparations of antivenins than hitherto. At the Rockefeller Institute we now have several large animals under immunization with the venoms of the rattlesnake and water moccasin.

In closing I may add that in the southern isles of Japan the trimeresurus antivenin has been freely used and the statistics indicate a sudden fall of the mortality among the persons bitten by this formidable reptile.

The benefit of any antivenin is naturally greater when it is administered promptly, and none is to be injected unless the specificity is respected.

Rockefeller Institute for Scientific Research.

ABSTRACT OF DISCUSSION

DR. JOSEPH MCFARLAND, Philadelphia: Against how many fatal doses of crotalus poison has 1 c.c. of the anticrotalus serum been able to protect and what kind of serum was used?

DR. H. NOGUCHI: Twelve doses to 1 c.c. injected intraperitoneally; the serum was goat serum.

DR. MCFARLAND: Sheep serum is better.

DR. JOHN A. VAN VALZAH, Daytona Beach, Florida: But how soon would the poison act after the subject was bitten by a snake?

DR. NOGUCHI, New York: In a human case? Very little experience has been had. One of the assistants in the laboratory was bitten in the little finger. After about five or ten minutes he became nervous and the finger felt painful. Permanganate of potassium solution was injected freely, but the patient became depressed and the swelling went up his whole arm within twenty-four hours. Eventually he recovered. This was in the days before the antivenins were employed.

ANTIRABIC VIRUS

A. M. STIMSON, M.D.

Passed Assistant Surgeon U. S. Public Health and Marine-Hospital Service

WASHINGTON, D. C.

Antirabic virus or vaccine, as used in the Pasteur treatment for the prevention of rabies or hydrophobia in exposed persons, consists of the spinal-cord material of rabbits which have died from rabies (or have been killed just before its termination), which has been induced by the subdural inoculation of the fixed virus of this disease. This fixed virus is obtained by the serial passage of the rabies as met in Nature (as, for instance, in mad dogs), through many successive rabbits. By this procedure it acquires finally a virulence which for any given strain of virus is fixed, and the incubation period of the disease caused by it in animals is uniform. At the same time its pathogenic properties have been modified so that it is less capable of causing rabies if inoculated subcutaneously.

In Pasteur's method of treatment, the spinal cord of the rabbit is dried for a time over caustic potash, at a temperature of 23 C., the result of this treatment being that the cord gradually loses its virulence, this so-called attenuation being probably a numerical decrease of infective units rather than a qualitative change. In inoculating persons who have been bitten by rabid animals those cords are administered first which have been dried so long that their infectious properties have become lost, and then on successive days cord is administered which has been dried for a shorter and shorter time, and which is consequently of increasing potency.

The virus or vaccine consists then of the spinal cord material of the rabbit, plus the micro-organism of rabies and its products, artificially modified as to its pathogenic properties.

It is administered subcutaneously, after being emulsified by rubbing up in a mortar, with a bland fluid such

as physiologic salt solution or bouillon. The anterior abdominal wall is the most suitable site for inoculations. The treatment lasts from two to three weeks, according to the formula adopted by the institution providing the treatment, and is usually modified according to the severity and site of the injury. Injections are given daily.

The immunity thus induced is of the "active" type, the patient producing in his own body the "antibodies" necessary to prevent the pathogenic effect of the rabies virus with which the person has been accidentally inoculated. These antibodies are demonstrable in the blood of immunized persons or animals. This immunity is comparable, therefore, to that induced by smallpox vaccine against smallpox, and is entirely different from the passive immunity conferred against diphtheria, by the injection of antidiphtheritic serum. Reference to antirabic virus or vaccine as a "serum" is evidently incorrect.

It has been shown that this virus, like that of smallpox vaccine, is uninfluenced as to its potency for some time (at least three or four weeks) by immersion in neutral glycerin, or by the presence of small proportions of other antiseptics (tricresol, phenol). Advantage has been taken of this fact, and the virus may now be sent to distances from the laboratory where it is prepared, by conserving it in this manner, and be fully potent when used, provided that too long a time has not elapsed since its preparation and that it has been kept cool during transit. Deterioration is less rapid when the virus is preserved in bulk than when it has previously been emulsified.

Antirabic virus has no favorable influence on hydrophobia, once the disease has developed. Its beneficial effects are solely prophylactic and are rendered possible only by the fact that the average incubation period of rabies is relatively long.

Since the introduction of prophylactic inoculation by Pasteur many modifications in details have been introduced, the principle remaining the same. A detailed description of these modifications cannot be given here. What has been said applies to the most commonly used method of immunization with desiccated cord.

The treatment fails in cases in which the incubation period is too short to allow the necessary time for immunity to develop, in cases in which it is resorted to too late, and in those rare cases in which, from unexplained peculiarities of personal make-up, the individual is incapable of producing antibodies. These failures amount to less than 1 per cent., whereas in untreated persons who have been exposed the mortality has been variously estimated at from 5 per cent. to 20 per cent. or more. Variations in mortality statistics are due largely to the preponderance or small number of serious or belated cases in different regions. The bites of mad wolves, as in portions of Russia, give a mortality in untreated persons which often reaches 50 or 80 per cent., because the injuries are very severe and likely to be about the head and neck.

Pasteur treatment is now available at some twenty or more institutions in the United States,¹ and may be obtained from the Surgeon-General, United States Public Health and Marine-Hospital Service, on application by health officers having moderate laboratory facilities for administration under their supervision.

1. For a list of these see the publication *The Prevalence of Rabies in the United States*, by the United States Public Health and Marine-Hospital Service, Washington, 1909; also *THE JOURNAL A. M. A.*, Sept. 25, 1909, III, 989.